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European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 77–82
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Single-step granulation/tabletting of different grades of lactose: a comparison with high shear granulation and compression

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Received 28 August 2003; accepted in revised form 3 March 2004

Available online 13 April 2004

Abstract

The influence of the particle size, particle morphology and crystallinity of lactose on the extrusion properties and on the quality of tablets were investigated using single-step granulation/tabletting as a tabletting technique. Results showed that particle size and type of lactose (α-lactose monohydrate, anhydrous β-lactose and spray dried lactose) affected the powder feeding, the process performance as well as the process capacity. Different grades of lactose yielded tablets with similar tensile strength, but significantly different disintegration time. Single-step granulation/tabletting always yielded tablets with a significantly higher tensile strength and similar or significantly lower disintegration time compared to high shear granulation and compression. The tensile strength of α-lactose monohydrate tablets (without and with PVP) did not change during one year of storage at 60% RH-25 °C and at 75% RH-40 °C, whereas a significant increase in disintegration time was observed. It can be concluded that although the lactose grade affected the performance and the optimal parameters of single-step granulation/tabletting, all lactose grades can be efficiently processed using this technique.
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Keywords: Single-step granulation/tabletting; Lactose; Particle size; Size morphology; High shear granulation and tabletting; Stability

1. Introduction

Recently, a novel tabletting method, called single-step granulation/tabletting, was developed and described by Keleb et al. [1]. This technique not only allowed continuous production, but also yielded stronger and faster disintegrating tablets than conventional granulation/tabletting. Further investigation of α-lactose monohydrate tablets produced by this technique revealed that tablet formation by single-step granulation/tabletting is mainly due to formation of solid bridges between particles without major particle deformation or fracture [1,2]. Therefore, the particle properties may have an influence on the tablet formation and tablet properties.

Lactose is the most widely used excipient in tablet formulation and available in different grades. Lactose exists in two isomeric forms and can be either crystalline or amorphous. These two polymorphic types of lactose possess different properties such as solubility, density, melting point and hardness. In addition, the different types of lactose are available in different particle size. It is well known that the different lactose grades have a different granulation and compression properties [3]. The first aim of this study was to investigate the influence of the physical properties of lactose on the single-step-granulation/tabletting process and on the properties of tablets obtained using this process and to compare the quality of those tablets with tablets produced by compression after high shear granulation. In addition, the stability of α-lactose monohydrate 200 M tablets prepared by single-step granulation/tabletting was evaluated.

2. Materials and methods

2.1. Materials

The different grades of lactose used were: crystalline α-lactose monohydrate (Pharmatose® 450 M, Pharmatose® 200M, Pharmatose® 100M, Pharmatose® 90M), anhydrous β-lactose (Pharmatose® DCL 21) and spray dried lactose (Pharmatose® DCL 11), all obtained from DMV

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doi:10.1016/j.ejpb.2004.03.007

Table 1
The physical properties of different grades of lactose

Grade	Crystallinity[a] (%)	Particle size[b] (μm)	Morphology	Bulk density (g/cm^3)	Solubility
α-Lactose monohydrate 90 M	100	135	Non-granular	0.76	1 in 5
α-Lactose monohydrate 100 M	100	130	Non-granular	0.75	1 in 5
α-Lactose monohydrate 200 M	100	40	Non-granular	0.55	1 in 5
α-Lactose monohydrate 450 M	100	20	Non-granular	0.47	1 in 5
Anhydrous β-lactose	100	150	Granular	0.67	1 in 2.2
Spray dried lactose	80–85	110	Granular	0.61	Unknown

[a] Crystalline fraction.
[b] Mean particle size determined by sieving (certificate of analysis, DMV).

(Veghel, The Netherlands). The physical properties of the different grades of lactose used are listed in Table 1. Polyvinyl-pyrrolidone (PVP, Kollidon® K30) was received from BASF (Ludwigshafen, Germany).

2.2. Methods

2.2.1. Single-step granulation/tabletting

Single-step granulation/tabletting 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, equipped with a standard screw profile and a circular 9 mm die attached to the extruder outlet. Processing parameters were set at 25 °C barrel temperature, 250 rpm screw speed, 5.6 kg h^{-1} total input rate and 11.5 and 9.5% water concentration for formulations without and with 2.5% PVP, respectively. These parameters are the optimal processing parameters for α-lactose monohydrate 200 M [1]. Each formulation was processed at these reference conditions. If the process blocked (for formulations without PVP) or discontinuous extrudate flow (for formulations containing PVP) was observed, further process optimisation was performed.

