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Twin screw granulation as a simple and efficient tool for continuous wet granulation

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Abstract

The modification of a twin screw extruder for continuous wet granulation was investigated. Modification of the extruder setup as well as the screw design allowed the continuous wet granulation of α-lactose monohydrate without the need of a wet sieving step. The robustness of twin screw granulation was evaluated by studying the influence of processing parameters and formulation variables on the process performance and on the properties of α-lactose monohydrate granules and tablets. The process reproducibility during long term production was evaluated. Screw speed (200–450 rpm) and total input rate (5.5–9.5 kg/h) had no significant influence on the granule properties, while the water concentration during granulation influenced the process as well as the granule properties. At a water concentration (calculated on wet granule basis) of 5.5–8.5%, continuous twin screw granulation of α-lactose monohydrate 200M was feasible and the granules obtained had good properties. PVP addition mainly affected tablet properties.

Tablets made from granules containing 2.5% PVP had a tensile strength above 0.94 MPa, a friability below 1% and a disintegration time ranging between 495 and 576 s. Tablets containing hydrochlorothiazide complied with the dissolution requirements as 60% was released after 5 and 15 min from tablets without PVP and with 2.5% PVP, respectively.

No problems were observed during continuous twin screw granulation over a period of 8 h and the granule and tablet properties were reproducible throughout the process. These results indicated that twin screw granulation is an efficient tool for continuous wet granulation.

Keywords: Continuous granulation; Twin screw granulator; Granule quality; Processing parameters; Formulation variables; Process continuity; Lactose monohydrate

1. Introduction

Wet granulation is considered one of the most important processes in the manufacturing of solid dosage forms. Production of solid dosage forms using granules has several advantages such as enhanced flowability, improved compactability, reduced segregation and less dust. The most commonly used wet granulation techniques are high shear and fluid bed granulation.

There is an increasing need for alternative processes that are more economic, reliable and reproducible, taking into consideration the possibility of automation and process continuity. Continuous processes offer two advantages: there is no difficult scale-up necessary resulting in a shorter development time and a 24 h automatic production line (lights-out operation) would be possible. Recently, this subject

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is gaining more interest and several techniques have been reported for continuous granulation.

Leuenberger (2001) reported a quasi-continuous granulation technique using a specially designed high shear mixer/granulator, which is connected to a multicell fluidized bed dryer. This technique resulted in granules with a similar or even better quality compared to those produced by conventional granulation equipment. Schroeder and Steffens (2002) used rotary screw extrusion for continuous wet granulation. Lindberg et al. (1987, 1988) were the first to report on the possibility of using a twin screw extruder for the continuous granulation of an effervescent paracetamol preparation. However, no data were presented on the suitability of these granules for compaction. In 1993, Kleinebudde and Lindner studied the twin screw extrusion process as a granulation tool. The influence of processing parameters and formulation variables on the extrudates was evaluated, but the quality of granules was not reported.

In previous reports (1999 and 2002) we studied twin screw extrusion in combination with an oscillating granulator for the wet granulation of α-lactose monohydrate. This technique was more efficient than high shear granulation and the granules produced had improved properties. However, wet sieving of the material discharged from the twin screw extruder was still required to obtain granules. The aim of this study was to eliminate this wet sizing step by changing the screw configuration. Some reports indicated that granule quality is influenced by this parameter: Lindberg et al. (1987, 1988) reported that a low agitation screw profile resulted in a higher yield on granulation and a lower granule porosity than a medium agitation screw profile. Similarly, Lindberg (1988) stated that screw configuration significantly influenced the porosity of granules. In addition, the process continuity, the maximal capacity and the influence of the processing parameters and formulation variables on the granule and tablet properties were evaluated.

2. Materials

α-Lactose monohydrate 200M was used as excipient (DMV, Veghel, The Netherlands) with a particle size distribution of: 60% $<$ 45 μm, 83% $<$ 75 μm, 92% $<$ 100 μm, 98% $<$ 150 μm, 100% $<$ 250 μm (DMV International, 1998). Polyvinylpyrrolidone (PVP, Kollidon® K30) as a binder (BASF, Ludwigshafen, Germany) and hydrochlorothiazide (Ludeco, Brussels, Belgium) was selected as a model drug for very poorly water soluble drugs.

