International Journal of Pharmaceutics 387 (2010) 71–78

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Influence of amorphous content on compaction behaviour of anhydrous α-lactose

S. Ziffels, H. Steckel*

Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstr. 76, 24118 Kiel, Germany

ARTICLE INFO

Article history:
Received 14 September 2009
Accepted 3 December 2009
Available online 15 January 2010

Keywords:
Amorphous lactose
Anhydrous α-lactose
Compaction behaviour
Crushing strength
Disintegration time
Powder properties

ABSTRACT

Modified lactoses are widely used as filler-binders in direct compression of tablets. Until today, little about the compaction behaviour of anhydrous α-lactose is known. In this study, a new method to prepare anhydrous α-lactose from α-lactose monohydrate by desiccation with heated ethanol was evaluated and the influence of amorphous content in the lactose powder prior to modification on powder properties, compaction behaviour and storage stability was determined. The modification process led to anhydrous α-lactose with decreased bulk and tapped density, increased flow rate and significantly higher specific surface area. Due to the higher specific surface area, the compaction behaviour of the anhydrous α-lactose was found to be significantly better than the compaction behaviour of powder blends consisting of α-lactose monohydrate and amorphous lactose. An influence of the amorphous content prior to modification could be observed only at higher compaction forces. In general, tablets of modified powders needed longer time to disintegrate directly after compression. However, the storage stability of modified tablets was found to be better compared to the amorphous-crystalline tablets which were influenced by storage conditions, initial crushing strength as well as amorphous content due to the re-crystallization of amorphous lactose during storage.

1. Introduction

Lactose is one of the most important pharmaceutical excipients in the production of solid oral dosage forms. In the application as a filler-binder in compaction process the compaction behaviour of the used lactose quality is of utmost importance for the production of hard tablets with good disintegration properties and, therefore, good liberation of the active ingredient. Lactose is known to exist in four different solid forms: α-lactose monohydrate, anhydrous α-lactose which can be divided into stable and unstable anhydrous α-lactose, anhydrous β-lactose and amorphous lactose. Each form exhibits different compaction behaviour. Until today, the compaction behaviours of most of the referred lactose forms are investigated reasonably well. α-lactose monohydrate is known to show brittle fragmentation during compaction, while the amount of plastic deformation is very low (Vromans et al., 1985). Particles of α-lactose monohydrate exhibit the typical tomahawk shape with very smooth surfaces (Begat et al., 2004). Fragmentation of the α-lactose monohydrate particles during compaction increases the specific bonding surface area and the higher the bonding surface area, the higher is the resulting crushing strength of the tablet (De Boer et al., 1986). To achieve high crushing strengths of pure α-lactose monohydrate tablets, higher compaction forces will be necessary. Therefore, lactose qualities of sieved α-lactose monohydrate available on the market are normally granulated prior to compaction to improve the compaction behaviour. Anhydrous β-lactose is also known to fragment during compaction, but it shows a much better compaction behaviour due to more spherical particles, rougher particle surfaces and a higher degree of fragmentation (Vromans et al., 1987). Available β-lactose qualities consist of about 85% β-lactose, the remaining 15% are composed of α-lactose monohydrate or anhydrous α-lactose (Bolhuis and Zuurman, 1995). The compaction properties of these β-lactose qualities are therefore made up of the consolidation mechanisms of the α-lactose monohydrate component as well as of the β-lactose component. A completely different compaction behaviour, however, was determined for amorphous lactose. Completely amorphous lactose which can be produced by spray drying of an aqueous lactose solution displays plastic deformation due to very soft and spherical particles with smooth surfaces. However, spray dried lactose qualities available on the market consist only of about 12–15% amorphous lactose, while the remaining substance consists of α-lactose monohydrate (Darcy and Buckton, 1998; Kussendrager et al., 1981). This composition is produced by spray drying a suspension of lactose crystals in a solution of lactose so that a core of α-lactose monohydrate embedded in an outer layer of amorphous lactose or aggregates of α-lactose monohydrate crystals glued together with layers of amorphous lactose are formed during the spray drying process (Vromans et al., 1986). The resulting compaction behaviour is therefore a mix of the fragmentation of

* Corresponding author. Tel.: +49 431 880 1330; fax: +49 431 880 1352.
E-mail address: hsteckel@pharmazie.uni-kiel.de (H. Steckel).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.12.009

the crystalline α-lactose monohydrate core and the plastic deformation of the amorphous lactose layers. Although the compaction behaviour of the referred lactose forms is investigated reasonably well until today, little about the compaction behaviour of anhydrous α-lactose is known yet. Anhydrous α-lactose can be produced from α-lactose monohydrate by thermal dehydration or alcohol desiccation with solvents like methanol. Thermal dehydration at temperatures above 130 °C leads to the formation of the stable anhydrous α-lactose. This stable form shows a non-hygroscopic behaviour during storage at a relative humidity below 50%. The maximum moisture uptake is 1% (Figura and Epple, 1995). By using alcohols like methanol or ethanol to desiccate α-lactose monohydrate, the unstable anhydrous α-lactose is formed. Storing this form at conditions below 50% relative humidity (RH) causes a higher moisture uptake up to 4% due to the higher hygroscopicity of the unstable product. This hygroscopic form of anhydrous α-lactose can also be produced by thermal dehydration of α-lactose monohydrate at temperatures of 100–130 °C (Majd and Nickerson, 1976). Compaction behaviour and consolidation mechanism of these various anhydrous lactose forms are rarely investigated until today and the results of the few studies published differ widely from each other. For example, Lerk et al. reported an increased binding capacity and excellent flow properties for anhydrous α-lactose after thermal dehydration of α-lactose monohydrate (Lerk et al., 1983), while Muñoz-Ruiz et al. found a decreased flowability and a minor compaction behaviour compared to spray dried lactose (Munoz-Ruiz et al., 1993). As amorphous lactose is known to improve the compaction properties of, for example, α-lactose monohydrate by adding small quantities prior to compaction (Lerk, 1993), the aim of this study was to investigate the alterations in compaction behaviour of anhydrous α-lactose induced by adding amorphous lactose to the raw material α-lactose monohydrate prior to desiccation with ethanol. The stability of the produced tablets during storage was investigated to get further information about alterations in the tablet stability due to addition of amorphous lactose prior to desiccation. Additionally, the influence of the addition of amorphous lactose was determined by comparing the powder properties of powder blends of amorphous and crystalline lactose before and after desiccation. For the production of anhydrous α-lactose out of crystalline α-lactose monohydrate a new method with heated ethanol was developed.

