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Continuous twin screw extrusion for the wet granulation of lactose

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Abstract

The suitability of continuous twin screw extrusion for the wet granulation of α-lactose monohydrate was studied and compared with conventional high shear granulation. The influence of process parameters (screw speed and total input rate) and formulation variables (water and polyvinylpyrrolidone (PVP) concentration) on the properties of granules (yield, particle size distribution, friability and compressibility) and tablets (tablet tensile strength, friability and disintegration time) was investigated. Variation of the formulation and process parameters had a major effect on the process feasibility. Optimization of these parameters is required to allow continuous processing and to ensure a high yield. Total input rate, screw speed and water concentration had a minor influence on the granule and the tablet properties. The addition of PVP had no major influence on the granule properties, but significantly affected the tablet characteristics. For granules formulated with and without PVP a yield above 50%, a friability below 30% and a compressibility below 15% was obtained. Tablets without PVP showed a tensile strength below 0.6 MPa, a friability above 1% and a disintegration time below 3 min, whereas tablets with PVP showed a tensile strength above 0.6 MPa, a friability below 1% and a disintegration time ranging from 8 to 15 min. High shear granulation was only possible when PVP was added and it required a higher amount of water. It was concluded that wet granulation of α-lactose monohydrate using continuous twin screw extrusion is a robust process and might offer a suitable alternative for high shear granulation in the pharmaceutical industry.

Keywords: Granulation; Continuous twin screw extrusion; Granule and tablet properties; High shear granulation; Lactose monohydrate

1. Introduction

In the field of solid dosage forms, wet granulation is still frequently used during tablet production. Over the past decades, several batch-wise wet granulation techniques, such as high shear and fluidized bed granulation, have been developed and extensively studied. As continuous processing offers significant advantages over batch production (automation and a reduction of batch to batch variation, labor cost and processing time), several types of equipment allowing contin-

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uous wet granulation have been developed, the main ones being continuously operating mixer granulators and fluidized bed granulators (Bonde, 1998). In addition, some reports indicated the potential of twin screw extrusion as a continuous wet granulation technique. Gamlen and Eardley (1986) studied the influence of formulation parameters on the quality of paracetamol extrudates. These authors stated that, despite the high incidence of extrudate surface defects, the extrusion technique was suitable for the granulation of paracetamol. Other researchers (Lindberg et al., 1987, 1988; Lindberg, 1988) showed that wet granulation via extrusion yielded granules with desired properties and that those properties were influenced by formulation and process variables. Kleinebudde and Lindner (1993) studied the twin screw extrusion/granulation process using lactose/microcrystalline cellulose, but did not evaluate granule characteristics. The purpose of the present work was to study the influence of formulation variables and process parameters on the production of α-lactose monohydrate granules using continuous twin screw extrusion and to compare this technique with high shear granulation, a well established wet granulation technique in the pharmaceutical industry.

2. Materials and methods

2.1. Preparation of extrudates and granules

α-Lactose monohydrate 200 M was obtained from DMV (Veghel, The Netherlands) and polyvinylpyrrolidone (PVP, Kollidon® K30) was received from BASF (Ludwigshafen, Germany). 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 and equipped with a standard screw profile with two mixing sections (Fig. 1). The die block (2.6 cm thick) is fixed to the extruder barrel. It is designed so that

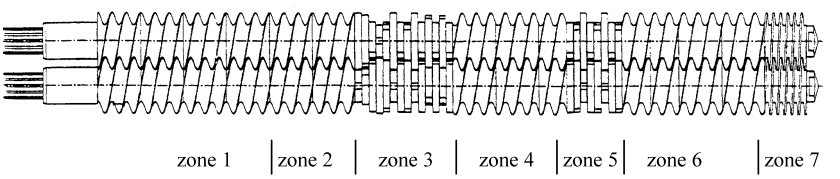

Fig. 1. Co-rotating standard screw profile: feeding zone (1), transition zone (2), mixing zone (3), transport zone (4), mixing zone (5), transport zone (6), feeding to the die zone (7).

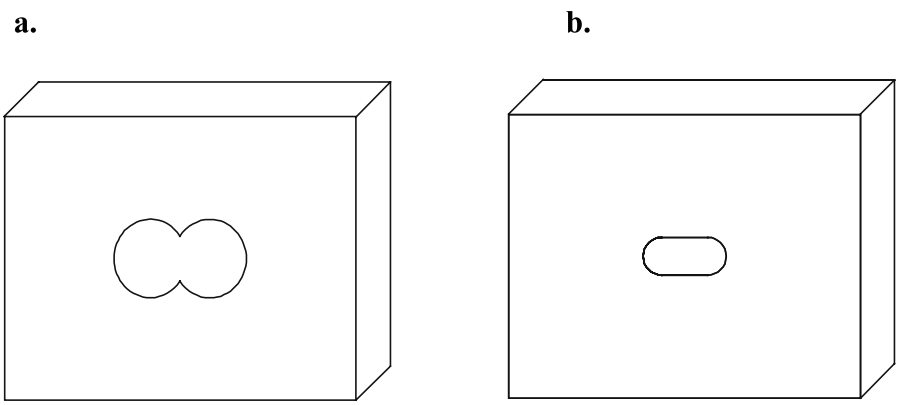

Fig. 2. (a) Side of the die block mounted to the extruder barrel with aperture shape to fit the screws ends. (b) Outer view of the die block with oval die outlet.

