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Research paper

Cold extrusion as a continuous single-step granulation and tabletting process

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Abstract

The potential of cold extrusion as a continuous granulation/tabletting technique was investigated. Extrudates (∅, 9 mm) were produced using twin-screw extrusion, cut manually into tablets (thickness, 4 mm) and dried at 25°C for 20 h. α-Lactose monohydrate (200 M) was used as an excipient, PVP (Kollidon® K30) and water as binders, and hydrochlorothiazide as the model drug. The influence of formulation (water content, PVP addition, drug incorporation) and process (total input rate and screw speed) parameters on the process (torque, die pressure, visual evaluation of tablets) and on the tablet properties (tensile strength, friability, disintegration time, porosity) was evaluated. Formulation, as well as process parameters, affected the process feasibility, but had only a minor effect on the tablet properties at conditions that allowed continuous tablet production. All α-lactose monohydrate tablets formulated without and with PVP and produced at optimum conditions showed tensile strengths above 0.7 and 1.5 MPa, friabilities below 1.0 and 0.9%, and disintegration times below 1 and 8 min, respectively. This technique allows single-step granulation/tabletting of pure α-lactose monohydrate, indicating that cold extrusion could be used as alternative tablet production technique for ingredients with poor compaction properties. As the tablets prepared by extrusion have a much higher porosity compared with conventional tablets, this technique could also be useful for tablet production of formulations with poor disintegrating properties.

Keywords: Extrusion; Continuous granulation and tabletting; Immediate release tablets; α-Lactose monohydrate; Process parameters; Twin-screw extrusion; Water content; Tablet properties; Binder

1. Introduction

Tablets can be compacted by direct compression or after a granulation step. Direct compression is always preferred, but is only possible for a limited number of substances due to problems such as poor powder flow properties, low tablet strength, capping and segregation. Granulation is designed to overcome these problems and usually results in better flowability and compactibility of the powder. In some cases, however, problems still exist during the large-scale production of tablets. There is also an increasing interest for continuous operation in the pharmaceutical industry. It is clear that a single-step continuous granulation/tabletting process could provide advantages, such as reduced investment and labour cost and easier automation of the process.

Several researchers have successfully used the hot-melt extrusion technique for the continuous production of, mainly sustained release, tablets [1–8], while the potential of cold extrusion as a continuous granulation technique has also been reported [9–13]. We recently investigated the granulation of α-lactose monohydrate using cold extrusion [14]. During these experiments, a remarkably high mechanical strength as well as a fast disintegration of extrudates, dried without wet sieving, was noticed. This indicated that a twin-screw extruder equipped with a proper die plate (e.g. having an aperture of 9 mm in diameter) could be suitable for the production of compact extrudates, which are consequently cut into tablets and dried. Hence, in this study, cold extrusion was examined as a single-step granulation/tabletting technique for the continuous production of tablets containing components with poor flow and compression properties.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate 200 M (DMV, Veghel, The Netherlands) was used as an excipient; water and polyvinylpyrrolidone (PVP Kollidon® K30, BASF, Ludwigsha-

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fen, Germany) were used as binders. Hydrochlorothiazide (Ludeco, Brussels, Belgium) was selected as a model drug for very poorly water soluble drugs.

2.2. Preparation of tablets

Extrusion was performed on a laboratory-scale, co-rotating twin-screw extruder (Model MP 19 TC 25, APV Baker, Newcastle-under-Lyme, UK), having a length-to-diameter ratio of 25/1 and equipped with stainless steel screws with a standard screw profile with two mixing sections. The axial mounted die plate has a cylindrical hole of 9 mm diameter. The α-lactose monohydrate powder and the binding liquid (pure water or aqueous PVP solution) were fed into the first zone of the extruder barrel. The powder was fed on top of the screws using a screw operated feeder, while the liquid was pumped into the barrel by means of a peristaltic pump (Watson Marlow Type 505L, Cornwall, UK). In cases where hydrochlorothiazide was present in the formulation, it was premixed with α-lactose monohydrate for 15 min in a planetary mixer (Kenwood, Hampshire, UK) at a mixing speed of 60 revs./min. All water fractions were calculated based on the wet extruded mass, whereas all PVP and drug concentrations were calculated based on dry tablet weight. The extruder was set at a constant temperature of 25°C. In order to ensure equilibration of the extruder at the test conditions, evaluation of the process feasibility and sampling were first started 10 min after the process was started.

Tablets (thickness, 4 mm) were manually cut using surgical blades immediately after extrusion and then oven-dried for 20 h at 25°C. After drying, tablets weighing between 245 and 265 mg were selected and stored in a desiccator at 60% RH for 24 h prior to evaluation.

The feasibility of continuous tabletting using cold extrusion was evaluated by varying the formulation and process parameters. First, the optimum water content was determined at a screw speed of 250 revs./min and a total input rate (= powder feeding rate + liquid feed rate) of 5.6 kg h^{-1}, i.e. the standard processing parameters determined during the continuous granulation of α-lactose monohydrate by means of extrusion [14]. Before assessing the influence of the process parameters, the reproducibility ($n = 6$) of the overall process was determined at the optimum water content, using pure water as a binding liquid as well as an aqueous PVP solution. Next, the influence of the process parameters (screw speed and total input rate) on the process and on the tablet quality was determined. Finally, the performance of this technique for the incorporation of drugs was investigated at optimum water content and process parameters.