2. Materials and methods

2.1. Materials

2.1.1. Crystalline lactose

CapsuLac® 60 (Meggle Wasserburg GmbH, Germany) was used as crystalline α-lactose monohydrate for the preparation of amorphous-crystalline powder blends. To ensure a completely crystalline material, CapsuLac® 60 was stored for 72 h at 25 °C and 60% RH in a temperature and climate test chamber (Modell SB 111/300, Weiss Technik GmbH, Germany). The residual moisture content of the material was found to be lower than 1.0%, tested with an infrared balance (MA 45, Sartorius AG, Germany).

2.1.2. Spray dried lactose

Amorphous lactose was prepared by spray drying a 15% (w/w) solution of CapsuLac® 60 in double distilled water with a Büchi mini spray dryer B-290 (Büchi Labortechnik GmbH, Germany). The process was carried out at standard conditions: the inlet temperature was adjusted to 152 °C and the outlet temperature to 70 °C by varying the pump rate. After spray drying, the amorphous state of the lactose was verified with X-ray diffraction using a Stoe X-ray powder diffractometer (Stoe & Cie, Germany) by analyzing the 2θ range from 5° to 50° (40 kV, 30 mA, 1.2 kW). The spray dried lactose was considered to be fully amorphous, when only the characteristic Halo signal could be detected in the diffractograms.

2.2. Methods

2.2.1. Powder blending

Powder blends of amorphous (spray dried) and crystalline lactose, containing 2.0%, 6.0% or 10.0% of amorphous lactose, respectively, were prepared. The spray dried and crystalline components were sieved separately (500 μm sieve) and weighed with a "sandwich" weighing procedure into a mixing vessel. Afterwards, the components were blended for 15 min in a Turbula blender (Typ T2C, Bachofen AG, Switzerland), the mixture was sieved and blended again for 15 min. Finally, a last sieving step was added. All weighing and sieving steps were carried out under nitrogen atmosphere in a glove box below 25 °C and 25% RH to avoid re-crystallization of amorphous lactose. The critical relative humidity for the re-crystallization of amorphous lactose is reported to be 58% at 25 °C (Price and Young, 2004; Steckel and Bolzen, 2005).

2.2.2. Modification into anhydrous α-lactose

Modification of the powder blends was performed by using ethanol 99.0% (v/v), denatured with 1.0% petrol ether. The ethanol was heated to 60 °C and added to the powder blends. Afterwards, the suspension was stirred for 15 min, excessive ethanol was decanted, a fresh portion of heated ethanol was added and the suspension was stirred for 15 min. Addition of ethanol and stirring of the suspension was repeated two times. Subsequently, the modified lactose was dried in a fluid bed dryer (TG 100, Retsch GmbH, Germany) until a residual moisture of below 1.0% was reached.

2.2.3. Bulk density/tapped density

Bulk and tapped density of unmodified and modified powder blends were determined using a graduated cylinder with a volume of 10 mL (J. Engelsmann, AG, Germany). The tapped density was calculated by dividing the mass of the sample through the volume of the powder apparent after 1250 tappings according Ph. Eur. The measurements were performed in triplicate.

2.2.4. Flow rate

The flow rate through a nozzle of 15 mm diameter was determined of the unmodified and modified powders with a Granutest Type GT-B (Erweka GmbH, Germany). All measurements were performed in triplicate.

2.2.5. Angle of repose

The angle of repose was investigated with a Granutest Type GT-B (Erweka GmbH, Germany). To avoid errors due to irregular tops the laser system determined only the slope of the cone shaped bulk material. The measurements were performed in triplicate.

2.2.6. Specific surface area

The specific surface area of the unmodified and modified powder blends was determined with a BET gas adsorption method. Degassing of the lactose powders was completed for 1 h under vacuum at 40 °C prior to analyzing the samples with a Gemini 2360 BET surface area analyzer (Micromeritics, Norcross, USA) using nitrogen as measuring gas. The BET multipoint method was used to calculate the specific surface area. All measurements were carried out in triplicate.

2.2.7. Scanning electron microscopy (SEM)

Pictures of the original powder blends and the modified powder blends were prepared with scanning electron microscopy using a Zeiss DSM 940 electron microscope (Carl Zeiss GmbH, Germany).

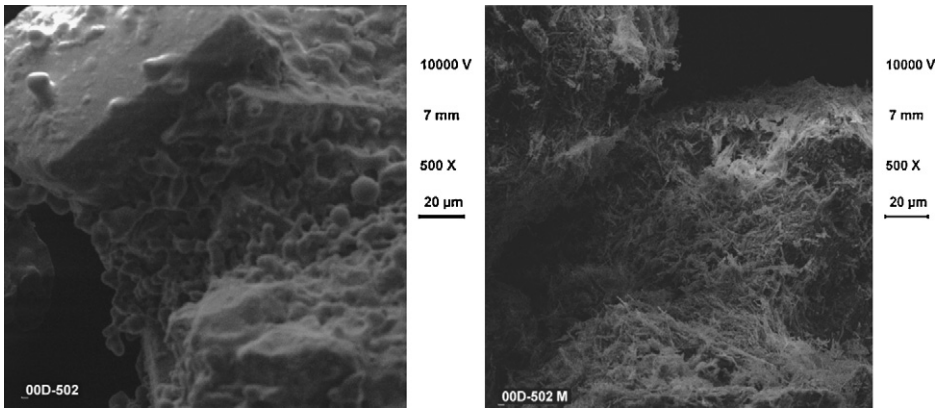

Fig. 1. Scanning electron microscopy pictures of amorphous-crystalline powder blends: powder blend with 6.0% amorphous content (left); powder blend with 6.0% amorphous content after modification with ethanol (right).