The granulation liquid (pure water or an aqueous PVP solution) was pumped into the extruder barrel using a peristaltic pump (Watson Marlow, Cornwall, UK).

All water concentrations mentioned are based on the wet extruded mass, while the PVP concentration is based on dry weight.

Immediately after extrusion, tablets (thickness: 4 mm) were manually cut using surgical blades [1]. The tablets were oven-dried at 25 °C for 20 h.

2.2.2. High shear granulation and tabletting

Formulations successfully processed by single-step granulation/tabletting were also processed by high shear granulation. The high shear granulation process was performed in a Gral 10 (Machines Collette, Wommelgem, Belgium) (capacity of high shear mixer: 8 l) at 500 rpm impeller speed, 3000 rpm chopper speed, a total load of 0.16 kg l^{-1} and 10% water concentration. These parameters are the optimal granulation parameters of α-lactose monohydrate 200 M [4,5]. After a 2 min mixing period of the powder, the required amount of granulation liquid (pure water or an aqueous 2.5% 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. All water concentrations mentioned are based on the wet extruded mass, while PVP concentration is based on dry weight.

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 (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. Similarly, tablets were prepared (without magnesium stearate) with die lubrication using magnesium stearate solution (1%, w/v) in ethanol.

2.2.3. Process characterization

Single-step granulation/tabletting was characterised by monitoring process parameters such as die pressure, power consumption and barrel temperature. These parameters give a clear indication on the processing performance. If the power consumption exceeded 80% of its maximum or the die pressure was above 5 bar the process was stopped in order to avoid machine damage. The high shear granulation process was evaluated for its ability to produce granules and hence tablets.

2.2.4. Tablet evaluation

Immediately after production, tablets were stored at 60% RH and 25 °C for 24 h before evaluation.

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

2.2.4.2. Tablet tensile strength. The hardness, thickness and diameter of the tablets ($n = 6$) was determined (Pharma Test, Hainburg, Germany). The tablet tensile strength T was calculated using the equation described by Fell and Newton [6]

$$T = 2F/(\pi dt)$$

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

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

2.2.4.4. Tablet porosity. The tablet porosity ε was determined ($n = 3$) using He-pycnometry (Micromeritics, Norcross, GA, US) by the following equation = (bulk volume − skeletal volume)/ bulk volume × 100.

2.2.5. Influence of storage on tablet properties

α-Lactose monohydrate tablets without and with 2.5% PVP prepared by single-step granulation/tabletting, were stored at 60% RH-25 °C and 75% RH-40 °C for one year. The tablets were evaluated for tensile strength, friability and disintegration time after 1, 90, 180 and 360 days.

2.3. Statistical analysis

The influence of lactose grades, production technique and storage on tablet tensile strength and disintegration time was determined using one-way ANOVA. To further compare of the influence of those factors on the tablet properties a multiple comparison among pairs of means of tensile strength and disintegration time was performed using Scheffé test with $P < 0.05$ as a significance level. The data were first tested for normality with a Kolmogorov–Smirnov test and for homogeneity of the variances with a Levene's test. Statistical analysis was performed using the computer program SPSS version 11.0.

3. Results and discussion

The influence of lactose particle size on the feasibility of single-step granulation/tabletting and on the properties of the tablets was investigated by comparing α-lactose monohydrate 450, 200, 100 and 90 M. The influence of lactose morphology and crystallinity was investigated by comparing anhydrous β-lactose, spray dried lactose and α-lactose monohydrate 90 M, which have a similar particle size but different particle morphology and crystallinity.

3.1. Influence of the particle properties on single-step granulation/tabletting process

3.1.1. Influence on powder feeding

Although, α-lactose monohydrate 200 M was easily fed from the feed hopper towards the extrusion barrel using a double screw feeder, the other lactose grades exhibited problems during feeding. α-Lactose monohydrate 100 and 90 M induced too much friction resulting in a gradual decrease in feeding rate and difficulties in the screw rotation or even blocking of the screw movement. α-Lactose monohydrate 450 M tended to stick at the hopper surface during feeding, mainly due to the cohesiveness of the powder leading to feeding inconsistencies. Powder feeding of anhydrous β-lactose exhibited similar problems as α-lactose monohydrate 90 M. However, spray dried lactose, which has a similar particle size but different shape (round particles) was reproducibly fed into the extruder barrel. These results indicated that not only particle size but also particle morphology affected feeding by the double screw feeder. These observations clearly indicated the need of the using of a suitable feeding system.