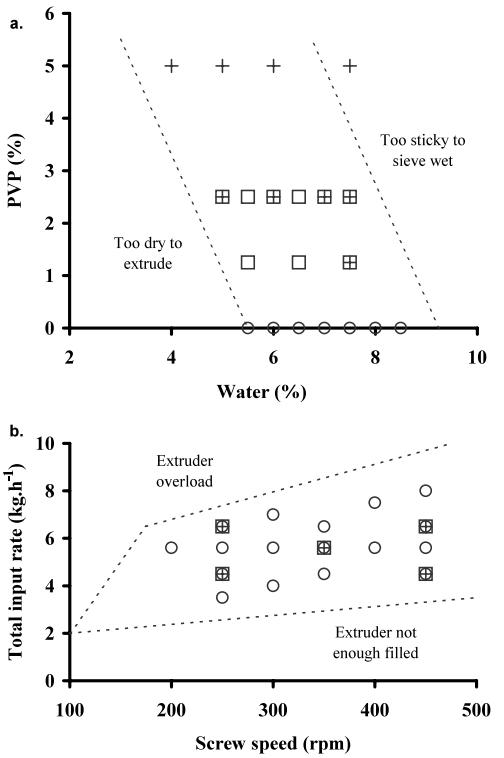

Fig. 3. Overview of the experiments performed to evaluate: (a) the influence of water concentration during extrusion and PVP-concentration (screw speed: 250 rpm; total input rate 5.6 kg h^{-1}); and (b) the influence of screw speed and total input rate (water concentration during extrusion: 7.5%, w/w) on the properties of α-lactose monohydrate granules. Method of binder addition: (○) without PVP; (□) wet addition of PVP; (+) dry addition of PVP.

it fits on the screw ends (last 0.8 cm) and then the aperture shape changes gradually into an oval hole of 2.2 × 1.0 cm (Fig. 2a and b). No additional screen was attached to the die block in order to avoid machine blocking.

During extrusion, the powder volume in the feed hopper was maintained at a constant level (85–100% of the total feeder capacity). Extrudates were prepared via wet and dry binder addition. 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). Powder and granulation liquid feed rates were determined prior to each experiment by repeatedly ($n = 3$) weighing the powder and the liquid amount delivered over a period of 5 min. In case of dry binder addition, PVP and α-lactose monohydrate were previously blended for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK).

The extruder was set at a constant temperature of 25 °C. Extrudates were collected 10 min after the process was started in order to allow the system to equilibrate. Immediately after extrusion the extrudates (400 g) were wet sized using a 1 mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and sieve. The granules were oven-dried at 25 °C for 20 h, sieved through a 1400 μm sieve and evaluated for yield, granule friability, compressibility and porosity.

Based on preliminary experiments using pure α-lactose monohydrate and water as a granulation liquid, a set of reference conditions for the extrusion process was selected: a screw speed of 250 rpm, a total input rate of 5.6 kg h^{-1} and a water concentration during extrusion of 7.5% (w/w).

These settings were used to evaluate the between day reproducibility ($n = 6$) of the extrusion process for α-lactose monohydrate as well as for a mixture α-lactose monohydrate with 2.5% PVP (wet addition). To evaluate the dissolution properties, hydrochlorothiazide (10%) (Ludeco, Brussels, Belgium) was added as a model drug to the formulation with and without 2.5% PVP and prepared at reference conditions. All water concentrations were based on the wet extruded mass, while PVP and hydrochlorothiazide concentrations were based on dry weight.

Fig. 3 gives an overview of the experiments performed to examine the influence of the water concentration, the PVP concentration and the method of PVP addition (Fig. 3a) and to evaluate the influence of screw speed and total input rate (the total amount of powder and granulation liquid fed during 1 h) (Fig. 3b).

During high shear granulation, α-lactose monohydrate at a load of 0.16 kg l^{-1} was granulated without and with 2.5% PVP (wet addition) in a Gral 10 (Machines Collette, Wommelgem, Belgium). Granulation was performed at different water concentrations (7.5, 10.0 and 12.5% w/w)

and impeller speeds (400, 500 and 600 rpm), while the chopper speed was kept constant at 3000 rpm. After a 2 min mixing period of the powder, the required amount of granulation liquid (water or an aqueous PVP solution) was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. Preliminary studies on the high shear granulation showed no differences in the granule properties between the granules wet sieved using an oscillating sieve and those sieved after drying. The granules prepared by high shear granulation were dried, sieved through a 1400 μm sieve to remove hard lumps and evaluated for yield, granule friability, compressibility and porosity.