For sample preparation small amounts of the powder blends were placed on aluminium holders and sputtered with a gold layer under argon atmosphere for 65 s in a Sputter-Coater (SCD 005, Bal-Tec AG, Liechtenstein).

2.2.8. Direct compression

The original and the modified powder blends were compacted into tablets with a single punch tableting machine Fette Exacta 11 (Fette GmbH, Germany) at compaction forces of 20, 30 and 40 kN. Flat-faced punches were used for the production of the tablets with a mass of 400 mg. Prior to compaction, 0.25% (w/w) magnesium stearate was added to the powder blends by mixing the powders for 2 min in a Turbula blender (Typ T2C, Bachofen AG, Switzerland). Additionally, tablets with an initial crushing strength of 70 and 120 N were produced for the testing of tablet storage stability.

2.2.9. Amorphous content

The remaining amorphous content of the modified powder blends was determined with isothermal microcalorimetry with a Thermal Activity Monitor (Type 2277, Thermometrics AB, Sweden). All experiments were carried out using the static ampoule method first described by Angberg et al. (1992). A quantity of 300 mg was weighed into 2 mL glass ampoules. The ampoules were sealed with aluminium caps after placing mini hygrostats filled with saturated sodium chloride solution into the ampoules to create an atmosphere of 75% RH. During an equilibration period of 10 min the sealed ampoule was placed in an equilibration position in the Thermal Activity Monitor to achieve the experiment temperature of 25 °C. All measurements were carried out in triplicate.

2.2.10. Crushing strength

The crushing strength of the tablets was investigated using a Pharmatest PTB 300 (Pharmatest GmbH, Germany). Determination of crushing strength was performed with ten tablets immediately after compaction and after the respective storage periods of the tablets.

2.2.11. Disintegration time

The disintegration time of six tablets was investigated immediately after compaction and after the respective storage periods of the tablets. An Erweka ZT4 disintegration tester (Erweka GmbH, Germany) was used with demineralised water at a temperature of 37 °C.

2.2.12. Storage

Tablets with initial crushing strengths of 70 and 120 N directly after compression were prepared from the original powder blends and the modified powder blends and stored for 56 days at 25 °C/60% RH and 40 °C/75% RH in a temperature and climate test chamber (Modell SB 111/300, Weiss Technik GmbH, Germany). After 1, 4, 7, 14, 28 and 56 days of storage, crushing strength and disintegration time of the tablets were investigated.

3. Results and discussion

3.1. Powder properties

A comparison of the scanning electron microscopy (SEM) pictures of the original and the modified powder blends elucidates completely different particle structures (Fig. 1). The picture of the original powder blends shows large particles of α-lactose monohydrate with smooth surfaces occupied with small, regular spherical particles of amorphous lactose. After modification of this powder blend with heated ethanol, the particles were found to have a very rough and uneven surface consisting of small anhydrous α-lactose needles. Due to this very rough surface texture, the bulk density of the modified powder blends is lower, especially compared to the bulk densities (Table 1) of the original powder blends containing 2.0% and 6.0% amorphous lactose. The particles of the modified powder blends do not fit into each other and a lot of free space remains between the acicular surface structures. However, there is a large decrease in bulk density between the original powder blends containing 2.0% and 6.0% amorphous lactose on the one hand and the 10.0% amorphous powder blend on the other hand (Table 1).

Table 1
Powder characteristics of amorphous-crystalline powder blends before and after modification with ethanol; standard deviation in brackets.

Powder blend (amorphous content)	Bulk density, g/mL	Tapped density, g/mL	Specific surface area, m^2/g	Flow rate, s/100 g	Angle of repose,°
2.0%	0.637 (*0.009*)	0.756 (*0.006*)	0.138 (*0.010*)	2.9 (*0.1*)	34.7 (*1.3*)
6.0%	0.650 (*0.004*)	0.790 (*0.011*)	0.218 (*0.001*)	3.4 (*0.3*)	39.7 (*0.2*)
10.0%	0.639 (*0.011*)	0.823 (*0.012*)	0.307 (*0.014*)	4.4 (*0.2*)	39.6 (*1.3*)
2.0% modified	0.396 (*0.009*)	0.572 (*0.005*)	2.845 (*0.019*)	6.1 (*0.1*)	40.5 (*1.0*)
6.0% modified	0.360 (*0.003*)	0.532 (*0.003*)	0.307 (*0.007*)	7.2 (*0.1*)	40.7 (*1.3*)
10.0% modified	0.399 (*0.011*)	0.526 (*0.020*)	3.425 (*0.002*)	6.6 (*0.2*)	41.3 (*1.8*)