α-Lactose monohydrate tablets (250 mg) were also prepared by direct compression (compression force, 10 kN) of the powder on an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat-faced double punch of 9 mm diameter. Prior to compression, the powder was blended for 1 min with 0.5% magnesium stearate (<90 μm; BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland).

2.3. Precision of powder and liquid feed rate

Prior to each experiment, the powder and liquid feed rates were verified by collecting and weighing ($n = 3$) the powder and the liquid discharged during 5 min.

2.4. Process evaluation

2.4.1. Power consumption and die pressure

Torque and die pressure were constantly monitored during each experiment. In order to avoid any damage to the extruder, the extrusion process was stopped if the torque reached 90% of its maximal value (i.e. 2.5 kW at a screw speed of 500 revs./min) or when a die pressure of 15 bar was recorded.

2.4.2. Evaluation of extrudates

The extrudates were visually inspected for any defects (discontinuous extrudate, shark-skinning or other deficiencies) and evaluated for their suitability to be cut into tablets (deformation due to cutting, smoothness of the cutting surfaces and the edges).

2.5. Tablet evaluation

2.5.1. Tablet porosity

The tablet skeletal volume was determined ($n = 10$) using He-pycnometry (Micromeritics, Norcross, GA) and the dimensions of the tablet were measured using a micrometer from which the bulk volume was calculated. The tablet porosity (ε) was determined ($n = 3$) by the following equation (Eq. (1)):

$$\varepsilon = (\text{bulk volume} - \text{skeletal volume})/\text{bulk volume} \times 100 \quad (1)$$

The pore size distribution was determined using mercury porosimetry (Autopore III, Micromeritics).

2.5.2. Tablet friability

The tablet friability was determined for ten tablets using a friabilator (Pharma-Test, Hainburg, Germany) at a speed of 25 revs./min for 4 min. The percentage weight loss was expressed as the tablet friability.

2.5.3. Tablet tensile strength

The diametral crushing force, the diameter and the thickness of tablets ($n = 6$) were determined by the diametral compression test (Pharma-Test). The tablet tensile strength (T) was calculated according to the following equation [15]: $T = 2F/\pi dt$, where F is the diametral crushing force; and d and t denote the tablet diameter and thickness, respectively.

2.5.4. Disintegration time

The disintegration time was determined ($n = 6$) using the

Table 1
Influence of the water content during extrusion on the process evaluation parameters for extrusion of α-lactose monohydrate formulated without PVP and with 2.5% (w/w) PVP at a screw speed of 250 revs./min and a total input rate of 5.6 kg h^{-1}

Formulation variables		Process evaluation parameters		
PVP (%; w/w[a])	Water (%; w/w[b])	Torque (%)	Die pressure (bar)	Remarks
0	9.5	–	–	Extrusion not possible, mass too dry
	10.5	29	3	
	11.5	24[c]	1[c]	
	12.5	27	2	
	13.5	20	0	Deformation of tablets during cutting
	14.5	17	0	Deformation of tablets during cutting
2.5	7.5	44	7	Extrudate very dry, difficult to cut
	8.5	28	7	Extrudate very dry, difficult to cut
	9.5	25[c]	3[c]	
	10.5	22	1	
	11.5	17	0	Deformation of tablets during cutting
	12.5	19	0	Deformation of tablets during cutting

[a] Based on dry tablet weight.
[b] Based on wet extruded mass.
[c] Average of six batches.

apparatus described in Eur. Ph. III (Pharma-Test). Tests were performed in distilled water at 37°C making use of disks.

2.5.5. Dissolution rate

Dissolution tests of hydrochlorothiazide tablets were performed in 900 ml HCl (0.1 N; 37 ± 0.5°C) using dissolution apparatus II (Vankel, Technology Group, Cary, NC) at a paddle speed of 100 revs./min (USP XXIV). 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, CT).

2.6. Statistical analysis

Before any analysis was performed, the data were tested for normal distribution with the Kolmogorov–Smirnov test and the homogeneity of variances was tested with Levene's test. If possible (at least five levels of the factor tested and multiple measurements at each point), significant correlations were determined using Pearson's correlation test ($P < 0.05$). For all significant correlations ($P < 0.05$), linear regression analysis was performed. When the coefficients (slope and intercept) obtained by linear regression were significant ($P < 0.05$), these were used to calculate the trend line.

When no correlation test could be performed, the influence of the studied parameter on the 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 the Scheffe test with $P < 0.05$ as a significance level. Friability results could not be analyzed as only one measurement was performed per factor level. For all statistical analyses, the computer program SPSS version 10.0 was used.