2.2. Compression of tablets

The granules ($F_{250-710\ \mu m}$) 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 9 mm at a compression force of 10 kN per tablet.

2.3. Evaluation of granules

2.3.1. 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 $F_{<250\ \mu m}$, $F_{250-1000\ \mu m}$ and $F_{>1000\ \mu m}$. The analysis was performed at minimal air pressure (0.4 bar) to avoid disagglomeration and/or disintegration of the granules during the test.

The surface of the granules was evaluated by scanning electron microscopy (SEM) (JSM 5600 LV scanning electron microscope, JEOL Europe, Zaventem, Belgium).

2.3.2. Granule porosity

The granule porosity was determined by the Autopore III mercury porosimeter (Micromeritics, Norcross, GA, USA).

2.3.3. Yield

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

2.3.4. 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 ($F_{250-1000\ \mu m}$) 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 $(I_{wt} - F_{wt}/I_{wt}) \times 100$.

2.3.5. Bulk and tapped density

The bulk volume (V_0) of 50 g granules ($F_{250-1000\ \mu m}$) 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 densities using the following equation:

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

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

2.4. Tablet evaluation

2.4.1. 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.

2.4.2. Tablet tensile strength

The hardness, thickness and diameter of the tablets ($n = 6$) were 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 (1968),

$$T = 2F/\pi dt,$$

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

2.4.3. Disintegration time

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

2.4.4. Dissolution test

Dissolution tests were performed on hydrochlorothiazide tablets in 900 ml HCl (0.1 N) using the USP apparatus II. 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 (Beckman DU-65, Fullerton, CA, USA).

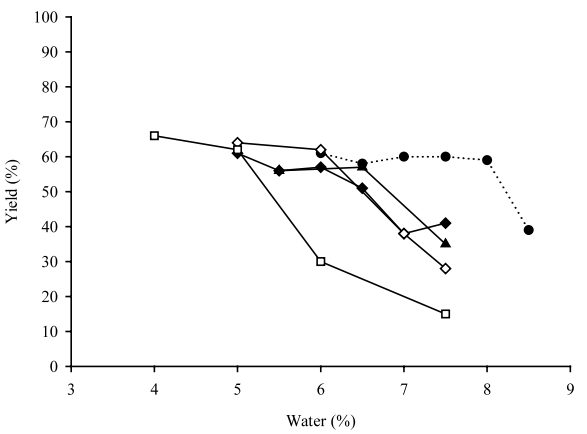

Fig. 4. Influence of water concentration during extrusion using extrusion on the yield of α-lactose monohydrate granules formulated without PVP (●) and with 1.25% PVP wet (▲), 2.5% PVP wet (◆), 2.5% PVP dry (◇) and 5% PVP dry (□) extruded at a screw speed of 250 rpm and a total input rate of 5.6 kg h^{-1}.

2.5. Statistical analysis

Statistical analysis was carried out using the software package SPSS version 10.0. First 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.

The influence of a studied parameter on the granule and tablet properties was determined using one-way ANOVA ($P < 0.05$). To further compare the effects of different parameters, a multiple comparison among pairs of means was performed using a Scheffe test with $P < 0.05$ as a significance level. The influence of PVP concentration and addition method was evaluated at the optimal range of water concentration only. Properties of granules and tablets prepared by continuous twin screw extrusion were compared with those obtained by high shear at the respective optimal water concentrations. Tablet friability and granule yield results could not be analyzed as only one measurement was performed per factor level.

3. Results and discussion

Table 1 reviews the data on the between day reproducibility of twin screw extrusion for the granulation of α-lactose monohydrate without and with 2.5% PVP. The data indicated that the extrusion process could be considered reproducible in relation to granule and tablet properties.

The performance of the twin screw extrusion as a granulation process at the different formulation and process parameters is visualized in Fig. 3a and b, respectively, and shows that the overall extrusion/granulation process was only possible within a specific range of these parameters. The formulation parameters clearly influenced the yield (Fig. 4), whereas varying the process parameters did not (data not shown). A minimum water concentration of 6% was required for the extrusion of α-lactose monohydrate without PVP,

Table 1
Between day reproducibility of the wet granulation process of α-lactose monohydrate via extrusion