3.1.2. Influence on the total input rate

To perform single-step granulation/tabletting adequate pressure at the die block is required to push the wet plastic mass through the die. For formulations without PVP sufficient pressure is required to avoid die blocking (probably due to drying of the extrudates in the die). For formulations with PVP a sufficient pressure is required to ensure good shape and continuous flow of the extrudates. The required pressure is only obtained at a certain degree of screw filling, which depends on the material properties. For instance, total input rate of 5.6 kg h^{-1} used previously for α-lactose monohydrate 200 M [1] was being too low for α-lactose monohydrate 100 and 90 M, which required a total input rate of at least 6.5 kg/h. On the other hand for α-lactose monohydrate 450 M the process was only possible a total input rate of 4.5 kg h^{-1}. Anhydrous β-lactose and spray dried lactose had a lower optimal total input rate (5.6 kg h^{-1}) when compared with α-lactose monohydrate 90 M. This indicated that particle size and particle morphology of lactose affected the total input rate and thus the capacity of the process.

3.1.3. Influence on the optimal water concentration

Water concentration during extrusion has a great influence on the extrudability [4,7]. At concentrations above the optimum level the mass became oversaturated and the resulting extrudates were difficult to manipulate, while concentrations just below the optimum yielded dry extrudates, which were difficult to cut. A further reduction of the water concentration blocked the process due to the high viscosity of the wet mass.

For formulations without PVP, the extrudability during single-step granulation/tabletting was highly influenced by the size of lactose particles as shown in Table 2. Without PVP, it was only possible to process α-lactose monohydrate 200 M at the reference screw speed. Other grades of lactose were difficult to process even at a higher water concentration due to improper viscosity and elasticity. Possibly the residence time at the reference screw speed is to short to produce a mixture with suitable properties to be extruded.

Addition of 2.5% PVP allowed single-step granulation/tabletting of all lactose grades studied. Comparison of the optimal water concentration during the process revealed that

Table 2
Process evaluation parameters obtained during single-step granulation/tabletting of different grades of lactose

Process parameters			Process evaluation parameters		Remarks
Input (kg/h)	Water (%)	PVP (%)	Temperature (°C)	Power consumption (%)	
α-Lactose monohydrate 90 M					
5.6	11.5	0			Process blocked due to die blocking
6.5	11.5	0			Process blocked due to die blocking
6.5	13.5	0			Wet extrudates
5.6	9.5	2.5			Discontinuous extrudates flow
6.5	9.5	2.5	40	51	
α-Lactose monohydrate 100 M					
5.6	11.5	0			Process blocked due to die blocking
6.5	11.5	0			Process blocked due to die blocking
6.5	13.5	0			Process blocked due to die blocking
5.6	9.5	2.5			Discontinuous extrudates flow
6.5	9.5	2.5	40	23	
α-Lactose monohydrate 200 M					
5.6	11.5	0	33	23	
5.6	9.5	2.5	36	25	
α-Lactose monohydrate 450 M					
5.6	11.5	0			Process blocked due to die blocking
4.5	11.5	0			Process blocked due to die blocking
4.5	15.5	0			Wet extrudates
5.6	9.5	2.5			Powder accumulated at inlet
4.5	9.5	2.5			Dry extrudates
4.5	10.5	2.5	45	27	
Anhydrous β-lactose					
5.6	11.5	0			Process blocked due to die blocking
5.6	15.5	0			Process blocked due to die blocking
5.6	20.0	0			Wet extrudates
5.6	9.5	2.5			Process stopped due to hard screw movement
5.6	10.5	2.5	36	31	
Spray dried lactose					
5.6	11.5	0			Process blocked due to die blocking
5.6	13.5	0			Process blocked due to die blocking
5.6	9.5	2.5	36	39	

this was affected by the particle size. Decreasing lactose particle size resulted in an increasing the water concentration required for single-step granulation/tabletting.

