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Studies on tableting properties of lactose. VIII. The effect of variations in primary particle size, percentage of amorphous lactose and addition of a disintegrant on the disintegration of spray-dried lactose tablets

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Summary

Disintegration of tablets compacted from spray-dried lactose samples was found to depend on the amount of amorphous lactose, the size of the primary particles and the compaction load, respectively. The poor disintegration properties of amorphous lactose was explained by pointing to the dissolution characteristics of the substance. Considerable improvement of the disintegration properties can be obtained by addition of suitable disintegrants.

Introduction

In the first parts of this series, the consolidation and binding properties as well as the dissolution and disintegration of different types of crystalline lactose have been studied (Vromans et al., 1985a and b; De Boer et al., 1986; Van Kamp et al., 1986a and b). Subsequently, the work has been continued with a study concerning the consolidation and compaction properties of spray-died lactose (Vromans et al., 1986, 1987). In the present paper, the disintegration properties of spray-dried lactose will be discussed.

It has been found that the disintegration of lactose tablets is strongly determined by the type of lactose. Unlubricated tablets compressed from either α-lactose monohydrate or crystalline β-lactose disintegrated very quickly in water as a result of rapid liquid uptake and fast release of the bonds. However, tablets from anhydrous α-lactose did not disintegrate at all but dissolved instead. This effect was thought to be attributable to the dissolution of anhydrous α-lactose during the penetration of water and the immediate precipitation in its less soluble hydrous form. In tablets compressed from roller-dried β-lactose, which contains about 20% anhydrous α-lactose, disintegration time increased on increasing compaction load (Van Kamp et al., 1986a), i.e. at a shift to smaller pores in the tablets (Vromans et al., 1985b). The effect of both the presence of a lubricant and the addition of a disintegrant on tablet disintegra-

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tion time was also found to be strongly dependent on the type of lactose used (Van Kamp et al., 1986b).

The consolidation and compaction properties of spray-dried lactose have been studied in the previous two papers in this series. For this purpose samples with different amorphous lactose content and different primary particle size were produced. It was concluded that amorphous lactose deforms plastically under load (Vromans et al., 1986). In spray-dried lactose, the amorphous part is situated as a binding layer on the α-lactose monohydrate particles. The binding properties were shown to be determined by the primary particle size and the amorphous lactose content (Vromans et al., 1987).

The aim of this study was to investigate the effect of primary particle size, amorphous lactose content and the addition of disintegrants on the disintegration time of tablets compressed from spray-dried lactose.

Materials and Methods

Materials

The preparation and characterization of the spray-dried lactose samples used in this study have been described in the previous part of this series (Vromans et al., 1987). Commercially available spray-dried lactose (DCLactose 11) was used as obtained from DMV (Veghel, The Netherlands). The disintegrants used were: sodium starch glycolate NF XV (Primojel, Avebe, Foxhol, The Netherlands), crospovidone NF XV (Polyplasdone XL, GAF, Frechen, F.R.G.) and croscarmellose sodium, type A (Ac-Di-Sol, FMC Europe SA, Brussels, Belgium). Magnesium stearate (Ph. Ned. grade) was supplied by Lamers and Indemans ('s-Hertogenbosch, The Netherlands).

Methods

The lactose samples were mixed with disintegrants during 15 min in a Turbula mixer at 90 rpm. If lubrication was desired, 0.5% magnesium stearate was added and mixing was continued for 5 min. Tablets were prepared by manually introducing 500 mg of the pure or mixed excipients into a 13 mm die of a punch and die assembly, mounted between the plates of a hydraulic press (Hydro Mooi, Appingedam, The Netherlands). The tablets were compressed at a specified load, both the compression and decompression rate being 2 kN/s. If not stated otherwise, the tablets contained no lubricant, in which case the die was prelubricated by compressing a magnesium stearate tablet. The crushing strength was measured with a motorized instrument (model 2E, Dr Schleuniger, Productronic Solothurn, Switzerland). The data given are the mean of at least 5 tablets. Disintegration time was measured using the Eur. Pharm. procedure without disks. Water at 37 °C was used as a test medium. The data given are the mean of at least 5 measurements.