This is due the fact, that with increasing amorphous content the amount of small particles in the powder increases as well. At 2.0% and 6.0% amorphous content, the small amorphous particles were able to fill up the surface irregularities so that the powder blends were closely packed. But the further addition of amorphous particles of 10.0% led to an excess of small particles with the effect that all surface irregularities of the α-lactose monohydrate are filled up and the remaining small amorphous particles covered the smooth surface as well. Therefore, the packing of the 10.0% amorphous powder blend is not as close as the packing of the 2.0% and 6.0% amorphous powder blends. The tapped density of the original powder blends increased with increasing amorphous content, because the higher the amount of small amorphous particles the closer the powder could be packed by tapping. However, tapping of the modified powder blends did not lead to a significant increase of the tapped density with increasing amorphous content prior to modification. This is due to the fact that the modified powder blends do not longer consist of both large and small particles with smooth surfaces, but in the SEM pictures the particle sizes of the anhydrous α-lactose particles seemed to be more regular and the rearrangement of the particles during tapping is also interfered by the very rough surface texture. Because of the increasing amount of small particles with increasing amorphous content of the original powder blends, the specific surface area was found to increase as well (Table 1). Increasing specific surface areas are attended by higher surface energies and, therefore, higher tendencies for adhesion and cohesion and this may affect the flowability of a powder, too. In this study, we found a decreasing flowability with increasing amorphous content and increasing specific surface area of the original powder blends (Table 1). Compared to the original, unmodified power blends, the modification process led to powders with slightly decreased flowability. The increase in amorphous content prior to modification from 2.0% to 6.0% reduces the flowability of the modified powder blends from 6.1 s/100 g to 7.2 s/100 g. Unexpectedly, the flowability of the 10% amorphous modified powder blend did not decrease to the same extent, but was found with 6.6 s/100 g between the flow rate of the 2.0% and the 6.0% modified powder blends. This worse flow rate for all three modified powder blends is due to the immensely increased specific surface area (Table 1). While the original powder blends have specific surface areas between 0.1 and 0.3 m^2/g, the modified powder blends were found to have values between 2.8 and 3.4 m^2/g. The specific surface areas of the modified powder blends increased with increasing amorphous content prior to modification. Although the SEM pictures did not reveal any fine particles, the increasing amorphous content prior to modification seemed to have an influence on the specific surface area. Until today it is also unclear, if the modification process with ethanol includes the whole particle or if only the outer surface is dehydrated to anhydrous α-lactose. In the spray dried amorphous lactose the equilibrium of α- and β-lactose in the spray drying solution is captured. Therefore, the amount of β-lactose increases as well with increasing amorphous content of the powder blends. During modification, the powder blends with higher amorphous content may dehydrate into anhydrous α-lactose and anhydrous β-lactose, which also is known to have a rough surface, while the powder blends with lower amorphous content may dehydrate into anhydrous α-lactose and a smaller amount of β-lactose as well. If only the outer surface is dehydrated during the modification process, this may lead to remaining α-lactose monohydrate after modification with a smoother surface. Summarizing these effects, the modification process of the powder blends with lower amorphous content may lead to a product with some remaining α-lactose monohydrate with smooth surfaces and a very low content of β-lactose with a rough surface. During modification of powder blends with higher amorphous content less α-lactose monohydrate with smooth surfaces will remain while more anhydrous α-lactose and anhydrous β-lactose will be produced. This effect may also lead to an increase in specific surface area besides the influence of smaller particle sizes. Although the flowability of the powder blends was influenced by the amorphous content, the angle of repose showed no significant increase with increasing amorphous content, neither for the original powder blends nor for the modified powder blends (Table 1).

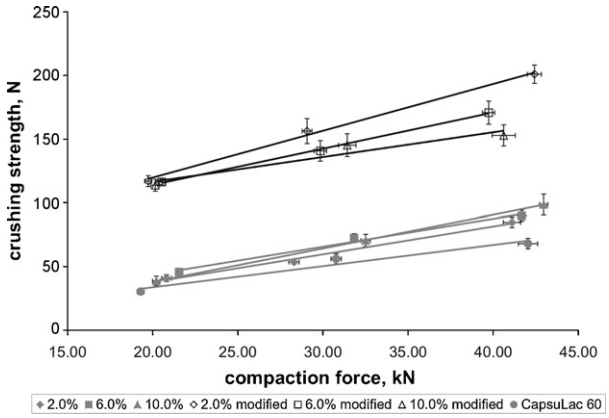

Fig. 2. Compaction behaviour of amorphous-crystalline powder blends before and after modification with ethanol.

3.2. Compaction behaviour

A linear relationship between the applied compaction forces and the resulting crushing strength of the tablets was found for both the original amorphous-crystalline powder blends and the modified powder blends. Higher compaction forces led to tablets with higher crushing strengths. However, the original powder blends were found to show completely different compaction behaviours compared to the modified powder blends (Fig. 2). Compaction of the original amorphous-crystalline powder blends with compaction forces of 20 kN led to tablets with crushing strengths of about 40 N, while compaction forces of 40 kN produced tablets with crushing strengths of about 80–90 N. The admixture of and an increasing content of amorphous lactose did not influence the compaction behaviour of the original amorphous-crystalline powder blends significantly at the applied compaction forces. Compaction of the modified powder batches led to completely different results. The crushing strengths of the tablets were found to rise immensely by minimum 60 N compared to the original powder blends. When compaction forces of 20 kN were applied, the tablets of all three modified powder blends were found to have crushing strengths of 113–116 N. At these low compaction forces the added amorphous content prior to modification seemed to have no influence on the crushing strength of the modified powder tablets. However, by raising the applied compaction forces up to 40 kN, tablets of the 2.0% amorphous modified powder blend crushed at forces of 200 N, tablets of the 6.0% amorphous modified powder blend crushed at forces of 170 N and tablets of the 10.0% amorphous modified powder blend crushed already at 152 N. Summing up these results, the increase in amorphous content prior to modification led to a decrease in the crushing strength of the tablets at higher compaction forces, while the crushing strength is not affected at lower compaction forces. These results can be explained by the higher amount of smaller particles in the 10.0% amorphous modified batch. While larger particles were perhaps not fully dehydrated during the modification process but probably only the surface, small particles should be dehydrated completely during the modification process. Because of the very rough and needle-like structure of anhydrous α-lactose, these small particles probably do not exhibit a hard core,