3. Results and discussion

3.1. Precision of powder and liquid feed rate

During determination of the precision of the powder feed rate, it was noted that at a constant screw speed, the powder feed rate decreased with decreasing powder level in the feeder. Therefore, the powder level in the hopper was always maintained between 85 and 100% of the total feeder capacity. Under these circumstances, reproducible (CV < 2%) powder feed rates were obtained at all feed rates used. For water, as well as for the PVP solutions, the variability of the liquid feed rate was below 1% at all pump speeds used.

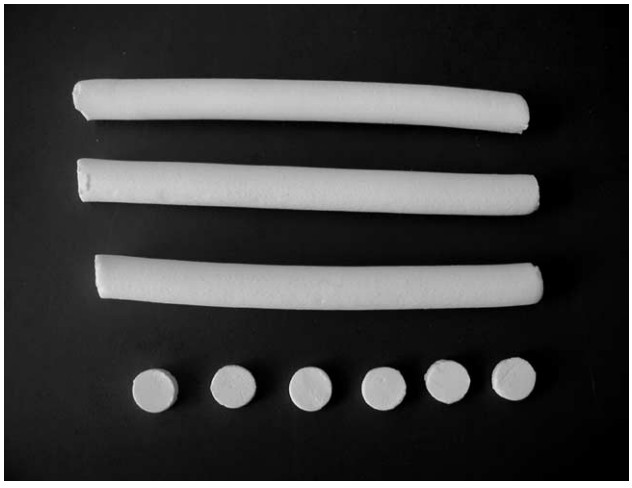

Fig. 1. Extrudates and tablets produced by cold extrusion of α-lactose monohydrate formulated without PVP at a screw speed of 250 revs./min, a total input rate of 5.6 kg h^{-1} and a water content during extrusion of 11.5% (w/w), respectively.

3.2. Determination of optimum water content

Table 1 shows the influence of the water content during extrusion on the process evaluation parameters. The water fraction of the wet mass had a dramatic influence on the extrusion process and on the cutting of the extrudates. When using standard process parameters, the production of α-lactose monohydrate tablets with an acceptable shape was feasible only at water contents of between 10.5 and 12.5% (w/w) and between 9.5 and 10.5% (w/w) for formulations without and with PVP, respectively. The lower water content required for continuous processing of formulations with PVP can be attributed to the lubricating effect of PVP. Within the respective optimum water content, the extrudates had a smooth surface, could be cut without causing any deformation and the resulting tablets exhibited smooth surfaces and edges (Fig. 1). Higher water contents resulted in poorly shaped tablets due to extensive deformation during cutting, while at lower water contents, continuous processing was impossible as, within 5 min, the torque and the die pressure exceeded their maximum set limit. Within the range of water content which allowed continuous extrusion,

