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Effect of binder on the relationship between bulk density and compactibility of lactose granulations

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Abstract

The effect of a binder on the relationship between the bulk density and compactibility of lactose granulations was studied by comparing binderless granules with granules containing hydroxypropylcellulose. Granulations were prepared from different grades of α-lactose monohydrate and anhydrous β-lactose, respectively, using two different wet granulation techniques. The results show that the effect of the binder on tablet strength is independent of the type of lactose used, but is significantly influenced by the consolidation and compaction behaviour of the lactose particles. The effectivity of the binder increases with a decrease of the bulk density of the granule powder bed. Tablets with a high crushing strength can be prepared from porous granules, containing a binder.

Keywords: Granulation; Bulk density; Binder; Consolidation; Compaction; Porosity; Lactose

1. Introduction

A large number of papers have discussed the relationship between granule porosity and the strength of tablets, compressed from these granules. Wikberg and Alderborn (1991, 1992a,b) found an increased tablet strength with increasing intragranular porosities for granulations prepared from lactose and a high dosage drug, respectively, by wet granulation in a high shear mixer with polyvinylpyrrolidone as a binder. Using an air permeability technique, lubricant sensitivity measurements and granule strength measurements, the authors demonstrated that increased granule porosity increased the degree of fragmentation and deformation/densification during the compaction process. The change in volume reduction behaviour affected the intergranular pore structure of the tablet, which governed the strength of the compact.

In other studies, however, no influence, or even a negative effect of granule porosity on tablet strength was reported (Healey et al., 1973; Veillard et al., 1982). Gamlen et al. (1982) and Ragnarsson and Sjögren (1982) compared the properties of granules prepared in a fluid bed and by wet massing, respectively. The higher compactibility of the more porous granules, pre-

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pared by fluidized bed granulation was ascribed to differences in binder distribution. On the other hand, Alderborn (1988) stated that the effect of binder distribution can only slightly be affected when using common granulation techniques such as fluid bed granulation and high speed mixers. Using a two-step granulation procedure, which resulted in a different binder distribution, Wikberg and Alderborn (1993) showed that a high granule porosity, in combination with a homogeneous intragranular binder distribution is advantageous for the compactibility of a granulation.

As the presence of a binder will affect both physical granule properties and the consolidation and compaction behaviour of granules, in a previous paper of the present authors the relationship between granule properties and their compactibility was studied for granules, prepared without a binder (Zuurman et al., 1994). It was found that the compactibility of binderless lactose granules, prepared by wet granulation with water as granulation fluid or by dry granulation is, in addition to the type of lactose used and the granule particle size, dependent on the bulk density of the granule powder bed. An increase in granule powder bulk density resulted in a decrease of its compactibility. It was shown that the differences in bulk densities, introduced by using different lactose starting materials and different granulation methods, were mainly caused by differences in the intragranular porosities. Compression of granules with a high intragranular porosity resulted in tablets with a small average pore diameter and a high crushing strength. This effect was attributed to an increased deformation potential as compared to granules with a low intragranular porosity.

As both the presence of a binder in a granulation and the introduction of a high intragranular porosity will enhance its compactibilty, it is of interest to single out their respective effects. The objective of the present paper was to evaluate the effect of a binder on the relationship between the bulk density and compactibility of lactose granulations by comparing binderless granules with granules containing hydroxypropylcellulose. The granulations were prepared by two different wet granulation techniques from several ungranulated types of α-lactose monohydrate and roller-dried β-lactose, respectively. In order to minimize the effect of binder distribution on the compactibility of the granules, granulation and drying techniques giving a uniform binder distribution were used (Alderborn, 1988). The effect of granule particle size on compactibility was excluded by taking one granule fraction for all the experiments.

2. Materials and methods

Different grades of ground α-lactose monohydrate and roller-dried β-lactose were supplied by DMV (Veghel, The Netherlands). Hydroxypropylcellulose, type EXF was obtained from Aqualon (Rijswijk, The Netherlands).

Granules were prepared from the lactose powders by two different granulation techniques:

2.1. Granulation in a high shear mixer granulator

1940 g lactose powder was mixed with 3% hydroxypropylcellulose in a high shear mixer granulator (Gral 10, Machines Colette, Wommelgem, Belgium) at an impeller speed of 600 rpm and a chopper speed of 3000 rpm for 2 min. Next, water was added using a peristaltic pump at a flow rate of 25 ml/min over a period of 10 min. After continued mixing for 2 min, the moist mass was passed through a 2 mm screen of an oscillating granulator (Erweka AR 4000, Erweka, Heusenstamm, Germany). The granules were dried for 16 h in a ventilated hot air oven at 50°C and rescreened through a 0.7 mm screen.