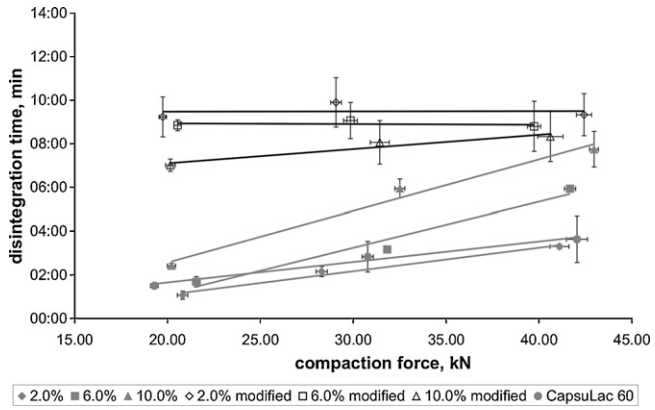

Fig. 3. Disintegration behaviour at different compaction forces of amorphous-crystalline powder blends before and after modification with ethanol.

but a very porous structure throughout the whole particle. During compaction these porous small particles need higher compaction forces to build up strong bonds because of the space excess in the porous structure and the resulting crushing strength of the tablets is lower. Therefore, tablets of the modified powder blends with high amorphous content prior to compaction show a decreased crushing strength at the same applied compaction forces. Compared to the raw material CapsuLac® 60, the addition of amorphous material led to an increase in crushing strength of the original amorphous-crystalline powder blends by 10–15 N, while the sum of addition of amorphous lactose and modification process led to anhydrous α-lactose with tremendously better compactibility and increasing crushing strengths of the tablets by values of 60 N difference.

Besides the huge differences in crushing strength, the disintegration behaviour also differed widely for all powder blends. Amorphous lactose is known to show plastic deformation during compression which has a positive effect on the tablet hardness of α-lactose monohydrate tablets. Although the difference in crushing strength was shown to be not significant at the applied compaction forces, the addition of amorphous lactose has a great influence on the disintegration properties of the tablets. Addition of increasing amounts of amorphous lactose led to an increase in the disintegration time of the resulting tablets (Fig. 3). At low compaction forces there were only small differences between the disintegration times of the original powder blend tablets apparent, but at higher applied compaction forces of 40 kN the increase in amorphous content led to an increase in disintegration time of about 2.5 min for tablets of the 6.0% amorphous powder blend and to an increase of about 4.5 min for tablets of the 10.0% amorphous powder blend. This is due to the fact that the part of plastic deformation increases as well with increasing amorphous content and therefore the bonds in the tablets grew stronger. However, the addition of 2.0% amorphous lactose did not lead to a significant change in disintegration time compared to the raw material CapsuLac® 60. Tablets of modified powder blends showed completely different disintegration behaviours. Disintegration time is increased for all tablets of modified powder blends. But the disintegration times of all tablets of modified powder blends are not affected by the applied compaction forces, the resulting crushing strength and the amount of amorphous lactose added prior to modification. These results confirm the results of Van Kamp et al. who found the same disintegration behaviour for anhydrous α-lactose tablets and explained the results with an increased initial solubility of anhydrous α-lactose and a dissolution of the anhydrous α-lactose tablets rather than a real disintegration (Van Kamp et al., 1986). The dissolution of the anhydrous α-lactose was caused by poor water penetration into the tablet because of small pore diameters and the precipitation

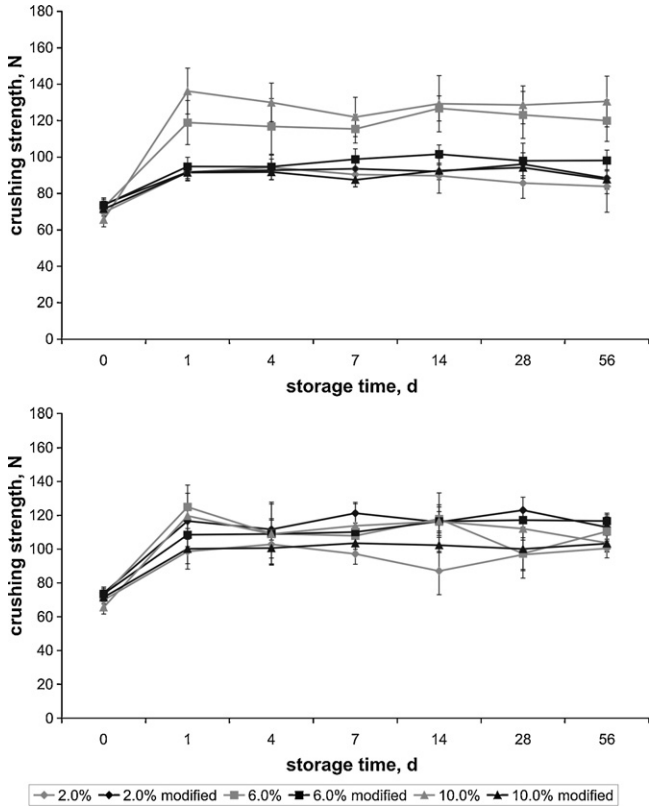

Fig. 4. Crushing strengths of 70 N tablets stored for 56 days at 25 °C/60% RH (top) and 40 °C/75% RH (below).

of α-lactose monohydrate inside the tablet. Therefore, the applied compaction forces and crushing strengths have no effect on the disintegration time.