3. Methods

3.1. Preparation of granules

The extrusion was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25:1. During granulation the powder volume in the feed hopper was maintained between 85 and 100% of the feeder capacity. Powder and granulation liquid feed rates were determined prior to each experiment by repeatedly weighing the powder and the liquid amount delivered over a period of 5 min. The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK). To evaluate the dissolution properties, hydrochlorothiazide (10%) (Ludeco, Brussels, Belgium) was added as a model drug to the formulation without and with 2.5% PVP. Prior to granulation, hydrochlorothiazide was blended with α-lactose monohydrate in a planetary mixer (Kenwood Major, Hampshire, UK) for 15 min at 60 rpm. The extruder was set at a constant temperature of 25 °C. Granules were collected 10 min after the process was started in order to allow the system to equilibrate. The granules were oven-dried at 25 °C for 20 h, sieved through a 1400 μm sieve and evaluated for yield, granule friability and compressibility. Based on preliminary experiments using pure α-lactose monohydrate and water as a granulation liquid a set of reference conditions for the extrusion process were selected: a screw speed of 250 rpm, a total input rate of 5.6 kg/h and a water concentration during granulation of 8.5 and 7.5% (w/w) for formulations without and with 2.5% (w/w) PVP, respectively. All water concentrations were based on the wet granule mass, while PVP and hydrochlorothiazide concentrations were based on dry weight.

The reference conditions were used to optimize the extruder configuration for continuous granulation. In

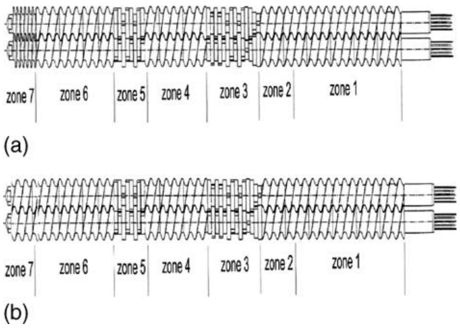


Fig. 1. Configuration of the co-rotating screw: feeding zone (1), transition zone (2), mixing zone (3), transport zone (4), mixing zone (5), transport zone (6), feeding to the die zone (7). (a) Standard screw profile, and (b) modified screw profile with two mixing zones.

a first approach the die was modified. For these experiments the extruder was equipped with a standard screw profile (Fig. 1a). The initial die configuration studied was a screen (∅ 1 mm) fixed to the outside of the die block, next the screen was replaced with a 1 mm perforated die plate (2 mm thick) and finally the process was run without the die block.

In a second approach, the screw profile was changed. At the end of the screw (zone 7) the discharge screw element was replaced by a conveying screw element (Fig. 1b). Using this modified screw profile, the process was run with and without the die block. The optimal configuration was determined by analyzing the granule yield. Optimization was continued till a granule yield similar to the semi-continuous extrusion granulation process (Keleb et al., 2002) was achieved.

To investigate the efficiency of this continuous granulation process, the granules were evaluated for friability, yield and compressibility. Tablets were evaluated for tensile strength, friability and disintegration. In addition, the between-day reproducibility ($n = 6$) of a formulation without and with PVP and the influence of processing parameters and formulation variables were evaluated.

The maximal capacity of the equipment at optimal configuration was assessed using maximal screw speed (450 rpm) and a water concentration of 7.5%. The granules obtained at each total input rate studied were evaluated.

The continuity of the process for α-lactose monohydrate containing 2.5% PVP was assessed by continuously running the process at reference conditions for 8 h and each hour evaluating the granules and tablets properties.

3.2. Compression of tablets

The granules ($F_{250\text{–}710\,\mu m}$) were blended with 0.5% (w/w) magnesium stearate (<90 μm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet.

3.3. Evaluation of granules

3.3.1. Particle size analysis

The particle size distribution of the granules ($F_{<1400\,\mu m}$) was determined using laser diffraction (Master Sizer, Malvern, UK) after suspending the particles in air. The volume diameter (d_v) was used to calculate the following fractions $F_{<250\,\mu m}$, $F_{250\text{–}1000\,\mu m}$ and $F_{>1000\,\mu m}$. The analysis was performed at minimal air pressure (0.4 bar) to avoid desagglomeration and/or disintegration of the granules during the test.

3.3.2. Yield

The yield of the granulation process (Y1) was calculated as $F_{<1400\,\mu m}(\%) \times F_{250\text{–}1000\,\mu m}(\%)/100$ where $F_{<1400\,\mu m}$ is the fraction of dried granules smaller than 1400 μm and $F_{250\text{–}1000\,\mu m}$ is the granule fraction between 250–1000 μm as determined by particle size analysis.

3.3.3. Friability of granules

The granule friability was determined in a friabilator (PTF E Pharma Test, Hainburg, Germany), at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of granules ($F_{250\text{–}1000\,\mu m}$) together with 200 glass beads (mean diameter 4 mm) to falling shocks. Afterwards the glass beads were removed and the weight of the granules retained on a 250 μm sieve (F_{wt}) was determined after vibrating for 5 min (Retsch VE 1000, Germany) at an amplitude of 2 mm. The friability was calculated as $((I_{wt} - F_{wt})/I_{wt}) \times 100$.

