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Research Papers

The relationship between bulk density and compactibility of lactose granulations

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Summary

The relationship between the bulk density and the compactibility of lactose granulations was studied. The granulations were prepared from different α-lactose monohydrate and roller dried β-lactose powders by wet granulation, using different techniques with only water as a binder, or by slugging. The results demonstrate that by the process of granulation of one lactose powder, granules with different bulk densities and different compactibilities can be prepared. In addition to the type of lactose used, the compactibility of the granule fractions is dependent on the bulk density of the granule fraction. Generally, with an increase of the bulk density, the compactibility of a granule fraction decreases. Little variation is observed between the intergranular porosities of the granule fractions. More differences are found between the intragranular porosities of the granule fractions. However, the compactibility of granule fractions of one lactose type is mainly determined by the total porosity of the granule powder bed. Mercury porosimetry determinations on tablets compacted from the granule fractions show a relationship between the tablet pore system and the compact strength: compression of granulations with a low bulk density results into tablets with a small average pore diameter and a high crushing strength. Obviously, the possibility to deform a granule fraction during compression, the deformation potential, is determined by the total porosity of the powder bed. A high deformation potential, i.e., a high compactibility, can be obtained by using a granulation procedure in which granulations with a low bulk density are produced.

Introduction

Lactose is a widely used excipient of which different types and fractions are available. Spray dried lactose, roller dried β-lactose, agglomerated lactose (Tablettose®) and coarse, regular grade sieved crystalline fractions of α-lactose monohydrate are used as filler-binders in tablets, prepared by direct compression. Ground fractions of α-lactose monohydrate, in particular the 200 and 450 mesh qualities, are commonly used as a filler in tablets, prepared by wet granulation. The consolidation and compaction properties of both lactose powders and physical mixtures have been studied previously (Vromans, 1987; Riepma et al., 1990, 1991, 1992). During granulation, the particles of the powder will agglomerate to coarser units with a different structure from the starting

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particles. This may have implications for their consolidation and compaction properties. In spite of the large number of publications on this subject, the effect of the physical properties of lactose granules on their compactibility has not been fully elucidated. Moreover, most studies are focussed on type and concentration of binders.

It has frequently been reported that the process conditions during wet granulation can affect the compactibility of the granulation. Rue et al. (1980) produced three paracetamol granulations with Protein S as a binder using different granulation methods. Roller-compacted granules showed the lowest compactibility, wet massed granules gave tablets with intermediate strength whereas the highest compactibility was found for granules prepared by spray drying. Gamlen et al. (1982) compared the structure of paracetamol granules, prepared by fluidized bed granulation and by wet massing. The fluidized bed granules were more porous than the wet massed granules. Moreover, tablets prepared from the fluidized bed granules were stronger than tablets from the wet massed granules for any compaction pressure or tablet porosity. In both studies, the differences in tablet strength were explained by differences in binder distribution.

In addition to type, concentration and distribution of binder, physical characteristics of granules, such as size, shape, strength and porosity are of interest as they can affect the compactibility of the particulate mass. Alderborn et al. (1987) found a correlation between fragmentation propensity of granules prepared of a high dosage drug with pvp as a binder and the tensile strength of tablets. This was explained by assuming that the fragmentation of the granules during compression increased the surface area available for intergranular attraction and thereby increased the tensile strength of the obtained tablets. In further work Wikberg and Alderborn (1991) showed that granule fragmentation during compaction was related to granule porosity before compaction. A granulation with a higher porosity had a higher fragmentation propensity, which resulted in stronger tablets.

The effect of the presence of a binder will affect both physical granule properties and the consolidation and compaction behaviour of the granules. This means that fundamental relationship between physical properties of granules and their compactibility may be complicated by the presence of a binder and can better be studied using granulations, prepared without a binder. In only few studies, however, granules without binder have been studied. Ganderton and Selkirk (1970) studied the effect of granule properties on the pore structure of tablets of sucrose and lactose. The degree to which inter- and intragranular pore structure within the tablets was sustained was found to be dependent on bulk density, size and strength of the granules. Ganderton and Hunter (1971) produced binderless granules of lactose and calcium phosphate, respectively by pan granulation and by massing and screening. It was found that increase in both moisture content and time of mixing increased granule density, i.e., decreased the intragranular porosity of the granules.

In a previous paper, Riepma et al. (1993) discussed the consolidation and compaction properties of lactose granules prepared from sieve fractions of α-lactose monohydrate and roller dried β-lactose, respectively, by dry granulation (slugging). The results demonstrated that the compactibility of the granule fractions was determined by the primary properties of the lactose powder, the granule size and the compaction force. Differences in physical properties between the granule particles, such as porosity and strength, were eliminated during compaction and were not found to affect the compactibility. It was shown that consolidation of the granule particles involved both intra- and intergranular porosity changes. Mercury porosimetry determinations on tablets compacted from the granule fractions revealed that the whole pore system determined compact strength. The observed differences in compactibility between the granules of the two lactose types were suggested to be caused by differences in the internal granular structure.