3.3. Storage stability

For the determination of storage stability, tablets with initial crushing strengths of 70 and 120 N were compacted from the original amorphous-crystalline powder blends with varying amorphous content and from the powder blends after their modification with ethanol. After storing the tablets at 25 °C/60% RH and 40 °C/75% RH for 56 days, differing values of crushing strength and disintegration time could be obtained dependent on the added amorphous content, the initial crushing strength of the tablets and the chosen storage conditions. In Fig. 4 the alterations in crushing strength of 70 N tablets are displayed for both storage conditions. During storage at 25 °C/60% RH the crushing strength of the tablets produced of the original powder blends increased during the first day of storage. This depends on the amorphous content of the tablets: the higher the amorphous content, the higher was the increase in crushing strength after 1 day of storage. The increase was found to be about 20 N for 2.0% amorphous tablets, about 45 N for 6.0% amorphous tablets and about 60 N for 10.0% amorphous tablets. Because of the re-crystallization of the amorphous parts inside the tablets, the crystal lattice of the lactose particles straightened, the particles rearranged themselves and, therefore, the bonds between the particles grew stronger. The amount of rearrangement and consolidation of the bonds was the highest for the tablets with the highest amorphous content, and this is why the 10.0% amorphous tablets showed the highest increase in crushing strength. During the modification process with ethanol, the amorphous parts in the powder blends were converted into anhydrous α- or β-lactose, so that for the tablets produced from modified powder blends only

a slight increase in crushing strength of 15–20 N was determined. The slight increase cannot be attributed to the re-crystallization of amorphous parts, but were the result of the general strengthening of bonds occurring for most tablets after compaction. This explanation is confirmed by the observation that the crushing strength of all tablets produced of modified powder blends increased by the same values and no influence of the added amorphous content prior to modification could be detected. After the first day of storage neither a substantial increase nor a decrease was determined for all 70 N tablets stored at 25 °C/60% RH, because re-crystallization and strengthening of bonds already took place during the first day of storage at the chosen storage condition. During storage of 70 N tablets at 40 °C/75% RH the influence of the amorphous content in the original powder blends could be seen as well for the tablets. The crushing strength increases with increasing amorphous content during the first day of storage, too. But the influence of the amorphous content could be seen for the tablets produced from modified powders as well. In contrast to the tablets made from the original powder blends, the slight increase of crushing strength of modified powder tablets is lower for 10.0% amorphous tablets than for 2.0% and 6.0% amorphous tablets. This observation can be explained by the ratio of α- and β-lactose created during the modification process. As mentioned earlier, the α/β equilibrium of a lactose solution in water is fixed in amorphous lactose, because the spray drying process is too rapid for another conversion into the preferred anomer (Roetman and Van Schaik, 1975). Therefore, after modification the absolute β-lactose content in the 10.0% amorphous powder blend is higher than in the 2.0% or 6.0% powder blend. As β-lactose is known to have a rough but still smoother surface than anhydrous α-lactose and, therefore, a smaller specific surface area, less bonds can be produced during the compaction process and therefore, the increase in crushing strength due to strengthening of bonds after compaction is lower for the tablets with a higher β-lactose content, in this case the 10.0% amorphous modified tablets. These results fit also very well to the observation that increasing compaction forces led to lower crushing strengths for tablets produced from modified 10.0% amorphous powder blends compared to tablets with 2.0% and 6.0% amorphous content, respectively (Fig. 2). The same behaviour during storage could be determined for tablets with initial crushing strengths of 120 N (Fig. 5). However, the values for the increase in crushing strength were found to be lower for all batches, because the particles in tablets with initial crushing strengths of 120 N are already bond together very strongly due to the higher compaction forces so that there is less space inside the tablets to allow for particle rearrangements as compared to the 70 N tablets.

Fig. 6 shows the disintegration behaviour for 70 N tablets during storage at both storage conditions. Tablets of the original powder blends with an amorphous content of 2.0% and 6.0% seem to be hardly affected by the storage at 25 °C/60% RH, because only a slight increase in disintegration time was found for the 2.0% amorphous batch. Notwithstanding, the 10.0% amorphous tablets disintegrate directly after compression within 6 min, but after 1 day of storage already within 2.5 min. As the re-crystallization of amorphous parts and the strong increase in crushing strength would suppose to observe an extended disintegration time after 1 day of storage, this value may also be an outlier. However, the increase in amorphous content did not lead to a proportional increase nor decrease in disintegration time at this storage conditions. Immediately after compression, disintegration time of the modified powder tablets is influenced by the amount of amorphous material present in the powder blends prior to modification. The 2.0% amorphous modified tablets disintegrate within 10 min, the 6.0% tablets within about 7 min and the 10.0% amorphous modified tablets disintegrate already within about 6 min. After 56 days of storage the disintegration time of the 2.0% amorphous modified tablets did not alter substantially, while the 6.0% and 10.0% modified tablets showed a

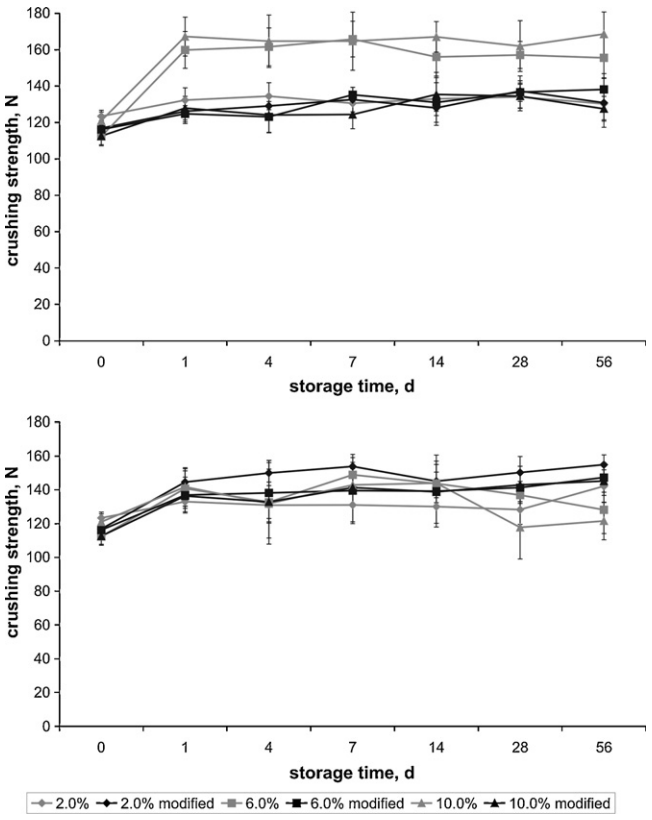

Fig. 5. Crushing strengths of 120 N tablets stored for 56 days at 25 °C/60% RH (top) and 40 °C/75% RH (below).