Formulation	Granule properties						Tablet properties		
	Friability (%)	Yield (%)	Particle size distribution (%)			Compressibility (%)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
			<250 μm	250–1000 μm	>1000 μm				
Without PVP	16	66	18	69	13	12.8	0.53	2.11	129
	12	63	20	67	13	9.0	0.55	1.82	149
	8	62	20	65	15	13.0	0.54	1.82	148
	24	51	38	54	9	13.5	0.48	2.12	106
	20	57	32	59	9	9.1	0.44	1.76	88
	24	58	30	64	6	8.9	0.50	2.02	120
Average	17	60	26	63	11	11.1	0.50	2.00	123
SD	6.5	5.3	8.1	5.5	3.4	2.26	0.04	0.16	24
With PVP	14	41	12	74	13	12.4	0.82	0.51	603
	20	40	19	72	9	14.2	0.82	0.72	571
	15	47	11	79	10	12.4	0.73	0.63	609
	22	41	18	69	14	12.4	0.85	0.71	563
	21	42	17	72	11	13.4	0.72	0.71	647
	25	37	13	73	14	12.6	0.79	0.79	694
Average	20	41	15	73	12	12.7	0.79	0.70	615
SD	4.2	3.3	3.4	3.3	2.1	0.72	0.05	0.10	49

Granules were produced ($n = 6$) at reference conditions without and with 2.5% PVP (wet addition) (water concentration during extrusion: 7.5% (w/w); screw speed: 250 rpm; total input rate: 5.6 kg h^{-1}). Tablets were compressed at 10 kN using the 250–710 μm granule fraction.

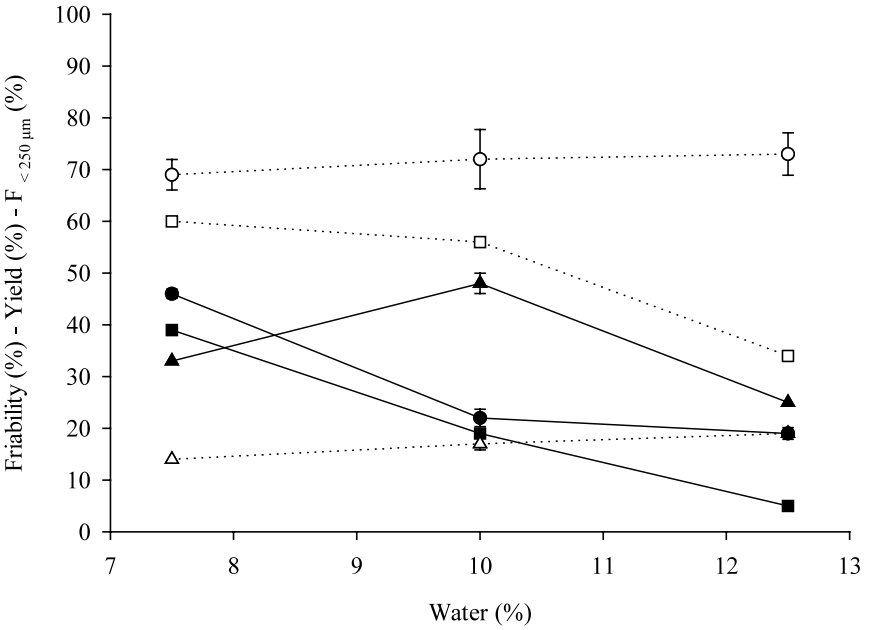

Fig. 5. Influence of water concentration during high shear granulation on the granule properties of α-lactose monohydrate granules formulated without PVP and with 2.5% PVP wet at 500 rpm impeller speed and 3000 rpm chopper speed. Granule friability (○) without PVP and (●) with PVP, yield (△) without PVP and (▲) with PVP and fines (□) without PVP and (■) with PVP.

as the frictional forces during extrusion were too high below this water concentration. The extrudates produced without PVP at a water concentration between 6 and 7.5% were smoothly wet sized and resulted in a yield of $\pm$60%. However, a further increase of the water concentration during extrusion to 8.5% dramatically decreased the yield to 39%. This low yield was due to sticking of the material to the sieve during wet sizing as the fraction above 1400 μm was always zero and the fraction below 250 μm remained almost constant and varied between 16 and 25%. In relation to the granule yield, the optimal water concentration during extrusion of pure α-lactose monohydrate ranged between 6 and 7.5%. On the other hand, the yield obtained from high shear granulation of α-lactose monohydrate without PVP never exceeded 20%, even at water concentrations above those used during extrusion (Fig. 5) (only the data obtained at 500 rpm are shown, since at this impeller speed the best results were obtained). This low yield obtained for high shear granulation is due to the improper agglomeration ($F_{<250\ \mu m}$ 31%) (Fig. 5) and to the high amount of hard lumps ($F_{>1400\ \mu m}$ 48%) at low water concentration (7.5%) and to the high amount of hard lumps ($F_{>1000\ \mu m}$ 56%) at high water concentration (12.5%). When comparing both techniques for the granulation of α-lactose monohydrate, it is clear that twin screw extrusion provides an interesting alternative for the conventional high shear granulation, not only because of the higher process efficiency, but also because it requires a considerably lower amount of liquid.