The objective of the present paper was to evaluate the relation between the bulk density and the compactibility of lactose granulations. The granulations were prepared by several wet granulation techniques or by dry granulation

(slugging) from several ungranulated powders of two types of crystalline lactose: α-lactose monohydrate and roller dried β-lactose, respectively. To exclude the effect of a soluble binder the wet granules were prepared with only water as a binder.

TABLE 1

Granule powder bulk density and compactibility of ungranulated powders of α-lactose monohydrate and roller dried β-lactose, respectively, and of granule fractions (125–250 and 212–425 μm) prepared from the powders

Starting material	Granulation method	Percentage of water used	Granule Fraction (μm)	ρ_d (g/cm^3)	C_s (N)
α-Lactose monohydrate					
250–300 μm	ungranulated		–	0.79	41
	slugging (5 kN)		212–425	0.58	32
	slugging (20 kN)		212–425	0.61	35
	slugging (40 kN)		212–425	0.64	33
150 mesh	ungranulated		–	0.66	49
	high shear mixer		212–425	0.52	40
200 mesh	ungranulated		–	0.47	56
	planetary mixer	11.4	125–250	0.49	58
	planetary mixer	15	125–250	0.53	50
	planetary mixer	20	125–250	0.55	48
	planetary mixer	22.5	125–250	0.55	47
	rotating dish		125–250	0.59	45
350 mesh	ungranulated		–	0.49	70
	planetary mixer	11.4	125–250	0.46	63
450 mesh	ungranulated		–	0.43	79
	planetary mixer	11.4	125–250	0.40	69
	planetary mixer	15	125–250	0.47	55
	planetary mixer	20	125–250	0.50	50
	rotating dish		125–250	0.49	48
	fluid-bed		212–425	0.43	54
	high shear mixer		212–425	0.51	37
	slugging (5 kN)		212–425	0.52	44
	slugging (20 kN)		212–425	0.59	35
	slugging (40 kN)		212–425	0.65	45
Roller dried β-lactose					
250–300 μm	ungranulated		–	0.65	96
	slugging (5 kN)		212–425	0.58	95
	slugging (20 kN)		212–425	0.61	93
	slugging (40 kN)		212–425	0.65	76
150 mesh	ungranulated		–	0.56	111
	high shear mixer		212–425	0.65	71
450 mesh	ungranulated		–	0.46	132
	fluid-bed		212–425	0.40	124
	high shear		212–425	0.60	74
	slugging (5 kN)		212–425	0.54	107
	slugging (20 kN)		212–425	0.61	100
	slugging (40 kN)		212–425	0.67	86
< 450 mesh	ungranulated		–	0.44	136
	planetary mixer	11.4	125–250	0.37	127
	planetary mixer	15	125–250	0.41	120
	planetary mixer	20	125–250	0.49	109
	rotating dish		125–250	0.67	83

Granulations were prepared by wet granulation, with water as a binder, or by dry granulation. Tablets were compressed at 20 kN. ρ_d, bulk density of the granule fractions; C_s, tablet crushing strength.

Materials and Methods

The materials used were different powders of α-lactose monohydrate and roller dried β-lactose, respectively, supplied by DMV (Veghel, The Netherlands).

All handling was performed at constant temperature (20 ± 1°C) and constant relative humidity (45 ± 5%).

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

Wet massing in a planetary mixer Ungranulated lactose powder was mixed with water in a planetary mixer (KM 250, Kenwood Ltd, Hants, U.K.) using a peristaltic pump with a flow rate of 10 ml/min. The moist mass was passed through a 2 mm screen of an oscillating granulator (model MG400, Frewitt, Fribourg, Switzerland). The granules were dried for 16 h in a ventilated hot air oven and rescreened through a 0.7 mm Frewitt screen.

Wet massing in a high shear mixer Ungranulated lactose powder was mixed with water in a high shear mixer granulator (Gral-10, Machines Colette, Wommelgem, Belgium) at an impellor speed of 650 rpm and a chopper speed of 3000 rpm. The moist mass was screened, dried and rescreened as described above.

Wet massing in a rotating dish Ungranulated lactose powder was granulated with water in a rotating dish (Erweka GmbH, Mainz, Germany). The water was sprayed on the lactose using a two fluid nozzle. The moist mass was screened, dried and rescreened as described above.

Fluid bed granulation Ungranulated lactose powder was granulated with water in a fluid-bed granulator (Strea-1, Aeromatic, Bubendorf, Switzerland). Water was sprayed onto the powder mass using a two fluid nozzle at a flow rate of 10 ml/min. The moist mass was screened, dried and rescreened as described above.