3.2. Influence of particle properties on the tablet properties

Without PVP, single-step granulation/tabletting was only feasible for α-lactose monohydrate 200 M. These tablets exhibited a tensile strength of 1.0 MPa, a friability of 0.74% and a disintegration time of 36 s. Compared to single step granulatio/tabletting α-lactose monohydrate 200 M tablets without PVP produced by compression after high shear granulation exhibited a significantly lower tensile strength (0.67 and 0.71 MPa for tablets produced with 0.5% magnesium stearate and with die lubrication, respectively) and a higher friability (1.67 and 1.74%, respectively). However, a significantly higher disintegration time (83 s) was only obtained for tablets produced with 0.5% magnesium stearate.

Fig. 1a shows the tensile strength of tablets with 2.5% PVP obtained by single-step-granulation/tabletting and by compression (after blending with magnesium stearate and after die lubrication) after high shear granulation. For tablets prepared by single step granulation/tabletting lactose particle size and particle morphology did not significantly affected tensile strength and it was always higher than 1 MPa. Comparing the lactose tablets with 2.5% PVP produced by both techniques revealed that single-step granulation/tabletting resulted in a significantly higher tensile strength for all formulations.

The friability was below 1% for all tablets containing PVP, except for α-lactose monohydrate 100 M tablets prepared by compression after high shear granulation.

Fig. 1b shows the disintegration time of tablets with 2.5% PVP obtained by single step-granulation/tabletting and by compression after high shear granulation. All tablets produced by single-step granulation/tabletting had a disintegration time below 400 s. Changing the particle size

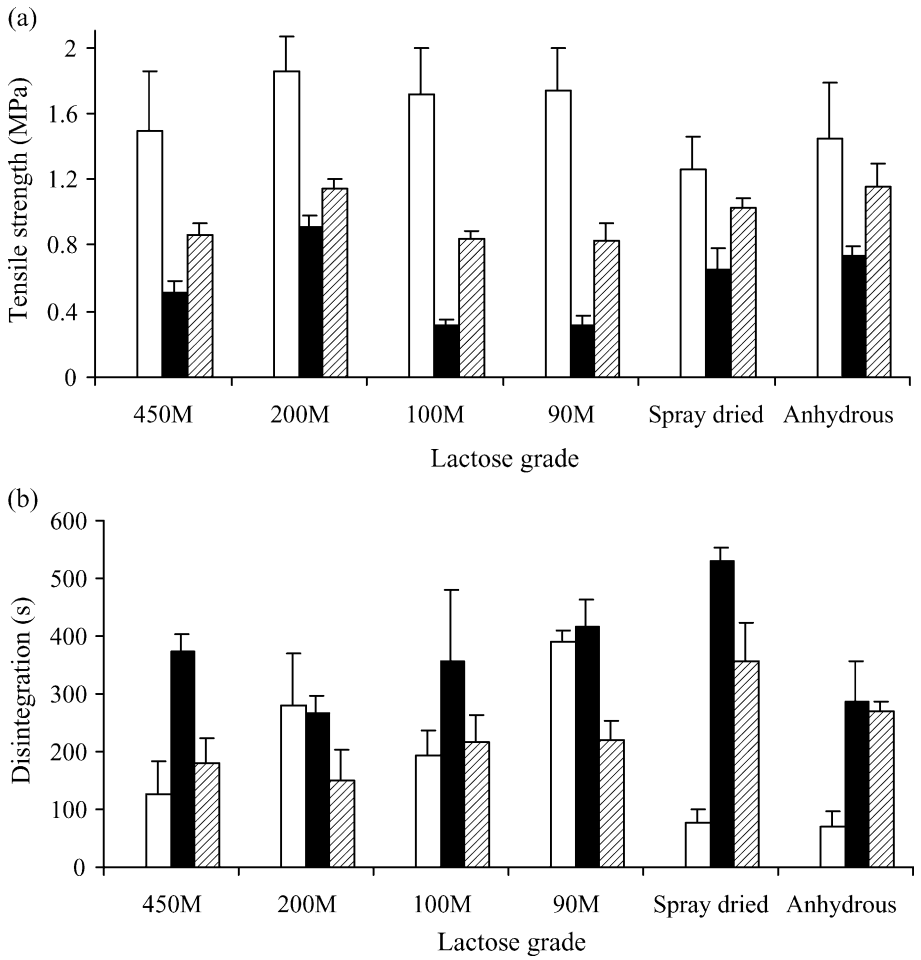

Fig. 1. (a) Tensile strength of tablets (mean ± standard deviation) produced with different grades of lactose with 2.5% PVP produced by single-step granulation/tabletting (□) and by compression after high shear granulation with (■) and without (▨) magnesium stearate. (b) Disintegration time of tablets (mean ± standard deviation) produced with different grades of lactose with 2.5% PVP produced by single-step granulation/tabletting (□) and by compression after high shear granulation with (■) and without (▨) magnesium stearate.

of α-lactose monohydrate significantly influence the disintegration time whereas, disintegration of α-lactose monohydrate 90 M tablets was significantly slower compared with spray dried lactose and anhydrous β-lactose probably due to solubility differences.