3.3.4. Bulk and tapped density

The bulk volume (V_0) of 50 g granules ($F_{250\text{–}1000\,\mu m}$) was recorded in a 100 ml measuring cylinder as well as the volume after 1500 taps (V_{1500}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Bulk and tapped densities were calculated as 50 g/V_0 and 50 g/$V_{1500,}$ respectively. The compressibility index (C%) was calculated from the bulk and tapped density using the following equation,

$$C\% = \left(\frac{\rho_f - \rho_i}{\rho_f}\right) \times 100$$

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

3.4. Tablet evaluation

3.4.1. Tablet friability

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

3.4.2. Tablet tensile strength

The hardness, thickness and diameter of the tablets ($n = 6$) was determined (PTB 311 Pharma Test, Hainburg, Germany) after a 24 h storage period at 25 °C and 60% RH. The tablet tensile strength T was calculated using the equation described by Fell and Newton (1970)

$$T = \frac{2F}{\pi dt}$$

where F, d and t denote the diametral crushing force, the tablet diameter and the tablet thickness, respectively.

3.4.3. Disintegration time

The disintegration time was determined ($n = 6$) using the apparatus described in Eur. Ph. (PTZ-E Pharma-Test, Hainburg, Germany). Tests were performed in distilled water at 37 °C using disks.

3.4.4. Dissolution test

Dissolution tests were performed on hydrochlorothiazide tablets in 900 ml 0.1N HCl using the paddle method (Vankel, Cary, NC, USA). The dissolution medium was maintained at 37 ± 0.5 °C, while the rotation speed was set at 100 rpm (USP XXIII). Samples (5 ml) were withdrawn after 5, 10, 15, 20, 25, 30, 45 and 60 min and concentrations were spectrophotometrically determined at 272 nm (Lambda 12 Perkin Elmer, Norwalk, US).

3.5. Statistical analysis

The influence of water concentration, screw speed and total input rate on the granule and tablet properties was determined using one-way ANOVA. Properties of granules and tablets prepared by continuous twin screw granulation over a period of 8 h were analyzed using one-way ANOVA. For further comparison a multiple comparison among pairs of means was performed using a Scheffé test with $P < 0.05$ as a significance level. The influence of PVP concentration was evaluated only within the optimal range of water concentration. The data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of the variances was tested with a Levene's test. Tablet friability and granule yield could not be statistically analyzed as only one measurement was performed per factor level.

Statistical analysis was carried out using the software package SPSS version 11.0.

4. Results and discussion

4.1. Influence of extruder setup

Previously Keleb et al. (2002) described extrusion of α-lactose monohydrate 200M using a twin screw extruder equipped with screws having a standard screw profile and with a die block (2.2 cm × 1.0 cm die aperture), yielding extrudates ranging from small flakes to large extrudates depending on the water concentration used. Modification of process parameters did not allow to obtain granules and an additional wet sizing step was always required. Although Lindberg et al. (1988, 1987) and Kleinebudde and Lindner (1993) reported on wet granulation using a twin screw extruder equipped with a perforated die, our attempts to granulate α-lactose monohydrate using a twin screw extruder equipped with a 1-mm screen failed due to a high power consumption, a high barrel temperature, screen distortion and/or screw blocking. Similar problems were observed when a perforated die plate was used instead of the screen. This failure could be explained by the low water concentration used in our study and the different material properties. Increasing the water concentration during extrusion avoided these problems, but this resulted in overwetted sticky extrudates and not in granules. As the densification of the material before the die seemed to be too high the twin screw extruder was used without the die block in combination with the standard screw profile (Fig. 1a) to avoid extrusion of the material. Using this configuration processing of α-lactose monohydrate at optimum water concentration resulted in a granulation yield of 16 and 22% for α-lactose monohydrate 200M without and with 2.5% PVP, respectively. Using the equipment without die block reduced the resistance to the material flow in the barrel and thereby the load on the machine. This configuration also allowed a higher total input rate, resulting in a higher granulation capacity.

The screw profile was modified as the discharge screw element was replaced by a conveying screw element (Fig. 1b). The effect of this screw modification was evaluated at reference conditions using the extruder with die block, and allowed to produce granules, but the yield was still very low (5.4 and 3% for α-lactose monohydrate formulations without and with PVP, respectively).