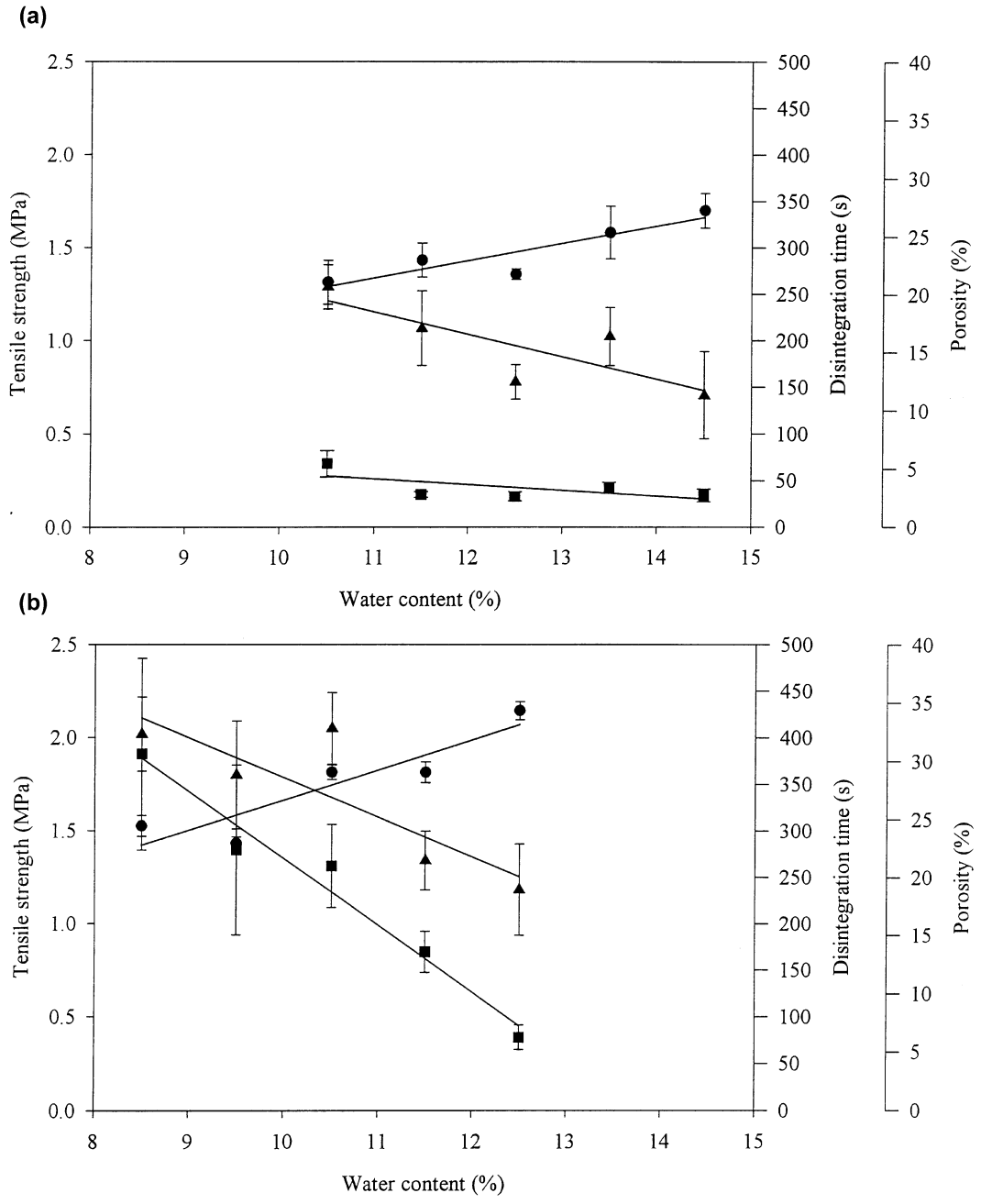

Fig. 2. Influence of the water content during extrusion on: (▲), the tensile strength; (●), the porosity; and (■), the disintegration time of α-lactose monohydrate tablets formulated without PVP (a) and with 2.5% (w/w) PVP (b) at a screw speed of 250 revs./min and a total input rate of 5.6 kg h^{-1}.

the torque varied between 20 and 30% of its maximal value and the die pressure did not exceed 10 bar.

The influence of water content during extrusion on the properties of α-lactose monohydrate tablets formulated without and with 2.5% (w/w) PVP is shown in Fig. 2a,b, respectively. The friability varied from 0.5 to 1.0% for tablets without PVP and from 0.6 to 0.8% for tablets with PVP. To evaluate the influence of water content on tablet properties, tablets produced at a water content above the optimum were also included despite their suboptimal shape. There was a significant positive correlation between the water content during extrusion and the porosity (without PVP, $r = 0.792$; with PVP, $r = 0.899$) and a significant negative correlation between the water content during extrusion and the tensile strength (without PVP, $r = -0.656$; with PVP, $r = -0.739$) and the disintegration time (without PVP, $r = -0.584$; with PVP, $r = -0.851$). ANOVA analysis revealed that at the lowest water content tested, these tablet properties were significantly different from those of tablets at the highest water content. It should, however, be noted that within the optimum range, these effects were limited and were only significant for formulations without PVP and not for formulations with PVP, where the optimum range (9.5–10.5%) is very small.

At all optimum water levels, tablets with an acceptable tensile strength (>0.5 MPa), friability (<1%) and disintegration time (<10 min) were obtained: tablets formulated without and with PVP have tensile strengths of above 0.75 and 1.85 MPa, friabilities below 1.0 and 0.8% and disintegration times below 1 and 5 min, respectively. Comparison of the properties of tablets produced at the same water content, but formulated without and with 2.5 % (w/w) PVP, revealed that the addition of PVP significantly increased the tensile strength, the porosity and the disintegration time. It can be concluded that optimization of the water content during extrusion is required for each formulation in order to allow continuous extrusion, but that within the possible working range, changes in the water content during extrusion had only a limited influence on the tablet properties.

3.3. Process reproducibility

To evaluate the reproducibility of the extrusion process of α-lactose monohydrate, the water content was maintained at 11.5 and 9.5% (w/w) for formulations without and with PVP, respectively. Table 2 shows the between-day variation ($n = 6$) of the process evaluation parameters and of the tablet properties. All experiments were performed at a screw speed of 250 revs./min and a total input rate of 5.6 kg h^{-1}. Variation of the torque measurements was below 10%, whereas the die pressure varied from 0 to 5 bar. In view of the small changes caused by varying formulation (Table 1) and process parameters (Table 3), it was clear that these parameters lack the necessary sensitivity to be used as indicators to optimize the process and that visual evaluation

Table 2
Between-day[a] variation of the properties of α-lactose monohydrate tablets manufactured by cold extrusion at 250 revs./min and a total input of 5.6 kg h^{-1} formulated without PVP and with 2.5% PVP (w/w) at a water content during extrusion of 11.5 and 9.5% (w/w), respectively

	Tablet properties			Process evaluation parameters	
	Tensile strength (MPa)	Friability (%)	Disintegration time (s)	Torque (%)	Die pressure (bar)
α-Lactose monohydrate (water content during extrusion 11.5%[b])					
	1.02	0.87	35	23	0
	1.23	0.62	37	27	1
	0.83	0.79	32	23	2
	0.91	0.66	33	23	1
	1.01	0.74	38	23	0
	1.32	0.78	41	24	0
Average	1.05	0.74	36	24	1
SD	0.19	0.09	3	2	1
CV%	18	12	9	7	114
α-Lactose monohydrate with 2.5%[c] PVP (water content during extrusion 9.5%[b])					
	1.68	0.50	294	25	2
	1.78	0.70	160	27	5
	2.16	0.61	432	25	5
	2.04	0.61	275	26	2
	1.85	0.55	295	20	0
	1.58	0.82	218	25	1
Average	1.85	0.63	279	25	3
SD	0.22	0.11	91	2	2
CV%	12	18	33	10	83

[a] $n = 6$.
[b] Based on wet extruded mass (w/w).
[c] Based on dry weight (w/w).