PVP addition dramatically affected the performance of both techniques. When, at a constant water concentration during extrusion of 7.5%, increasing concentrations of PVP were added to α-lactose monohydrate, the yield gradually decreased to less than 15% at 5% PVP (Fig. 4). Varying the water concentration at the different PVP concentrations revealed that the optimal water concentration during extrusion decreased with increasing PVP concentration and ranged from 5.5 to 6.5, 5.5 to 6.5 and 4 to 5% for 1.25, 2.5 and 5% PVP, respectively (Fig. 4). The possibility of

wet granulation using extrusion at a considerable lower water concentration when PVP was added can be explained by the lubricating activity of PVP resulting in a reduction of frictional forces and of the heat generated during granulation and due to the binding capacities of PVP.

For high shear granulation, no different PVP concentrations were tested, but the addition of 2.5% PVP dramatically increased the yield at all water concentrations tested. However, only at 10% water, a yield of $\pm 50\%$ was obtained (Fig. 5). When comparing the granulation efficiency, it can be concluded that for high shear granulation of α-lactose monohydrate the addition of PVP and a higher water concentration during the process were required than for extrusion. This difference can be attributed to the different way of addition of the binding liquid and to the higher densification during twin screw extrusion (Kristensen et al., 1985a). These data indicated that twin screw extrusion is more efficient as a wet granulation technique for α-lactose monohydrate than high shear granulation.

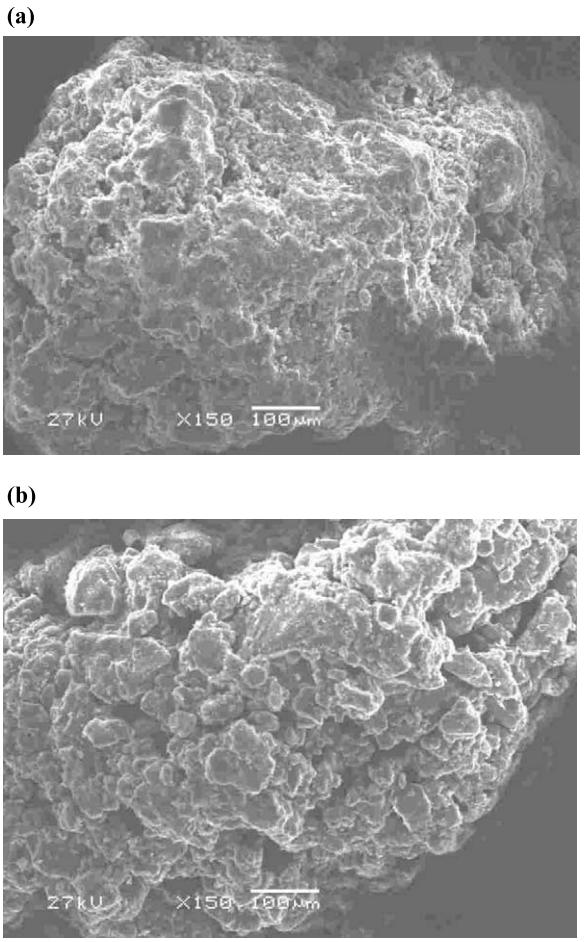

Fig. 6. Scanning electron micrographs of α-lactose monohydrate granules produced by extrusion at a reference condition (7.5% water concentration, 250 rpm screw speed and 5.6 kg h^{-1} total input rate). (a) Without PVP. (b) With PVP (2.5% w/w, wet).

Fig. 6a and b shows SEM pictures taken from dried granules ($F_{250-1000\ \mu m}$) produced by extrusion at the reference conditions. The surface of the granules produced without PVP was rather smooth and the individual particles could not be clearly identified (Fig. 6a). This is possibly due to the partial dissolution of α-lactose monohydrate particles as a result of the high shearing forces during extrusion. When examining the granules with 2.5% PVP, the original particles were still discernible (Fig. 6b). Similar observations were made for granules prepared using high shear granulation (Fig. 7a and b) with the exception that these granules appeared more porous. The porosity was measured for the granules produced by extrusion at reference conditions and ranged between 5.8 and 7.5%, independently of the PVP concentration. The porosity of granules produced using high shear granulation at 7.5% water and 500 rpm impeller speed was 49.7 and 40.4% for formulations with and without PVP, respectively, which was confirmed by the SEM observations. The difference in porosity can be explained by the different degree of densification of both techniques.

The influence of water and PVP concentration on the properties of granules prepared using twin screw extrusion was investigated. Optimizing the water concentration during extrusion was important for the process performance and to ensure an acceptable yield (50%) at the different PVP concentrations, but it had no important influence on the other granule properties. The compressibility never exceeded 15%, indicating a good flowability of the granules (Railker and Shwartz, 2000). The friability of the granules increased with increasing water concentration, but remained below 30%.