However, removing the die block and using the modified screw profile resulted in a yield of 54 and 43% for α-lactose monohydrate without and with PVP, respectively (Table 1), while no lumps (>2 mm) were produced. This unexpected increase of the yield was mainly due to a decrease in large agglomerates. Removal of the die block and replacement of the discharge screw element by a conveying screw element dramatically reduced the pressure built up at the end of the barrel and avoided compression of the granules. This configuration resulted in a comparable yield with the extrusion granulation technique combined with wet sieving (60%) as reported by Keleb et al. (2002). In addition the $F_{<125\,\mu m}$ was below 3 and 9% for formulations with and without PVP, respectively. As the twin screw extruder with this optimal configuration yielded granules while no extrusion took place the process will be further referred to as twin screw granulation. In a second part of the study, the granulation process using this

Table 1
Between day reproducibility of the twin screw granulation of α-lactose monohydrate

Granule properties							Tablet properties		
PVP	Friability (%)	Yield (%)	Particle size distribution			Compressibility (%)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
			<250 μm	250–1000 μm	>1000 μm				
0	14	55	12	68	20	10	0.64	1.70	173
	23	53	25	62	13	10	0.87	1.66	157
	24	53	24	65	11	14	0.77	1.69	155
	21	58	17	69	14	14	0.81	1.47	169
	21	55	10	66	24	13	0.75	1.59	159
	22	47	29	54	17	13	0.74	1.41	140
Average	21	54	20	64	17	12	0.80	1.60	159
S.D.	3.5	3.8	7.7	5.5	4.8	1.8	0.08	0.12	11.6
2.5	12	44	12	62	26	13	1.29	0.67	497
	17	47	12	64	24	15	1.23	0.86	494
	10	46	10	65	25	13	1.21	0.83	506
	12	41	6	62	31	13	1.18	0.83	474
	13	42	11	63	27	13	1.23	0.82	520
	10	38	4	58	38	13	1.14	0.73	562
Average	12	43	9	62	29	13	1.21	0.79	509
S.D.	2.6	3.4	3.4	2.4	5.2	0.8	0.05	0.07	30

Granules were produced ($n = 6$) at reference conditions without and with 2.5% PVP (wet addition) (water concentration during granulation: 7.5 and 8.5% (w/w) for formulation with and without PVP respectively, screw speed: 250 rpm; total input rate: 5.6 kg/h). Tablets were compressed at 154 MPa using the 250–710 μm granule fraction.

twin screw granulation technique was further investigated.

Table 1 shows the properties of granules and tablets obtained after twin screw granulation at reference conditions. α-Lactose monohydrate granules without and with 2.5% PVP had a granule friability below 21%, a yield above 43% and a compressibility below 13%.

α-Lactose monohydrate tablets without PVP showed a tensile strength of 0.80 MPa, a friability of 1.60% and a disintegration time of 159 s. Addition of PVP improved the friability (0.79%) and the tensile strength (1.21 MPa) and increased the disintegration time to 509 s. The quality of α-lactose monohydrate granules and tablets produced by twin screw granulation indicated the efficacy of this process. The between-day reproducibility showed that the process is reproducible with respect to the granule and tablet properties (Table 1).

4.2. *Influence of formulation*

4.2.1. *Influence of water concentration*

The influence of water concentration during granulation on the granule properties is shown in Fig. 2a and b. The water concentration had a crucial influence on the granulation process as well as on the granule yield ($F_{250–1000\,\mu m}$) confirming earlier findings (Kleinebudde and Lindner, 1993; Keleb et al., 2002). Granulation is only feasible within a certain water concentration range. The determination of the optimum water concentration was based on the yield on granulation. The optimum water concentration is lower when PVP was added and was 8.5 and 7.5% for the granulation of α-lactose monohydrate without and with PVP, respectively. These water concentrations are lower than those used for other conventional wet granulating techniques, such as fluid bed granulation or high shear granulation. Moreover, experiments showed that this water concentration can be further reduced by increasing the PVP concentration to 5% (Keleb et al., 2002). Granulation at a low water concentration not only allowed to reduce the drying time, but could also allow to perform drying in a continuous way.

At optimum water concentration a yield of about 50% was obtained and no lumps (>2 mm) were formed. Decreasing the water concentration resulted in a higher $F_{<250\,\mu m}$ mainly due to insufficient granulation, while increasing the water concentration above the optimum level resulted in a gradual increase of the granule fraction $F_{>1400\,\mu m}$, probably due to overwetting of the agglomerates. However, the $F_{<125\,\mu m}$ was below 5 and 11% for all formulations with and without PVP, respectively. At considerably higher water concentrations the granulation process yielded large flakes instead of granules. This observation stresses the need for an accurate and constant feeding of the binding liquid and of the powder during the granulation process. Variations in the feeding rate would result in variable water concentrations and hence have important an impact on the granulation process as well as on the granule yield.