Table 3
Influence of the screw speed and the total input rate on the process evaluation parameters for extrusion of α-lactose monohydrate formulated without PVP and with 2.5% (w/w) PVP at a water content during extrusion of 11.5 and 9.5% (w/w), respectively

Formulation variables		Process parameters		Process evaluation parameters		
PVP (%; w/w[a])	Water (%, w/w[b])	Total input rate (kg h^{-1})	Screw speed (revs./min)	Torque (%)	Die pressure (bar)	Remarks
0	11.5	5.6	200	27	0	
			250	24[c]	1[c]	
			300	24	0	
			350	16	0	
			400	> 90	> 15	Die blocking
			450	> 90	> 15	Die blocking
2.5	9.5	5.6	200	28	3	
			250	25[c]	3[c]	
			300	24	1	
			350	25–27	1–6	Discontinuous extrudate flow
			400	23–31	1–3	Discontinuous extrudate flow
			450	22–30	1–4	Discontinuous extrudate flow
0	11.5	3.5	250	> 90	> 15	Die blocking
		4.5		> 90	> 15	Die blocking
		5.6		24[c]	1[c]	
		6.5		26	3	
		7.5		–	–	Powder accumulation at inlet
2.5	9.5	3.5	250	21–25	0–5	Discontinuous extrudate flow
		4.5		22–25	0–7	Discontinuous extrudate flow
		5.6		25[c]	3[c]	
		6.5		26	2	
		7.5		–	–	Powder accumulation at inlet

[a] Based on dry tablet weight (w/w).
[b] Based on wet extruded mass (w/w).
[c] Average of six batches.

is required. However, these parameters are worth recording as they allow early detection of problems (die blocking, excessive friction, etc.), enabling the process to be stopped before any damage to the extruder occurs.

For tablets formulated without PVP, the tablet tensile strength was above 0.8 MPa, the friability below 0.9% and the disintegration time below 1 min, while tablets formulated with 2.5% (w/w) PVP had a tablet tensile strength above 1.5 MPa, a friability below 0.85% and a disintegration time below 8 min. From these results, it was clear that for cold extrusion of α-lactose monohydrate formulations without PVP, as well as with PVP, resulted in good quality tablets. This was in contrast to the manufacturing of α-lactose monohydrate tablets by direct compression or compression of granules, where PVP addition or very high compression forces are required to obtain an acceptable tablet tensile strength and friability [14,16–21]. These data indicate that cold extrusion could be useful as a single-step granulation and tabletting technique for materials that normally require granulation.

3.4. Influence of process parameters

In Table 3, the process evaluation parameters obtained at different screw speeds and total input rates are presented. If for pure α-lactose monohydrate, the screw speed was progressively increased above 350 revs./min at a constant input rate of 5.6 kg h^{-1}, blocking of the die occurred. A similar effect was observed when the total input rate was decreased to 4.5 kg h^{-1} or below at 250 revs./min. In both cases, the extruder load was decreased, leading to insufficient filling of the screws and a pressure too low to push the mass through the die. This induced accumulation and drying of α-lactose monohydrate at the die, leading to partial die obstruction. On the contrary, decreasing the extruder load during extrusion of α-lactose monohydrate with PVP did not result in die blockage, but a discontinuous flow of the extrudates was noticed. This indicates again the lubricating effect of PVP during cold extrusion of α-lactose monohydrate. This was also reflected in the large within-run variation of the torque and die pressure. Increasing the total input rate to 7.5 kg h^{-1} at a constant screw speed of 250 revs./min resulted in screw overloading. In order to obtain a higher throughput, the total input rate as well as the screw speed have to be increased. These findings indicated that in this extrusion process, the full screw transport capacity must be used and the feed rate should be optimized in order to prevent die blocking and to guarantee a continuous discharge of the extrudate.

The total input rate did not affect tablet properties, even if it was decreased from 6.5 to 3.5 kg h^{-1} at a constant screw speed of 250 revs./min. It is also important to note that tablet properties remained the same even if the extrudate output was discontinuous. Fig. 3 shows the influence of the screw

speed on the properties of α-lactose monohydrate tablets formulated: (a), without PVP; and (b), with PVP. The friability varied from 0.65 to 0.99% for tablets without PVP and from 0.5 to 1.07% with PVP, but was always below 1% at conditions that allowed continuous tablet production. The screw speed also had no effect on the properties of tablets formulated without PVP, while there was a significant positive correlation between screw speed and porosity ($r = 0.843$) and a significant negative correlation between screw speed and tensile strength ($r = -0.632$) and disintegration time ($r = -0.844$) for tablets formulated with PVP. ANOVA analysis revealed that varying the screw speed only resulted in significant differences for disintegration time and porosity. This difference between the effect of screw speed on the disintegration time of tablets formulated without and with 2.5% (w/w) PVP could be due to the higher viscosity of the liquid phase penetrated into the pores in the presence of PVP. This increase in viscosity will dramatically affect the penetration rate of the liquid into the tablet. In this case, disintegration is probably mainly determined by the amount of liquid that can penetrate into the tablet, and is thereby strongly affected by changes in porosity. For tablets without