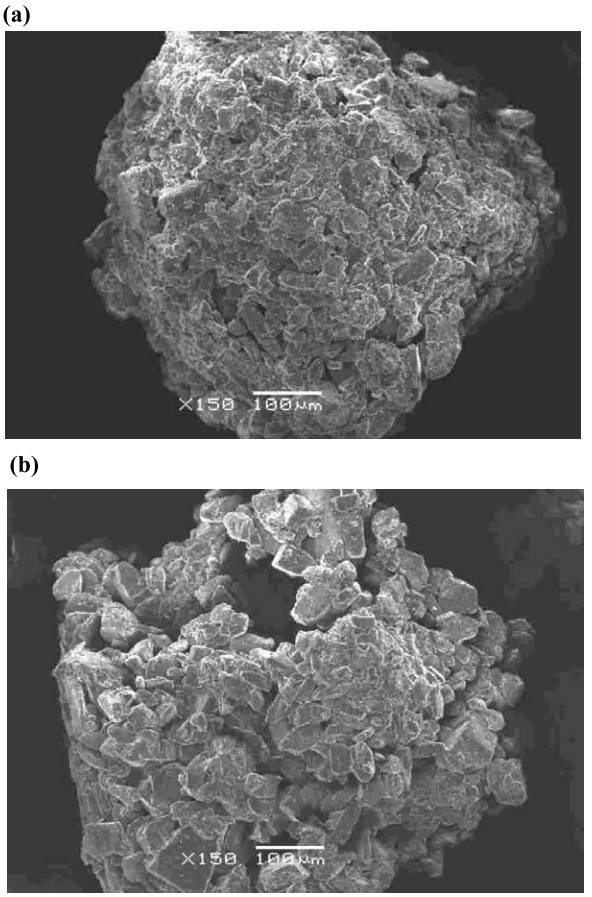

Fig. 7. Scanning electron micrographs of α-lactose monohydrate granules produced by high shear granulation at 10% water, 500 rpm impeller speed and 3000 rpm chopper speed. (a) Without PVP. (b) With PVP (2.5% w/w, wet).

The high yield and the low granule friability are probably due to the high densification of the wet mass during extrusion and the excellent mixing performance of the extruder, thereby ensuring a good distribution of the granulating liquid and an increase of contact area between the individual particles allowing more bonds to be formed. PVP addition did not significantly affect the granule properties prepared by extrusion at all concentrations tested. α-Lactose monohydrate granules without PVP produced by high shear showed a higher granule friability ($>60\%$), a lower yield ($<20\%$), a higher $F_{<250\ \mu m}$ ($>35\%$) and a higher compressibility ($<20\%$) than those prepared by extrusion (Fig. 5). The granules containing 2.5% PVP produced by high shear granulation at a water concentration of 10% showed similar properties (Fig. 5) as those prepared by extrusion at the respective optimum water concentration (5.5–6.5%).

The influence of the water concentration during extrusion and of PVP on the tablet properties is shown in Fig. 8a–c. Increasing the water concentration during extrusion tended to decrease the tablet friability and resulted in a significant, though not important, increase in tablet tensile strength. The addition of PVP (1.25%) decreased the tablet friability to less than 1% and significantly increased the tablet tensile strength to about ± 0.7 MPa and the disintegration time above 6 min. Increasing the PVP concentration to 5% resulted in a significant increase of tablet tensile strength and disintegration time. In view of the tablet tensile strength and friability, at least 1.25% PVP was required during granulation of α-lactose monohydrate using extrusion. However, it should be stressed that PVP addition was not required to achieve a high yield, whereas, at least 2.5% PVP was required for the high shear granulation of α-lactose monohydrate. Although without PVP, good tablet properties were obtained from granules prepared by high shear, the yield of this granulation technique for pure α-lactose monohydrate was too low.

Comparison of the properties of the tablets prepared from granules produced by high shear granulation (Fig. 9) with those obtained by extrusion (Fig. 8) revealed that tablets from granules prepared by high shear showed a significantly higher tensile strength and faster disintegration time for the formulation without as well as with PVP.

When comparing the granule and tablet properties obtained for different ways of PVP addition, no significant differences were observed except for the tablet disintegration time at a water concentration during extrusion of 5%. The average $t_{90\%}$ dissolution time of the tablets (with 2.5% PVP) containing hydrochlorothiazide was 25 ± 1 min and complied with the USP XXIII monograph requiring that not less than 60% of the drug is dissolved within 60 min.