Table 2 shows the properties of tablets obtained from granules produced at different water concentrations. Analysis of these results revealed that the water concentration had no significant influence on the tablet properties. For α-lactose monohydrate tablets without PVP the tensile strength ranged between 0.49 and 0.75 MPa, the friability was above 1.41% and the disintegration time ranged between 124 and 200 s. For α-lactose monohydrate tablets with 2.5% PVP the tensile strength ranged between 1.02 and 1.17 MPa, the friability between 0.39 and 0.68% and the disintegration time between 459 and 575 s. At all water concentrations the tablets with PVP had a significantly higher tensile strength and disintegration time than those without PVP.

4.2.2. *Influence of PVP concentration*

The addition of 2.5% PVP resulted in a lower $F_{250\,\mu m}$, a significantly lower granule friability and a higher $F_{>1400\,\mu m}$. The shift in granule size distribution towards large particles is mainly due to good binding properties of PVP (Wikberg and Alderborn, 1992; Wan et al., 1996). Reducing the PVP concentration to 1.25% PVP resulted in a similar granule friability and $F_{<250\,\mu m}$ as those obtained for 2.5% PVP, but it slightly increased the yield and decreased $F_{>1400\,\mu m}$ as shown in Fig. 3. The $F_{<125\,\mu m}$ was below 5 and 11% for formulations with and without PVP, respectively.

The addition of PVP (1.25 or 2.5%) significantly increased tablet tensile strength, decreased tablet friability to below 1% and significantly increased tablet disintegration time, however it remained below 10 min (Table 2). Similar properties were obtained for α-lactose monohydrate tablets containing 1.25 and

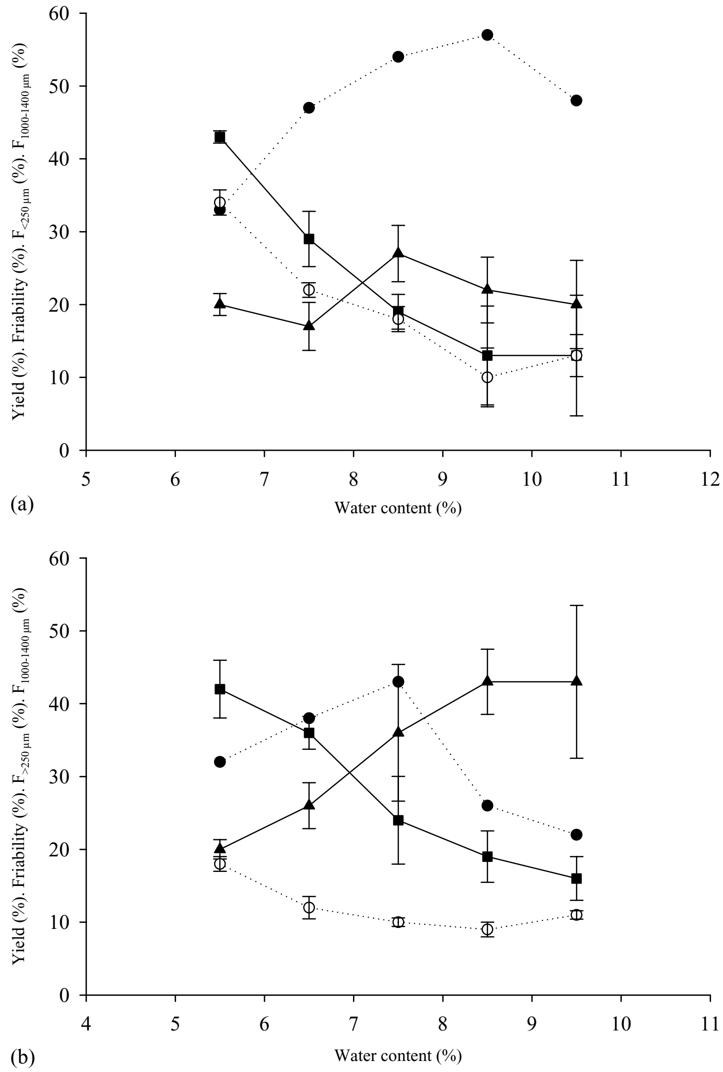


Fig. 2. Influence of water concentration during granulation on the properties of α-lactose monohydrate granules granulated at a screw speed of 250 rpm and a total input rate of 5.6 kg/h. (●) Granule yield, (▲) granule fraction (1000–1400 μm), (○) granule friability, (■) granule fraction < 250 μm. (a) Formulated without PVP and (b) formulated with 2.5% PVP.

2.5% PVP. These results indicated that 1.25% PVP would be sufficient for the granulation of α-lactose monohydrate using twin screw granulation.