Comparison of tablet disintegration time obtained by both techniques indicated that single-step granulation/tabletting yielded tablets with a significantly lower disintegration time compared with those produced by compression after high shear granulation, except for tablets prepared from α-lactose monohydrate 90 and 200 M, which had a similar disintegration time.

3.3. Stability of tablets produced by single-step granulation/tabletting

It is well known that the properties of α-lactose monohydrate tablets can be affected by storage [8] and that this is mainly due to change in the bonding. Tablets obtained by single-step granulation/tabletting are bond mainly by solid bridges, whereas tablets prepared by compression are bond mainly by intermolecular bonds. The properties of these tablets could be affected differently during storage according to the type of bonds acting between tablet particles. Therefore, the stability of tablets of α-lactose monohydrate 200 M produced by single-step granulation/tabletting was evaluated during one year storage at 60% RH-25 °C and 75% RH-40 °C.

Table 3 shows the influence of storage on the properties of tablets without and with 2.5% PVP produced by single-step granulation/tabletting. Storage did not result in significant changes in the tensile strength, while a significant increase in the disintegration time was observed for both formulations at both storage conditions. The disintegration time always remained below 400 s. This is in contrast to Stubberud et al. [8] who reported that lactose monohydrate tablets prepared by compression hardened during storage and indicate that the effect of storage on the mechanical properties of tablets is dependent on the bonding mechanism.

Table 3
The influence of long term and accelerated stability conditions on the properties of α-lactose monohydrate tablets without and with 2.5% PVP produced by single-step granulation/tabletting

PVP (%)	Time (d)	60% RH-25 °C			75% RH-40 °C		
		Tensile strength (MPa)	Friability (%)	Disintegration (s)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
0	1	1.09 (0.17)	0.65	27 (7)	1.07 (0.10)	0.99	42 (12)
	90	1.07 (0.16)	0.58	32 (20)	0.93 (0.25)	0.64	45 (20)
	180	0.97 (0.18)	0.82	53 (13)	0.96 (0.18)	0.84	99 (17)
	360	1.03 (0.15)	0.80	43 (10)	1.10 (0.13)	0.70	125 (49)
2.5	1	1.47 (0.14)	0.42	162 (37)	1.29 (0.31)	0.73	182 (44)
	90	1.60 (0.20)	0.57	193 (42)	0.99 (0.36)	0.79	313 (28)
	180	1.32 (0.22)	0.59	172 (69)	1.34 (0.22)	0.65	223 (92)
	360	1.63 (0.24)	0.90	297 (86)	1.27 (0.14)	0.59	358 (40)

Standard deviations are given between parentheses.

Comparing the tablet properties obtained at different conditions revealed no significant influence on the tensile strength, while a significantly higher disintegration time was observed for the tablets stored at 75% RH and 40 °C. The high disintegration time at 75% RH-40 °C could be attributed to a decrease in the tablet porosity from 24.6 to 18.1%. This change in porosity was mainly due to the continuous swelling and transformation of PVP from the glassy state to a rubbery state at elevated humidity and temperature [9,10].

4. Conclusion

This study showed that the particle size and morphology of lactose can have a major impact on the performance of single-step granulation/tabletting. However, selection of the proper lactose grade and optimisation of the total input rate as well as PVP and water concentration can easily solve these problems. Tablets of different grades of lactose produced by single-step granulation/tabletting possess better qualities compared to those obtained by compression after high shear granulation.

The stability study revealed that the physical properties of lactose tablets prepared by single-step granulation/tabletting were maintained during storage.

It can be concluded that single-step granulation/tabletting can be applied to different grades of lactose. Moreover, this technique is efficient and allows continuous processing.

Acknowledgements

The authors would like to thank DMV (Veghel, the Netherlands) for supplying the different types of lactose and BASF (Ludwigshafen, Germany) for providing PVP. E. Keleb wishes to thank the faculty of Pharmacy (Al-Fateh University, Tripoli, Libya) for providing the post-graduate research grant.

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