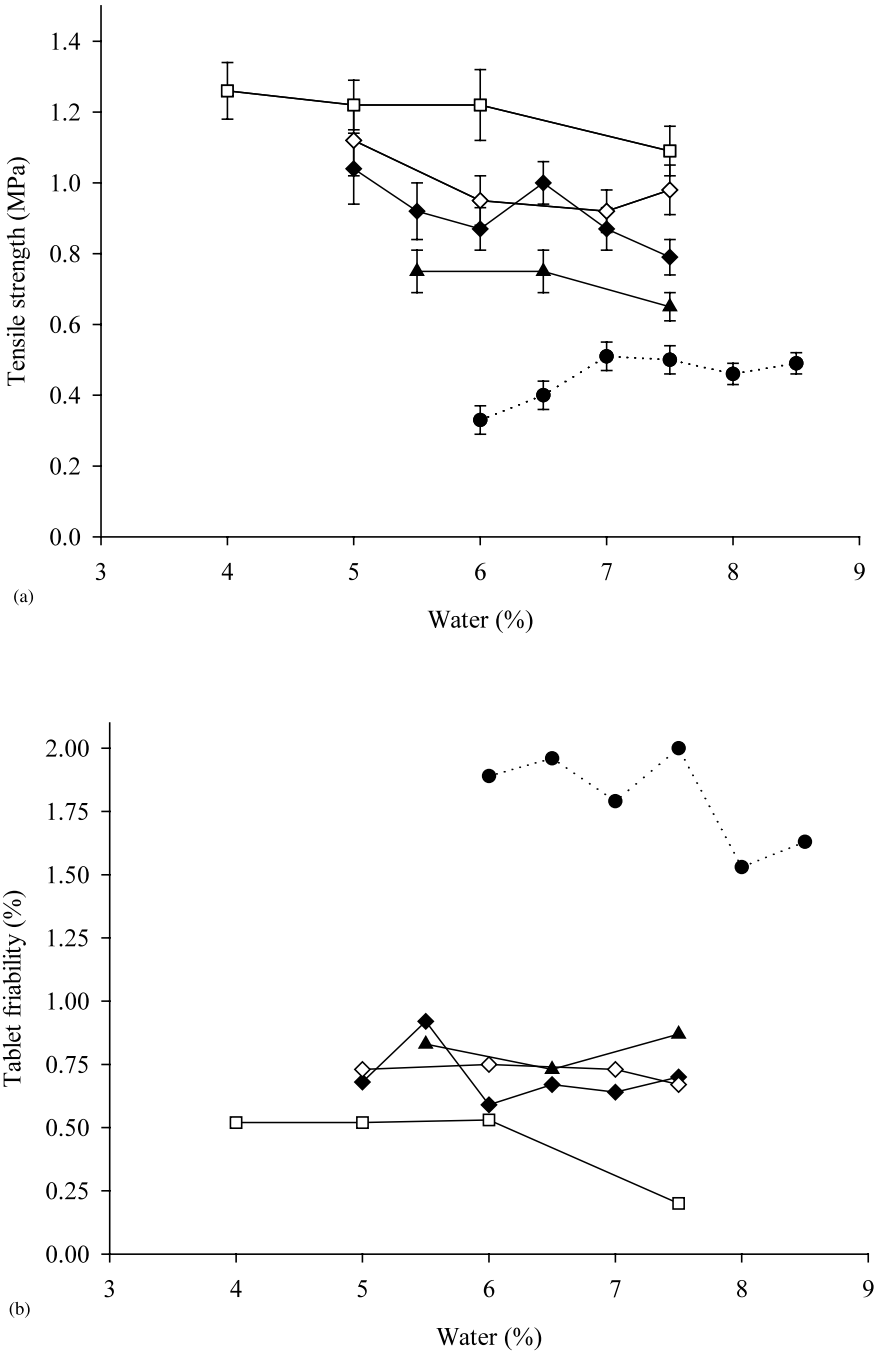

Fig. 8. Influence of water concentration during extrusion on the tablet properties of α-lactose monohydrate granules formulated without PVP (●) and with 1.25% PVP wet (▲), 2.5% PVP wet (◆), 2.5% PVP dry (◇) and 5% PVP dry (□) extruded at 250 rpm screw speed and 5.6 kg h^{-1} total input rate. (a) Tablet tensile strength; (b) tablet friability; and (c) disintegration time.