2.2. Fluid-bed granulation

Lactose powder was granulated in a fluid-bed granulator (Strea-1, Aeromatic, Bubendorf, Switzerland) with a 3% hydroxypropylcellulose solution in water. The granulation fluid was sprayed onto the powder mass using a two fluid nozzle at a flow rate of 15 ml/min, until 3% hydroxypropylcellulose (calculated as dry powder) was added. The granules were dried and rescreened as described above.

Granule bulk density was measured as previously described (Zuurman et al., 1994). The intragranular porosity of granule particles was measured using an Autopore II 9220 mercury porosimeter (Micromeretics, Norcross, GA, USA). Pores < 13.5 μm were assumed to be located in the granule particles.

Tablet preparation and measurement of crushing strength were performed as previously described (Zuurman et al., 1994).

3. Results and discussion

Table 1 shows the crushing strength of tablets, compacted from granule fractions (212–425 μm) prepared from α-lactose monohydrate and roller-dried β-lactose, respectively. The granules were prepared using two different wet granulation techniques without a binder and with 3% hydroxypropylcellulose, respectively. Moreover, Table 1 lists the bulk densities of the lactose granulations both without and with binder.

Just as could be expected, the presence of a binder resulted in an increased crushing strength of the tablets, as compared with tablets without binder. The bulk density was generally lower for granule fractions containing a binder, particularly for granulations prepared from roller-dried β-lactose.

The relationship between the bulk density of the granulations and the crushing strength of tablets, compressed from the different granulations, is plotted in Fig. 1, completed with data for binderless granules from previous work (Zuurman et al., 1994). Fig. 1 shows that the crushing strength of tablets, prepared from granules containing a binder, depends on the granule powder bulk density, just as has been found previously for binderless lactose granules (Zuurman et al., 1994). Even when a binder is present in the granulation, there is a relationship between the bulk density of the powder bed and the tablet strength, irrespective the particle size distribution of the starting material used and the method of granulation. Neither the presence of a binder nor the granulation method affects the difference in compactibility between α-lactose monohydrate and roller-dried β-lactose. For both types of lactose, the increase in tablet crushing strength as an effect of the presence of the binder is correlated to the granule bulk density.

In previous work, it was shown that differences between bulk densities of binderless lactose granulations are mainly caused by differences in their intragranular porosities (Zuurman et al., 1994). A

Table 1
Granule powder bulk density and compactibility of granule fractions (212–425 μm), prepared from α-lactose monohydrate and roller-dried β-lactose, respectively

Starting material	Granulation method	Without binder		With binder	
		ρ_d (g/cm^3)	C_s (N)	ρ_d (g/cm^3)	C_s (N)
α-Lactose monohydrate					
150 mesh	high-shear mixer	0.52	40	0.51	79
	fluid bed	[a]	[a]	0.42	99
350 mesh	high shear mixer	0.47	50	0.47	82
	fluid-bed	[a]	[a]	0.39	106
450 mesh	high shear mixer	0.51	37	0.48	75
	fluid-bed	0.43	54	0.38	124
Roller-dried β-lactose					
150 mesh	high-shear mixer	0.65	71	0.52	135
	fluid-bed	[a]	[a]	0.40	160
450 mesh	high shear mixer	0.60	74	0.51	128
	fluid-bed	0.40	124	0.35	178

[a] Could not be granulated.
ρ_d, bulk density of the granule fractions; C_s, tablet crushing strength.

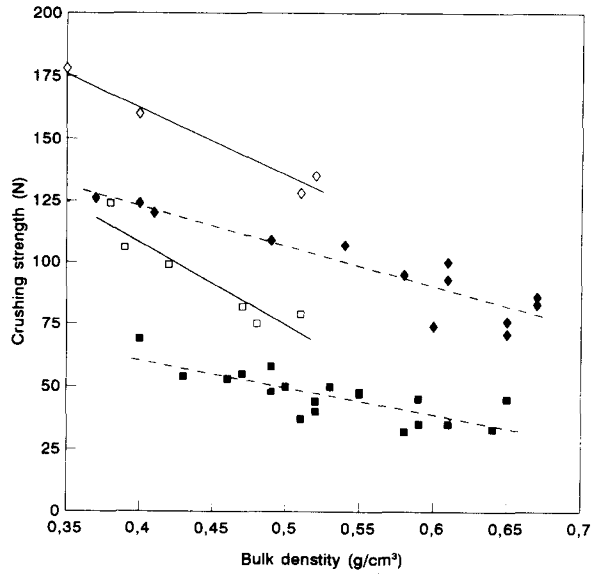

Fig. 1. Crushing strength of tablets, compressed from different lactose granule fractions (212–425 μm) vs the bulk density of the granulations before compression. The granulations were prepared without binder (closed symbols) or with hydroxypropylcellulose as a binder (open symbols) by two different wet granulation techniques from α-lactose monohydrate (□,■) and roller-dried β-lactose (◇,◆) powders, respectively.