Results and Discussion

In the previous study (Vromans et al., 1987), different sieve fractions of α-lactose monohydrate, suspended in solutions of lactose, were spray-dried in order to obtain products with various amorphous lactose contents. The compactibility of the samples appeared to be a function of both the primary particle size and the amount of amorphous lactose. The effect of these parameters on disintegration time is represented in Table 1 for tablets compressed at 75 MPa. It can be noticed that the disintegration time increases both with the size of the primary particles and the amorphous lactose content. The effect of compaction pressure on disintegration is given in Fig. 1. The disintegration time increases considerably on compaction for tablets with 15% or 30% amorphous lactose. Moreover, it can be observed that the disintegration mechanism changes gradually from real disintegration for tablets compressed at low compaction pressure to dissolution at pressures of 150 or 225 MPa. Tablets compressed from samples with a high amorphous lactose content dissolve slowly. With these products, the disintegration time appears to be hardly affected by the compaction load. A similar finding has been reported by Khan and Rhodes (1976) in an investigation of tablets, prepared from commercially available spray-dried lactose. The deleterious effect of the amorphous

TABLE 1

Disintegration time of tablets from spray-dried lactose with different amorphous lactose contents, prepared from sieve fractions of α-lactose monohydrate. Compaction pressure 75 MPa

Size of the primary particles (μm)	Disintegration time (s) ± S.D.			
	Percentage amorphous lactose			
	15	30	50	75
1– 8	56 ± 10	112 ± 12	562 ± 23	671 ± 10
8–16	52 ± 6	192 ± 25	629 ± 23	638 ± 14
16–24	56 ± 5	383 ± 30	645 ± 20	577 ± 13
24–32	35 ± 2	540 ± 14	613 ± 14	565 ± 16
32–45	289 ± 8	636 ± 15	658 ± 21	573 ± 16

component on the disintegration of tablets of spray-dried lactose can be explained by pointing to the dissolution behaviour of amorphous lactose in water. The initial solubility of amorphous lactose is higher than that of any crystalline lactose. When the amorphous substance is moisturized,

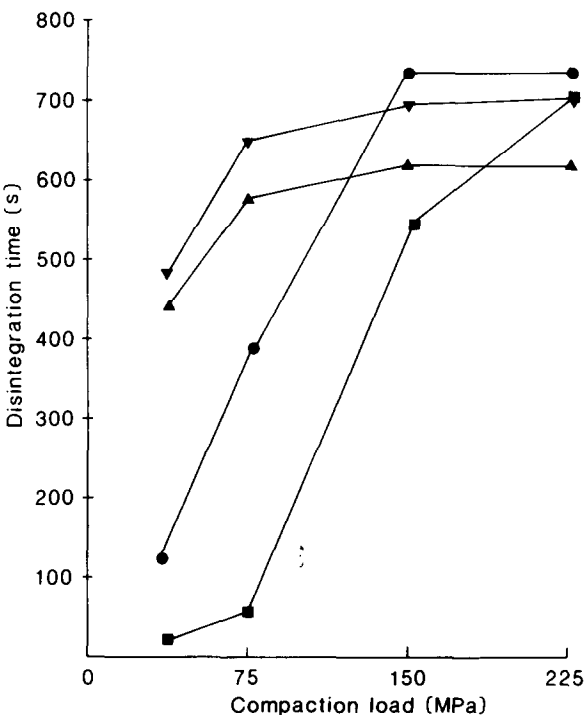

Fig. 1. Effect of percentage amorphous lactose on the disintegration time of spray-dried lactose tablets at different compaction load levels. ■, 15%; ●, 30%; ▼, 50%; and ▲, 75% amorphous lactose.

the outer layer of the powder bed dissolves forming a viscous gel, which includes the crystallization of lactose. Consequently, the internal part of the powder is mostly not wetted. For this reason, it is obvious that the penetration of water into tablets will be hindered by high percentages of amorphous lactose. With tablets containing less glass, the effect will depend on pore size; on increasing compaction load there is a shift towards a smaller mean pore size (Vromans et al., 1985b, 1986). In small pores the water penetration rate is slow and the surface area is relatively large. As a consequence of this the amorphous lactose will dissolve and crystallize sooner, thus increasing the disintegration time.

In fact similar considerations apply regarding the effect of primary particle size on disintegration (Table 1). In previous work (Vromans et al., 1986, 1987), it was concluded in the case of spray-dried lactose that the amorphous part of the products forms a binding layer on the crystalline particles. At a fixed percentage of amorphous lactose, the thickness of the layer will depend on the primary particle size. In Fig. 2 the disintegration time of tablets compacted at 75 MPa is depicted as a function of the calculated thickness of the amorphous lactose layer, derived from the permeametry surface area S_v (Vromans et al., 1987) and the amorphous lactose content, where it is assumed that the glass is proportionally distributed over the particle surface. The figure clearly illustrates the relation between the thickness of the layer and the disintegration time. It is obvious that there is a direct relationship until dissolution of the tablet becomes the predominant mechanism of disintegration.