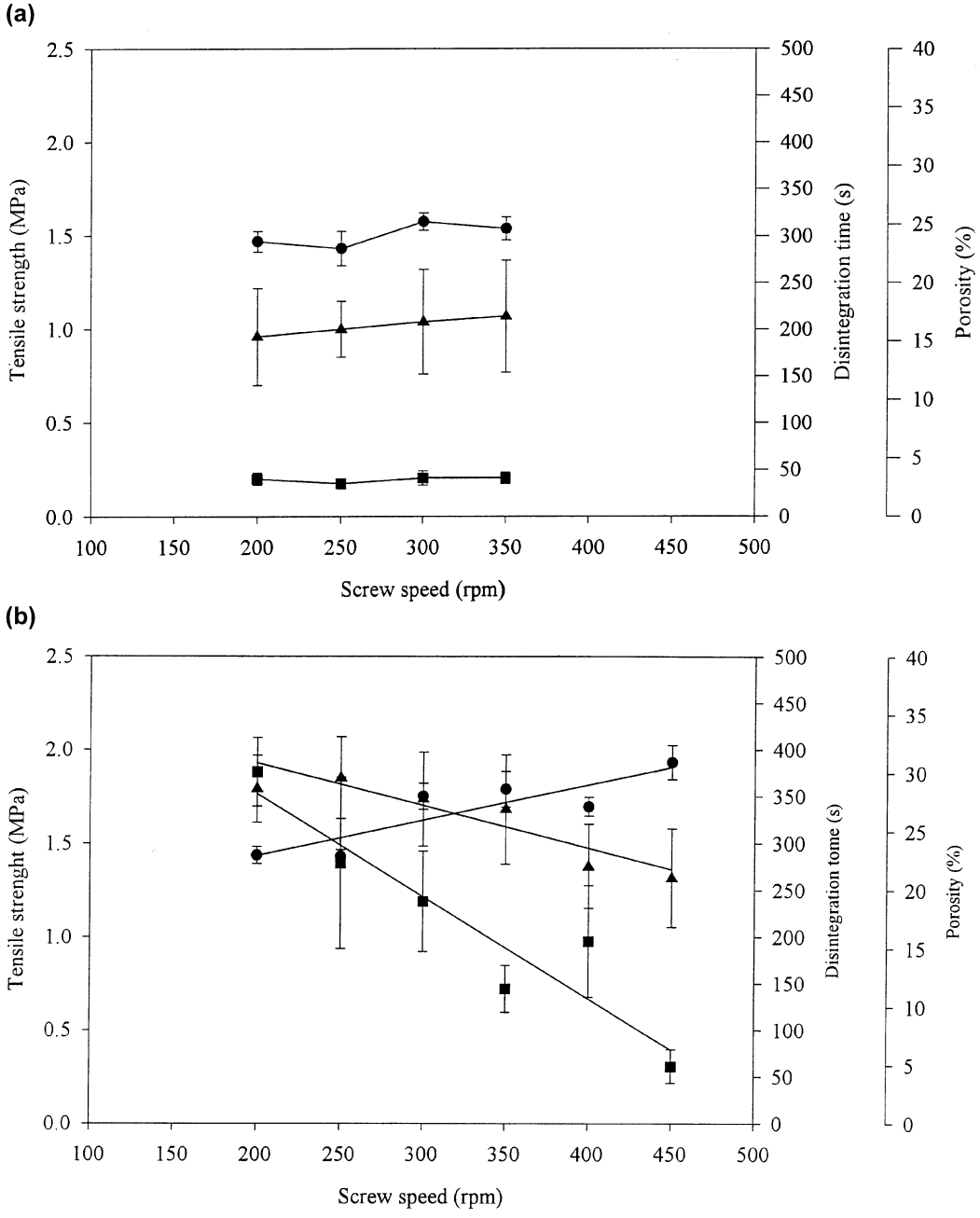

Fig. 3. Influence of the screw speed on: (▲), the tensile strength; (●), the porosity; and (■), the disintegration time of α-lactose monohydrate tablets formulated without PVP (a) and with 2.5% (w/w) PVP (b) at water contents during extrusion of 9.5 and 11.5% (w/w), respectively and a total input rate of 5.6 kg h^{-1}.

PVP, the disintegration is probably mainly determined by the dissolution rate of α-lactose monohydrate. As α-lactose monohydrate is freely soluble in water, the disintegration is not affected by changes in porosity.

From these experiments, it can be concluded that the screw speed as well as the total input rate should be optimized to allow continuous processing. Varying these parameters within the optimum working range did not affect the tablet quality, except for the screw speed, which influenced the disintegration time of tablets formulated with 2.5% (w/w) PVP.