4.3. Influence of processing parameters

4.3.1. Influence of the screw speed

Screw speed had a significant effect on some properties of granules containing PVP (Fig. 4), while it did not affect the properties of pure α-lactose monohydrate 200 M granules. Increasing the screw speed from 200 to 450 rpm at a constant total input rate had no significant influence on the granule friability, while it resulted in a decrease of the granulation yield from 48 to 32% and in an increase of the fraction $F_{>1400\,\mu m}$ from 31 to 50%. This effect was probably due to incomplete filling of the granulator barrel as the screw speed increased, creating less friction and collisions between agglomerates thus allowing the granules to grow. The effect was only observed when PVP was added, indi-

Table 2
The influence of the process parameters and the formulation variables on the properties of tablets made from granules produced using twin screw granulation

Parameters				Tablet properties		
Screw speed (rpm)	PVP (%)	Total input rate (kg/h)	Water (%)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
Influence of water concentration						
250	0	5.6	6.5	0.75	2.17	124
			7.5	0.74	2.17	124
			8.5	0.69	1.41	140
			9.5	0.49	1.47	144
			10.5	0.71	1.61	165
					1.42	200
250	2.5	5.6	5.5	1.02	0.39	459
			6.5	1.02	0.63	493
			7.5	1.09	0.68	510
			8.5	1.27	0.67	523
			9.5	1.17	0.68	575
Influence of PVP concentration						
250	0	5.6	7.5	0.76	1.60	159
250	1.25	5.6	7.5	1.22	0.92	352
250	2.5	5.6	7.5	1.21	0.79	509
Influence of screw speed						
200	0	5.6	8.5	0.68	1.61	219
250				0.66	1.63	204
300				0.66	1.64	175
350				0.67	1.48	176
400				0.68	1.72	185
450				0.70	1.47	204
200	2.5	5.6	7.5	1.22	0.68	545
250				1.18	0.58	543
250				1.18	0.58	543
300				1.10	0.59	557
350				0.94	0.67	530
400				1.25	0.66	553
450				1.22	0.63	535
Influence of total input rate						
250	0	5.6	8.5	0.77	1.88	205
		6.5		0.78	1.82	192
		7.5		0.75	1.43	179
		8.5		0.70	1.42	173
		9.5		0.71	1.11	157
250	2.5	5.6	7.5	1.14	0.73	562
		7.5		0.75	1.43	179
		8.5		0.70	1.42	173
		9.5		0.71	1.11	157
250	2.5	5.6	7.5	1.14	0.73	562
		6.5		1.04	0.51	523
		7.5		1.11	0.49	576
		8.5		1.09	0.77	544
		9.5		1.02	0.47	525
Maximum capacity						
450	2.5	5.6	7.5	1.22	0.63	535
		10.5		1.10	0.90	496
		12.5		1.12	0.56	468
		16.5		1.15	0.86	502
		18.5		1.11	0.51	501

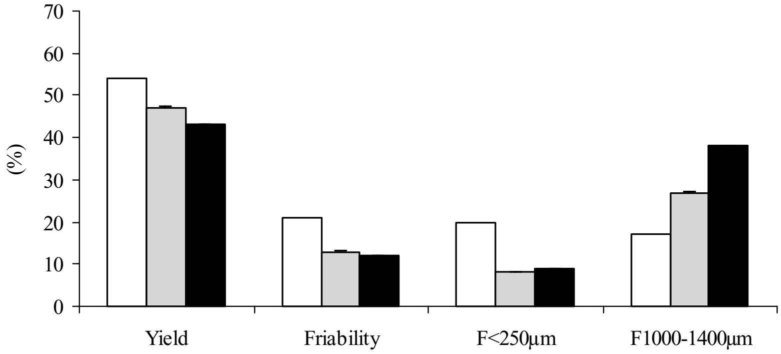


Fig. 3. Influence of PVP concentration on the properties of α-lactose monohydrate granules containing 0 (□), 1.25 (▨) and 2.5% PVP (■).

cating the strong adhesion and binding properties of PVP. The compressibility was always below 15% indicating good flow properties of the granules.

Table 2 shows that the screw speed had no significant influence on the tablet properties.

4.3.2. *Influence of total input rate*

The influence of total input rate on the granule properties is shown in Fig. 5a and b. It is clear that increasing the total input rate had no influence on the granule properties except on the granulation yield, which increased as the total input rate increased. As for the effect of screw speed, this can be explained by the differences in the degree of filling of the granulator barrel. At a higher total input rate, the filling degree of the barrel was higher, causing an increase in friction and collisions between the agglomerates and resulting in more agglomerate breakdown and hence increasing the yield. The compressibility was always below 15%, indicating the good flow properties of the granules.