Previously it was found that water penetration into tablets and hence the disintegration time can considerably be enhanced by the incorporation of a suitable disintegrant (Van Kamp et al., 1986c). The effectiveness of the disintegrant strongly depends on the dissolution properties of the tablet ingredients (Van Kamp et al., 1986b and c). In Figs. 3 and 4 the effect of 3 different disintegrants on the disintegration time is given for tablets compressed from spray-dried lactose (manufactured from primary particles of 16–24 μm) with different amorphous lactose contents. When com-

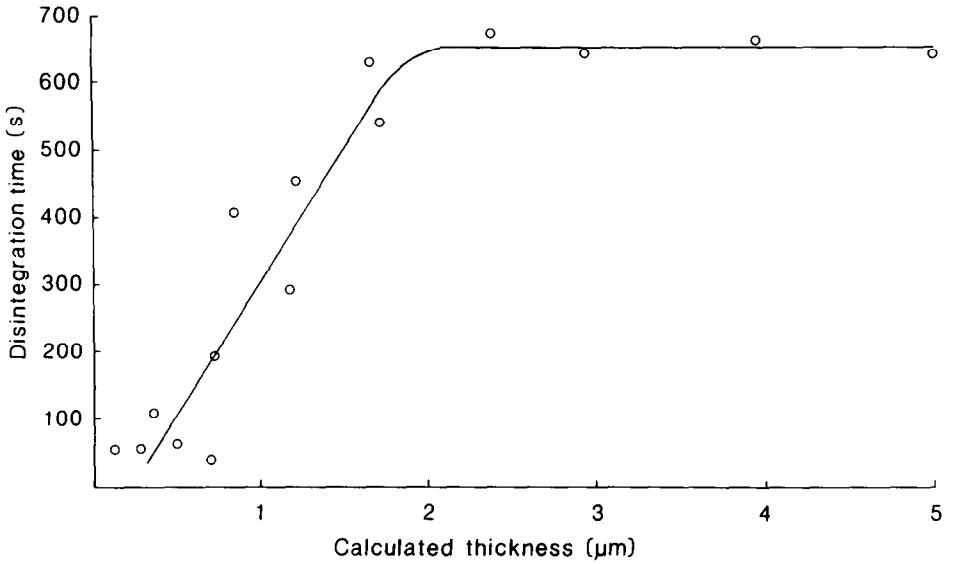

Fig. 2. Effect of calculated thickness of the amorphous layer upon the primary particles on the disintegration time of spray-dried lactose tablets, compacted at 75 MPa.

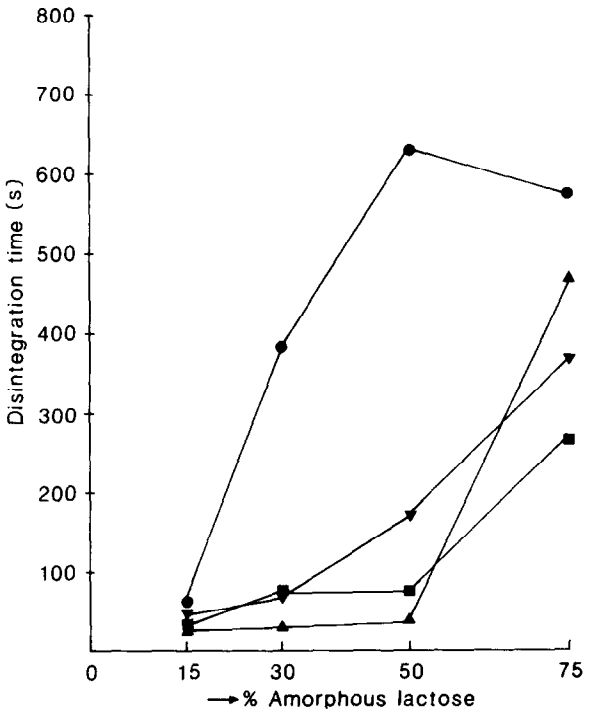

Fig. 3. Effect of different disintegrants (4%) on the disintegration time of tablets compressed from spray-dried lactose with a primary particle size of 16–24 μm and different amorphous lactose content at 75 MPa. ●, without disintegrant; ▲, crospovidone; ▼, sodium starch glycolate; ■, croscarmellose sodium.