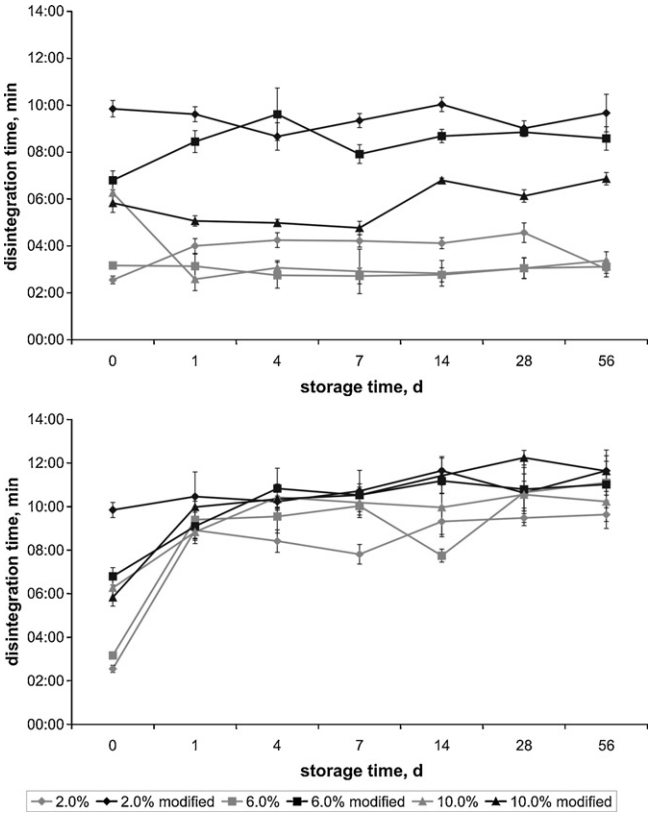

Fig. 6. Disintegration time of 70 N tablets stored for 56 days at 25 °C/60% RH (top) and 40 °C/75% RH (below).

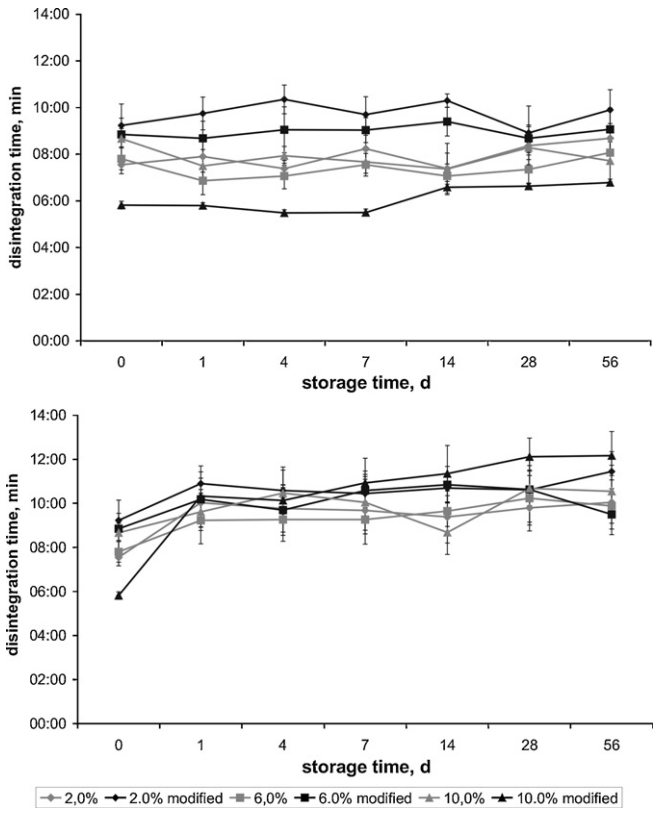

Fig. 7. Disintegration time of 120 N tablets stored for 56 days at 25 °C/60% RH (top) and 40 °C/75% RH (below).

slight increase. The completely different disintegration behaviour of the tablets produced of original powder blends compared to the tablets of modified powder blends is explainable by a lower initial solubility of anhydrous α-lactose and the very good solubility of amorphous lactose. During the disintegration test tablets of anhydrous α-lactose do not disintegrate into particle aggregates but dissolute altogether starting from the outer surface and the disintegration medium seemed not to really penetrate into the tablet. Van Kamp explained this disintegration behaviour of anhydrous α-lactose tablets with the very small pore size distribution and the precipitation of anhydrous α-lactose as α-lactose monohydrate in the pores of the tablet after the contact to water (Van Kamp et al., 1986). Because of the missing amorphous parts after the modification process the modified tablets did not show alterations in disintegration time due to re-crystallization of amorphous lactose. However, during storage at 40 °C/75% RH tablets of modified powder blends with amorphous contents of 6.0% and 10.0% showed significant increases in disintegration time by about 2 min (6.0%) and 4 min (10.0%), respectively, already after 1 day of storage. This may be due to the fact that at this high relative humidity the β-lactose content created during the modification process is converted into anhydrous α-lactose and α-lactose monohydrate (Angberg et al., 1991) with lower initial solubilites than anhydrous β-lactose (Van Kamp et al., 1986). Tablets from the original powder blends containing varying amounts of amorphous lactose disintegrate significantly slower after 1 day of storage at 40 °C/75% RH. The disintegration time increases up to 9–10.5 min after 1 day of storage due to the re-crystallization of amorphous lactose in the tablets. These results fit to the already described increase in crushing strength.