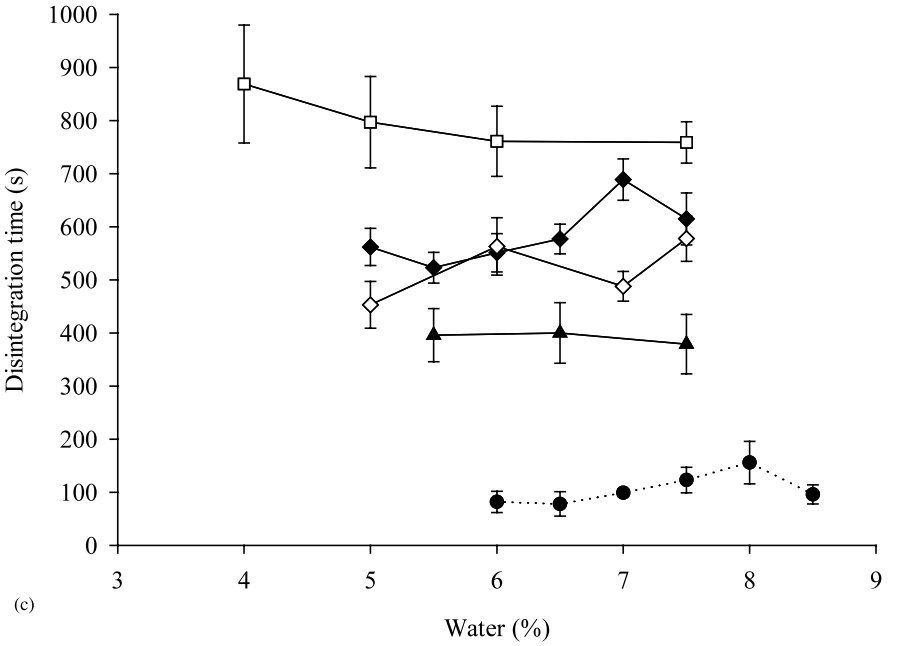

Fig. 8. (*Continued*)

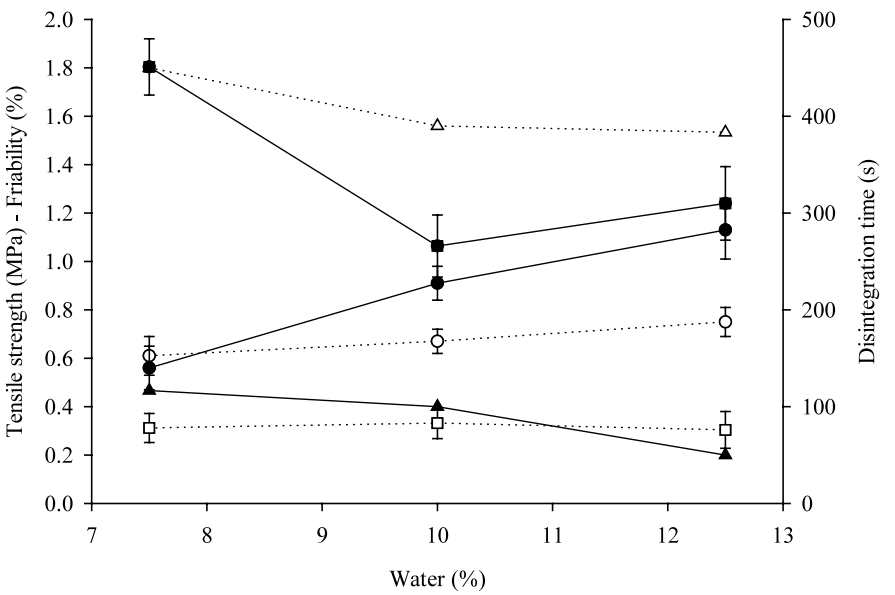

Fig. 9. Influence of water concentration during high shear granulation on the tablet properties prepared from α-lactose monohydrate granules formulated without PVP and with 2.5% PVP wet at 500 rpm impeller speed and 3000 rpm chopper speed. Tablet tensile strength (○) without PVP and (●) with PVP, friability (△) without PVP and (▲) with PVP and disintegration time (□) without PVP and (■) with PVP.

Variation of the screw speed and the total input rate clearly affected the process feasibility. Combining a low screw speed with a high total input rate led to increased friction, whereas a too low total input rate resulted in insufficient filling of the extruder barrel (Fig. 3b). Changing the screw speed from 200 to 450 rpm did not influence the granule or the tablet properties, with the exception of the granule friability, which significantly increased (but remained below 30%) with increasing screw speed. The total input rate did not significantly influence the granule and tablet properties. Thus optimizing the screw speed and the total input rate is required for the feasibility of the process, however, these parameters have no important influence on the granule and tablet properties.

4. Conclusion

It can be concluded that twin screw extrusion is a suitable alternative for the wet granulation of α-lactose monohydrate. Optimizing the process parameters and the water concentration are required to obtain an acceptable yield, but had no important effect on the granule or the tablet properties. Although good granule properties were obtained without PVP, the addition of PVP was required to improve tablet properties. In contrast to extrusion, high shear granulation allowed no granulation without PVP and required a higher water concentration for the granulation of formulations containing PVP. It can be concluded that the technique of extrusion granulation is more efficient as granulation technique than high shear granulation. Besides, it has the advantage of allowing semi-continuous granulation. Further experiments are ongoing in order to adapt the process so that the wet sizing step can be avoided.

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