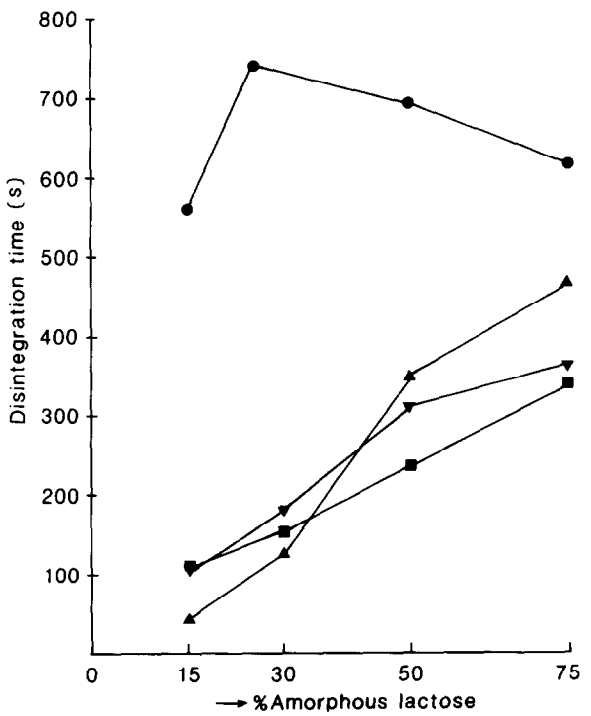

Fig. 4. Effect of different disintegrants (4%) on the disintegration time of tablets compressed from spray-dried lactose with a primary particle size of 16–24 μm and different amorphous lactose content at 150 MPa. Symbols as in Fig. 3.

pressed at 75 MPa (Fig. 3), a short disintegration time could be obtained with all disintegrants at percentages of glass lower than 50%. At 150 MPa (Fig. 4), however, the disintegration times already increase at lower percentages. It is obvious that crospovidone is the most effective disintegrant for tablets with a small amount of amorphous lactose. This may be caused by the typically capillary action of crospovidone, which allows a very rapid progress of the penetration front in the tablets (Van Kamp et al., 1986b). In the large pores of tablets compressed at low loads, the rate of water uptake will be larger than the dissolution rate of amorphous lactose. Similar results were found previously in the case of roller-dried β-lactose with crospovidone as a disintegrant (Van Kamp et al., 1986b). Figs. 3 and 4 show, however, that an increase in compaction load or amorphous lactose content decreases the effectiveness of the disintegrant. Both effects enhance the dissolution and gelling effect of amorphous lactose in such a way that it cannot be counteracted by crospovidone. At high amorphous grades, the penetration of water will be stopped completely so that the disintegration time will be mainly determined by dissolution of lactose from the outside of the tablets, just as it was found in a previous study on anhydrous α-lactose (Van Kamp et al., 1986b). Croscarmellose sodium was found to be the most effective disintegrant. This is most probably caused by a combination of capillary action of the fibrous particles and the moderately swelling capacity of the disintegrant (Van Kamp et al., 1986b).

The commercially available spray-dried lactose DCLactose 11 commonly contains about 15% amorphous lactose. This quantity was found to increase compactibility considerably (Vromans et al., 1986). Table 2 lists crushing strength and disintegration time of tablets compressed from the commercial product and from its mixtures with disintegrants, both lubricated and unlubricated, respectively. The tablets were compressed at two different compaction pressures. As could be expected from the data in Fig. 1, the disintegration times of unlubricated tablets strongly depend on the compaction load. Obviously, the water penetration is so fast at low compaction pressure, that the tablets disintegrate before a gel or precipitate could block up the pores. At higher loads, dissolution, gelling and precipitation will dominate. This process is more pronounced in the case of lubricated tablets, where the rate of water penetration is also decreased by the high contact angle of the lubricant-coated pore walls (Van Kamp et al., 1986c). Table 2, however, shows that the disintegration time can be decreased by the incorporation of a disintegrant. Although short disintegration times were obtained with all disintegrants used, it is evident that crospovidone was the most effective one, which could be expected from the results depicted in Figs. 3 and 4.

TABLE 2

Crushing strength and disintegration time of tablets compressed from commercially available spray-dried lactose (DCLactose 11) or DCLactose 11/disintegrant blends, both unlubricated and lubricated with 0.5% magnesium stearate

	Compaction pressure (MPa)	Cr. strength (kg)		Disintegr. time (s)	
		unlubr.	lubr.	unlubr.	lubr.
no disintegrant	75	7.3	4.4	30	720
	150	13.5	8.6	504	> 900
4% sodium starch glycolate	75	6.7	3.4	30	33
	150	12.1	7.0	79	62
4% croscarmellose sodium	75	7.2	2.6	39	43
	150	12.0	6.6	73	62
4% crospovidone	75	7.5	4.4	17	19
	150	14.0	9.6	39	32

In conclusion, the disintegration time of spray-dried lactose tablets depends on primary particle size, amorphous lactose content and compaction load, respectively. Although amorphous lactose has a strong intrinsic negative effect on tablet disintegration, this can easily be counteracted by the incorporation of a suitable disintegrant, particularly when the amorphous lactose content is rather low as in the case of commercially available spray-dried lactose.

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