Table 2 shows that total input rate had no significant influence on the tablet properties.

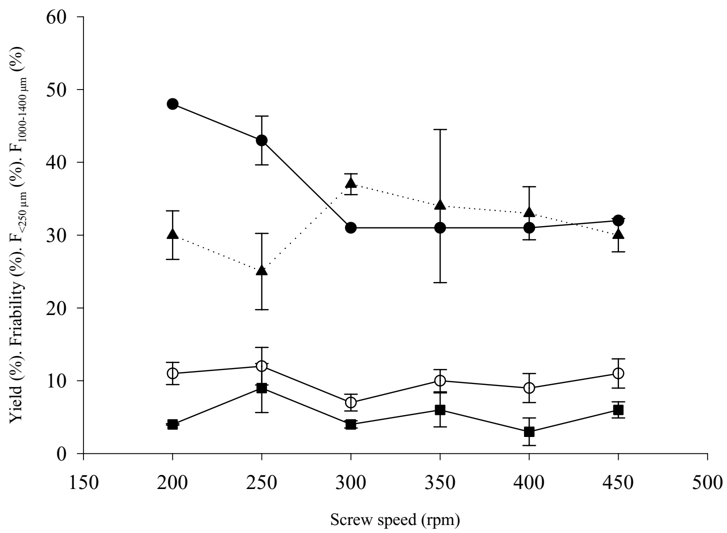


Fig. 4. Influence of screw speed on the granule properties of α-lactose monohydrate granules with PVP granulated at a water concentration of 7.5% and a total input rate of 5.6 kg/h (●) granule yield, (▲) granule fraction (1000–1400 µm), (○) granule friability, (■) granule fraction < 250 µm.

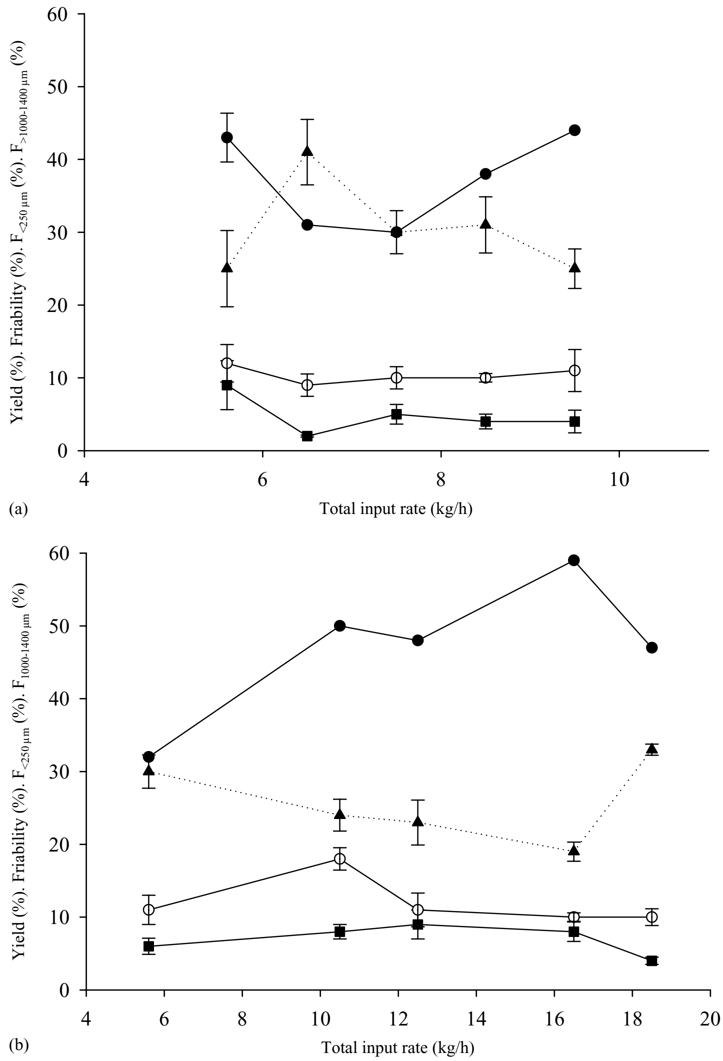


Fig. 5. Influence of total input rate on the properties of α-lactose monohydrate granules with PVP granulated at a water concentration of 7.5% and screw speed: (a) 250 rpm, (b) 450 rpm. (●) Granule yield, (▲) $F_{1000–14000\,\mu m}$, (○) granule friability (■), $F_{<250\,\mu m}$.