Storage of tablets with an initial crushing strength of 120 N at 25 °C/60% RH showed no significant alteration in disintegration time during the whole period (Fig. 7). However, faster disintegration times directly after compression were found for 120 N tablets made from modified powder blends with an amorphous content of 10.0% prior to modification due to the higher β-lactose creation during modification as well, while the disintegration time of 120 N tablets of the original powder blends is unaffected by the amorphous content. The 10.0% modified tablets disintegrated even about 2 min faster than the 10.0% original tablets. During storage at 40 °C/75% RH the disintegration times of all tablet batches increased slightly during the first day of storage whereas the increase of the 10.0% amorphous lactose was found to be the highest, because the amount of β-lactose inside the tablet converts to anhydrous α-lactose and α-lactose monohydrate during this period of storage. After the conversion no significant alteration could be determined, both for the modified tablets as well as for the tablets produced from the original powder blends.

4. Conclusions

Modification of powder blends containing crystalline and amorphous lactose with heated ethanol led to modified powders consisting of mainly anhydrous α-lactose. The amount of β-lactose probably increased with increasing amorphous content prior to modification. An immense increase in specific surface area of the modified powder blends determined the decreased bulk and tapped density as well as the worse flowability. However, due to the higher specific surface area, the compactibility of the modified powders was significantly increased. Compression at the same compaction forces led to tablets with increased crushing strength by minimum 60 N. While disintegration time of tablets from blends of amorphous and crystalline lactose was influenced by the applied compaction forces, tablets of modified powder blends were not influenced in their disintegration time. Although the disintegration time of modified tablets was found to be higher directly after compression, it was only slightly affected during storage at higher temperatures and higher relative humidity. In contrast, disintegration time of tablets from the non-modified powder blends highly increased during storage at both chosen storage conditions.

References

Angberg, M., Nystroem, C., Castensson, S., 1991. Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies. III. Crystallographic changes due to water vapor uptake in anhydrous lactose powder. Int. J. Pharm. 73, 209–220.

Angberg, M., Nystroem, C., Castensson, S., 1992. Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies. V. A new approach for continuous measurements in abundant water vapor. Int. J. Pharm. 81, 153–167.

Begat, P., Morton, D.A.V., Staniforth, J.N., Price, R., 2004. The cohesive-adhesive balances in dry powder inhaler formulations. I. Direct quantification by atomic force microscopy. Pharm. Res. 21, 1591–1597.

Bolhuis, G.K., Zuurman, K., 1995. Tableting properties of experimental and commercially available lactose granulations for direct compression. Drug Dev. Ind. Pharm. 21, 2057–2071.

Darcy, P., Buckton, G., 1998. Crystallization of bulk samples of partially amorphous spray-dried lactose. Pharm. Dev. Tech. 3, 503–507.

De Boer, A.H., Vromans, H., Lerk, C.F., Bolhuis, G.K., Kussendrager, K.D., Bosch, H., 1986. Studies on tableting properties of lactose. Part III. The consolidation behavior of sieve fractions of crystalline α-lactose monohydrate. Pharm. Weekbl., Sci. Ed. 8, 145–150.

Figura, L.O., Epple, M., 1995. Anhydrous alpha-lactose: a study with DSC and TXRD. J. Therm. Anal. 44, 45–53.

Kussendrager, K., De Hoog, P., Van Leverink, J., 1981. Some physical properties of spray-dried lactose with respect to stability and compression. Acta Pharm. Suec. 18, 94–95.

Lerk, C.F., 1993. Consolidation and compaction of lactose. Drug Dev. Ind. Pharm. 19, 2359–2398.

Lerk, C.F., Andreae, A.C., De Boer, A.H., Bolhuis, G.K., Zuurman, K., De Hoog, P., Kussendrager, K., Van Leverink, J., 1983. Increased binding capacity and flowability of alpha-lactose monohydrate after dehydration. J. Pharm. Pharmacol. 35, 747–748.

Majd, F., Nickerson, T.A., 1976. Effect of alcohols on lactose solubility. J. Dairy Sci. 59, 1025–1032.

Munoz-Ruiz, A., Monedero Perales, M.C., Velasco Antequera, M.V., Payan Villar, T., Munoz-Munoz, N., Jimenez-Castellanos, M.R., 1993. Rheology and compression

characteristics of lactose-based direct compression excipients. Int. J. Pharm. 95, 201–207.
Price, R., Young, P.M., 2004. Visualization of the crystallization of lactose from the amorphous state. J. Pharm. Sci. 93, 155–164.
Roetman, K., Van Schaik, M., 1975. The β/α-ratio of lactose in the amorphous state. Neth. Milk Dairy J. 29, 225–237.
Steckel, H., Bolzen, N., 2005. Calorimetric study on amorphous lactose during and after re-crystallization at different relative humidity. Pharm. Ind. 67, 709–712.
Van Kamp, H.V., Bolhuis, G.K., Kussendrager, K.D., Lerk, C.F., 1986. Studies on tableting properties of lactose. IV. Dissolution and disintegration properties of different types of crystalline lactose. Int. J. Pharm. 28, 229–238.
Vromans, H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D., Bosch, H., 1986. Studies on tableting properties of lactose. VI. Consolidation and compaction of spray-dried amorphous lactose. Acta Pharm. Suec. 23, 231–240.
Vromans, H., Bolhuis, G.K., Lerk, C.F., Van De Biggelaar, H., Bosch, H., 1987. Studies on tableting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. Int. J. Pharm. 35, 29–37.
Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D., 1985. Studies on tabletting properties of lactose. Part I. The effect of initial particle size on binding properties and dehydration characteristics of lactose. Acta Pharm. Suec. 22, 163–172.