Dry granulation by slugging 'Dry' granules were prepared by crushing flat-faced tablets (slugs) of 500 mg with a diameter of 13 mm using a pestle and a mortor. The slugs were compressed at a load of 5, 20 and 40 kN, respectively, using a programmable hydraulic press (ESH Testing Ltd, Brierley Hill, U.K.).

The bulk density of the ungranulated lactose powders and the granule fractions was measured by pouring about 50 g of the powder into a measuring glass cylinder. The data given are the means of six measurements.

The intragranular porosity of granule particles was measured by mercury porosimetry using the method described by Strickland et al. (1956). Pores < 13.5 μm were assumed to be located in the granule particles. The data are the means of two measurements.

The intergranular porosity of granule fractions was calculated from the true density of lactose (1.54 g/cm^3 for α-lactose monohydrate and 1.59 g/cm^3 for roller dried β-lactose), the bulk density of the granule fractions and the intragranular porosity.

Ungranulated lactose powders and granule fractions were compacted into 500 mg, 13 mm tablets with a force of 20 kN using a programmable hydraulic press (ESH Testing, Ltd, Brierley Hill, U.K.). If necessary the die was prelubricated with magnesium stearate.

Compact strength was determined 30 min after compaction with a Schleuniger 4M tester (Dr. Schleuniger Production AG, Solothurn, Switzerland). The presented data are the means of at least 10 compacts.

Pore size distributions of compacts were determined via mercury porosimetry (Carlo Erba series 2000 porosimeter). The compacts were evacuated at about 10 Pa prior to the measurement for at least 15 min. The values are the means of at least two compacts.

Results and Discussion

Table 1 shows the crushing strength of tablets, compacted at 20 kN from (ungranulated) α-lactose monohydrate and roller dried β-lactose powders, respectively, and from granule fractions (125–250 and 212–425 μm) prepared from these powders. The granules were produced by various wet granulation techniques with only water as a binder and by dry granulation (slugging), respectively. Moreover, Table 1 lists the bulk densities

of the lactose powders (starting materials) and the lactose granulations.

It can be seen that starting from one lactose powder, granulations with both very different compactibilities and bulk densities were prepared. This means that these differences were introduced as a result of the granulation process. For instance, the granule fractions (212–425 μm) prepared by fluid bed granulation from α-lactose monohydrate 450 mesh and roller dried β-lactose 450 mesh, respectively, show relatively lower bulk densities and relatively higher compactibilities as compared with the granules produced by a high shear mixer granulator or slugging. In addition, for granules prepared by wet massing in a planetary mixer, an increase in the amount of water used during the granulation step results in an increase in the granule powder bulk density and a decrease in the granule compactibility. The observed differences in compactibility between granules prepared in a fluid bed granulator, as compared with those produced by a high shear mixer granulator correspond with the results reported by Gamlen et al. (1982) and by Ragnarsson and Sjögren (1982). In these studies, the differences in compactibility were attributed to differences in binder distribution. From the results with the binderless lactose granules in Table 1 it is evident that other factors than binder distribution must be responsible for the differences in granule compactibility.

From Table 1 it is obvious that there might be a relationship between the bulk density of granulations and their compactibility. Therefore, in Fig. 1 the crushing strength of tablets, compressed from the different granulations listed in Table 1, has been plotted as a function of the bulk density of these granulations. Fig. 1 demonstrates that an increase in bulk density results in a decrease in the tablet strength. Remarkably, the granules prepared from one lactose type (α-lactose monohydrate or roller dried β-lactose) demonstrate the same relationship between the bulk density of the powder bed and tablet strength, irrespective of the particle size distribution of the starting material used and the method of granulation. Furthermore, it is shown that the compactibility of the granulations depends on the lactose type

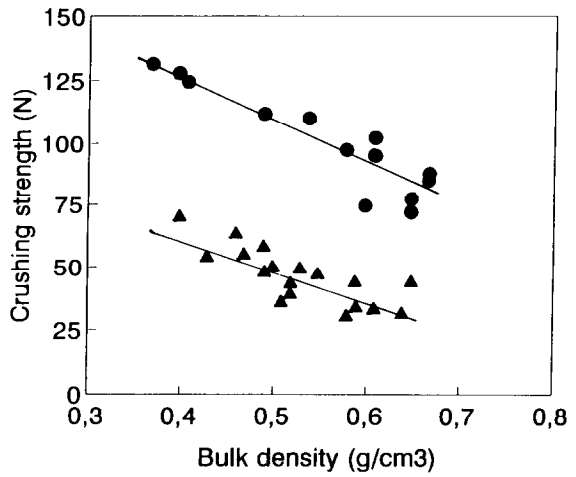

Fig. 1. Crushing strength of tablets compressed from different lactose granule fractions (125–250 and 212–425 μm) vs the bulk density of the granulations before compression. The granulations were prepared by wet or dry granulation from α-lactose monohydrate (▲) and roller dried β-lactose (●) powders, respectively.

used, consistent with previous findings (Riepma et al., 1993).