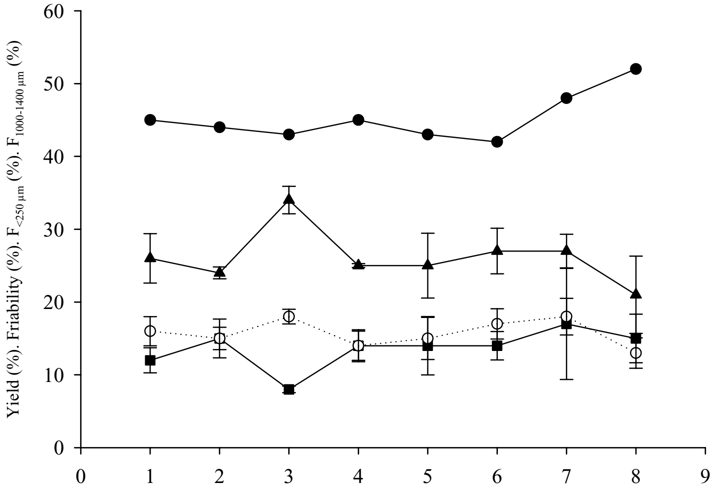
4.4. Maximal capacity

The capacity of the twin screw granulator was also determined for α-lactose monohydrate 200M with 2.5% PVP. As shown in Fig. 5b and Table 2, the total input rate could be increased from 5.5 up to 18.5 kg/h with limited influence on the granule and tablet properties.

Beyond 18.5 kg/h the powder accumulated at the inlet of the granulator barrel. As the power consumption measured at this high input rate remained at 30% (a value similar to that recorded at lower total input rates) this is an indication that the machine is not fully loaded at 18.5 kg/h and that the capacity of the granulation process can possibly be increased by modifying the powder inlet system of the granulator barrel.

4.5. Process continuity

The continuity of twin screw granulation was evaluated over a period of 8 h. No problems were noticed



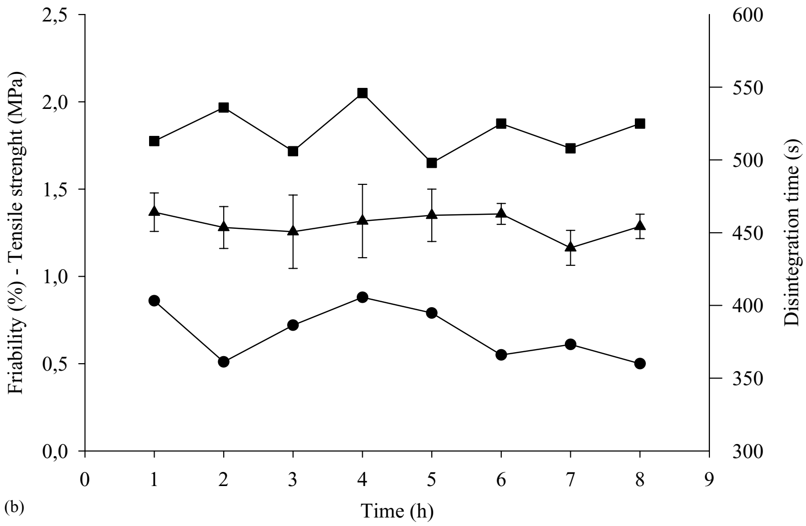


Fig. 6. (a) Properties of α-lactose monohydrate granules with PVP produced by continuous twin screw granulation over a period of 8 h granulated at a water concentration of 5.5%, screw speed of 250 rpm and a total input rate of 5.6 kg/h. (●) granule yield, (▲) granule fraction (1000–1400 µm), (○) granule friability (■), granule fraction < 250 µm. (b) Properties of tablets made from of α-lactose monohydrate granules with PVP produced by continuous twin screw granulation over a over a period of 8 h. (●) Friability, (▲) tensile strength, (■) disintegration time.

during the 8 h of granulation. Moreover, the power consumption always ranged between 26 and 28%, and the barrel temperature between 56 and 66 °C. The granule and tablet properties are shown in Fig. 6a and b, respectively. Analysis of the results revealed no significant differences in granule and tablet properties over the entire granulation period. From this it can be concluded that the twin screw granulator is suitable for continuous wet granulation of α-lactose monohydrate 200M.

5. Conclusion

The twin screw granulation process optimized in this study allowed continuous and efficient wet granulation of α-lactose monohydrate 200M. Acceptable tablet properties were obtained only when PVP was added as a binder during granulation.

Optimization of water concentration and controlling the water and powder feeding rate during granulation was essential for the process performance and continuity. Increase of the screw loading improved the granulation performance, especially for formulations containing PVP.

The study showed that twin screw granulation is a promising continuous wet granulation technology.

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