3.5. Cold extrusion for the incorporation of drugs

Incorporation of 10% hydrochlorothiazide in α-lactose monohydrate tablets formulated without and with 2.5% (w/w) PVP had no effect, either on the process feasibility or the tablet properties. All tablets containing hydrochlorothiazide formulated without and with 2.5% (w/w) PVP had a tablet tensile strength above 1.1 and 1.7 MPa, a friability below 0.85 and 0.8% and a disintegration time below 1 and 5 min, respectively. Content uniformity measurements revealed that each tablet contained between 95 and 105% of the theoretical concentration. All tablets containing hydrochlorothiazide complied with the USP XXIII dissolution specifications (60% dissolved within 30 min): 73 and 71% hydrochlorothiazide being released after 10 min from tablets without and with PVP, respectively.

3.6. Comparison of α-lactose monohydrate tablets prepared by direct compression and by cold extrusion

The properties of α-lactose monohydrate tablets prepared by direct compression and by cold extrusion are shown in

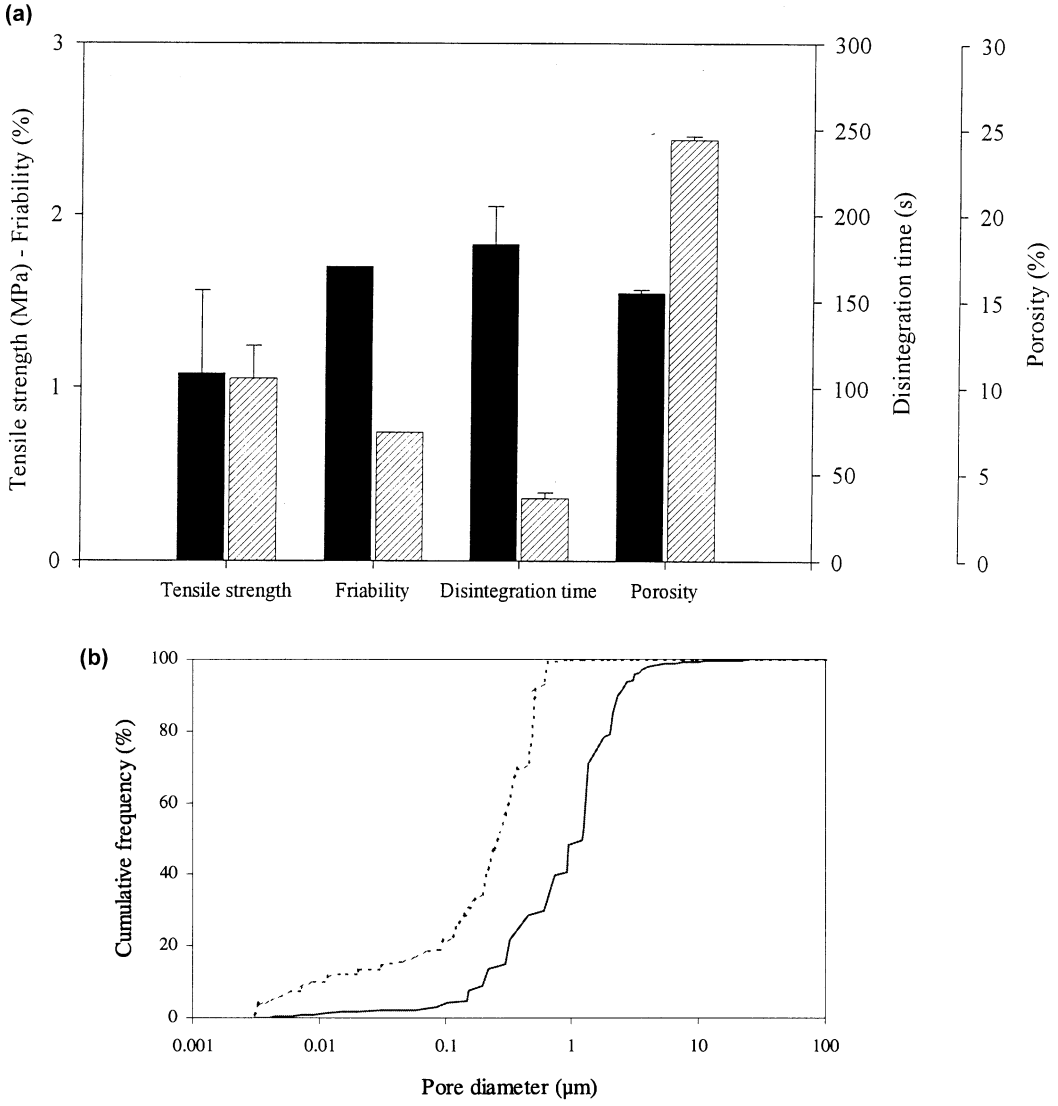

Fig. 4. Tensile strength, porosity, friability and disintegration time (a) and pore size distribution (b) of α-lactose monohydrate tablets prepared by: (■, - - -), direct compression (9 mm diameter, 250 mg, 10 kN); and (▨, —), cold extrusion (water content during extrusion 11.5% (w/w), screw speed 250 revs./min and total input rate 5.6 kg h^{-1}).