relationship has been found between intragranular granule porosity and tablet crushing strength for binderless granulations prepared from lactose (Zuurman et al., 1994) and microcrystalline cellulose (Johansson and Alderborn, 1994), respectively. Table 2 lists both the total porosity of the powder bed and intragranular porosity of the different lactose granulations, prepared without and with binder, respectively. The intragranular porosity of granulations with binder was generally lower than that of binderless granulations, in spite of the increased total porosity of the powder bed. As it may be expected that addition of a binder has a limited effect on the intergranular porosity of the granulations, it must be assumed that the data for the intragranular porosity are too low for granules containing binder. A part of the pores may be closed by the binder film and cannot be intruded by mercury. This is consistent with the results of Wikberg and Alderborn (1992b), where a discrepancy was found between the total volume of mercury which penetrated compacts, prepared from granules with binder and the total pore volume calculated from the weight and dimensions of the compact.

A partial closure of the intragranular pores would be the reason that, in contrast to binderless granules, no relationship was found between the measured intragranular porosity of granules containing binder (Table 2) and the crushing strength of tablets, prepared from these granules (Table 1). The total porosity or bulk density of a granule bed, measured by volumetric measuring a

Table 2
Total porosity of the granule bed and intragranular porosity of lactose granule fractions (212–425 μm), prepared without and with binder, respectively

Starting material	Granulation method	Without binder		With binder	
		ϵ_{total}	ϵ_{intra}	ϵ_{total}	ϵ_{intra}
α-Lactose monohydrate					
150 mesh	high-shear mixer	0.66	0.17	0.67	0.13
	fluid bed	–	–	0.73	0.08
350 mesh	high shear mixer	0.69	–	0.69	0.18
	fluid-bed	–	–	0.75	0.16
450 mesh	high shear mixer	0.67	0.29	0.69	0.18
	fluid-bed	0.74	0.33	0.75	0.22
Roller-dried β-lactose					
150 mesh	high-shear mixer	0.65	0.15	0.67	0.15
	fluid-bed	–	–	0.75	0.17
450 mesh	high shear mixer	0.62	0.17	0.68	0.12
	fluid-bed	0.75	0.37	0.78	0.30

ϵ_{total}, total porosity of the granule powder bed; ϵ_{intra}, intragranular porosity.

weighed quantity, includes the real intragranular and intergranular porosities. Therefore, in contrast to the intragranular porosity, it is correlated with the compactibility, both for binderless granules and for granules containing a binder (Fig. 1).

Fig. 1 shows for both types of lactose that the effectivity of the binder is related to the porosity of the granules before compaction. This effect can be explained by the differences in consolidation and compaction behaviour of lactose granules with different porosities. Granules with a high intragranular porosity show more marked fragmentation and deformation/densification during compression than granules with a lower porosity and a higher strength (Wikberg and Alderborn, 1991, 1992a; Zuurman et al., 1994). This increased fragmentation and deformation of the granules leads to the formation of smaller intergranular pores in the tablet and a reduced intergranular separation distance. As intergranular attraction is weaker than intragranular attraction, lactose tablets tend to fail between the granules rather through them under mechanical stress. Fragmentation and deformation of lactose granules with a high intragranular porosity will improve the tablet strength by both a decreased granule separation distance and an increased external surface of the granules. The presence of a binder at the intergranular interface improves both the plasticity of the mass and interparticulate bonding, and will contribute to the additional tablet strength as compared with tablets without a binder. An optimal effect of the binder will be obtained for granules with a high intragranular porosity, because fragmentation and deformation during compression leads to a small granule separation distance and an increased intergranular surface area over which the binder can act.

In conclusion, the present results show that the effectivity of hydroxypropylcellulose in lactose granules on tablet strength is independent on the type of lactose used but is significantly influenced by the consolidation and compaction behaviour of the lactose particles. The effectivity of the binder increases with a decrease of the bulk density of the granule powder bed. Tablets with a high crushing strength can be prepared from porous granules, containing a binder.

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