Fig. 4. Tablets prepared by extrusion have a significantly higher porosity and have larger pores than those prepared by compression. This difference could explain the significantly faster disintegration of tablets prepared by extrusion. However, the tensile strength of tablets prepared by extrusion is not significantly different to that of tablets prepared by direct compression. These differences in tablet properties could be explained by different bonding mechanisms involved in the different tablet manufacturing techniques used. During cold extrusion, only limited compression of the material occurs, while the dissolved α-lactose monohydrate fraction will crystallize on drying, forming solid bridges. During mechanical compression of α-lactose monohydrate, the applied forces are much higher and will cause α-lactose monohydrate to fragment and to bind mainly through intermolecular bonds (hydrogen bonds and Van der Waals interactions). However, these intermolecular bonds are much weaker (1–10 kcal/mol) than solid bridges (50–200 kcal/mol)

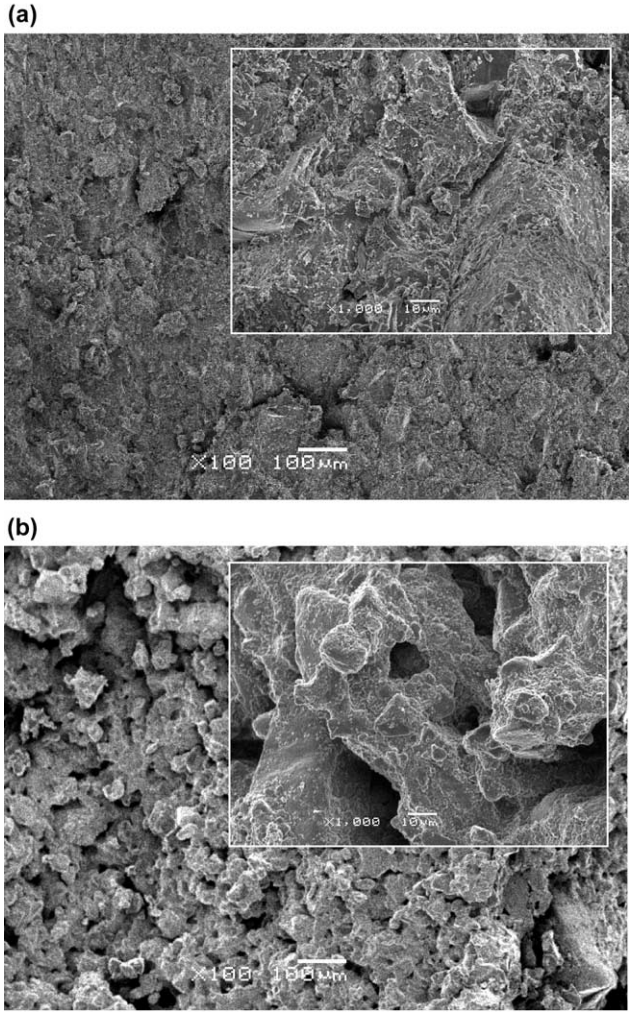

Fig. 5. SEM pictures of α-lactose monohydrate tablets prepared: (a), by direct compression (9 mm diameter, 250 mg, 10 kN); and (b), by cold extrusion (water content during extrusion 11.5% (w/w), screw speed 250 revs./min and total input rate 5.6 kg h^{-1}).

[22]. The similar tensile strength of tablets prepared by cold extrusion and by direct compression indicated that the intermolecular bonds formed during compression are more numerous compared with the solid bridges formed during cold extrusion. This is confirmed by the porosity data (Fig. 4) and by SEM pictures (Fig. 5) which clearly show that tablets prepared by extrusion have much larger pores than conventional tablets prepared by compression. The strength of solid bridges is mainly determined by the amount of solids deposited in the solid bridges and by the rate of crystallization [23]. Both factors are more likely to be affected by formulation variables, such as water content during extrusion and PVP addition, than by process parameters. This could explain the fact that tensile strength is only affected by changes in water content during extrusion and PVP addition, but not by varying the process parameters. These data clearly show that cold extrusion results in tablets with a similar tensile strength, and a higher porosity and lower disintegration time compared with conventional tablets prepared by direct compression. Similar phenomena, i.e. a higher porosity and faster disintegration time for the same tensile strength as tablets prepared by compression, were seen by Bi et al. [24] after wet compression of α-lactose monohydrate granules. However, to obtain tablets with an acceptable tensile strength, a compression force of above 500 kN, which is much higher than the compression force routinely used in tablet production, was required

4. Conclusions

From this study, it clear that cold extrusion allows single-step continuous tabletting of pure α-lactose monohydrate, in contrast to conventional tabletting which requires a high compression force or PVP addition. Optimization of the formulation and process parameters is a prerequisite for the feasibility of the process, but these parameters had only a minor influence on the tablet properties under conditions which allow continuous tablet production. The high porosity of tablets prepared by cold extrusion indicates that this technique might also be suitable for tablet production of formulations with poor disintegration properties.

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