Fig. 2 depicts the relationship between compactibility, expressed as the tablet crushing

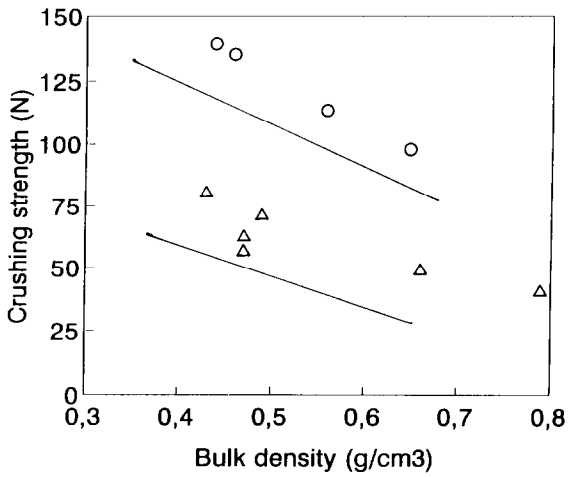

Fig. 2. Crushing strength of tablets compressed from different ungranulated α-lactose monohydrate (△) and roller dried β-lactose (○) powders, respectively, vs the bulk density of the powders. The lines refer to the relationships as shown in Fig. 1. (Upper line) Roller dried β-lactose; (lower line) α-lactose monohydrate.

strength, and the bulk density for the starting materials. The continuous lines in Fig. 2 refer to the relationship as shown in Fig. 1. As demonstrated by Fig. 2, the ungranulated powders of both lactose types show different bulk densities, which are caused by different particle size distributions. In addition, it is evident that for the ungranulated lactose powders the strength of the compacts also decreases as the bulk density of the starting material increases. Obviously, the compactibility of the ungranulated lactose powders is determined by both the lactose type used and the particle size distribution (Vromans et al., 1985; De Boer et al., 1986), as well as by the porosity of the powder bed. However, tablets compacted from the starting materials show higher strengths at a certain bulk density as compared with those compacted from the granule fractions. This result corresponds with the results of previous work (Riepma et al., 1991): the strength of tablets compacted from binary blends of a coarse fraction mixed with a finer fraction of α-lactose monohydrate was found to depend upon the bulk density of the powder mass. A high bulk density resulted in a low compactibility of the powder blends. This result was explained by a decreased fragmentation potential of the single particles within the powder mass.

Powder bulk density is a function of the true density of the material and the total porosity of the powder bed. For a bed of granules, the total porosity is determined by both the intergranular and the intragranular porosity. To evaluate the contribution of both porosities to granule powder bulk density, Table 2 presents the total porosity of several of the granule fractions (212–425 μm) prepared from the two lactose types, together with the inter- and intragranular porosity. For a number of granulations, prepared via slugging, the intragranular porosity was not determined by mercury porosimetry, but was calculated from the dimensions of the slugs and the lactose density. The data in Table 2 demonstrate relatively small differences between the intergranular porosities of the granule fractions, ranging between 0.49 and 0.60, irrespective the starting material and the method of granulation. These values agree well with the value of 0.50 as found for the intergranular porosity of lactose granules prepared by wet massing, as reported by Ganderton and Hunter (1971). In contrast, Table 2 shows considerable differences between the intragranular porosities of the granule fractions, dependent on the granulation procedure applied. For the granules, prepared by dry granulation, this variation is caused by different compression forces used for slugging. Due to a higher degree of densification, the intragranular porosity of granules prepared in a high shear mixer granulator is lower than that of granules prepared in a fluid bed granulator, in agreement with the work of Ganderton and Selkirk (1970).

Fig. 3 shows tablet crushing strength as a function of intragranular and intergranular porosity, respectively. The left-hand part of Fig. 3 shows that for α-lactose monohydrate the intragranular

TABLE 2

Total porosity of the granule powder bed, intergranular porosity and intragranular porosity of lactose granule fractions (212–425 μm)

Starting material	Granulation method	ϵ_{total}	ϵ_{inter}	ϵ_{intra}
α-Lactose monohydrate				
250–300 μm	slugging (5 kN)	0.62	0.51	0.23
	slugging (20 kN)	0.60	0.54	0.12
	slugging (40 kN)	0.58	0.55	0.08
150 mesh	high shear mixer	0.66	0.59	0.17
450 mesh	fluid-bed	0.72	0.58	0.33
	high shear mixer	0.67	0.54	0.29
	slugging (5 kN)	0.66	0.53	0.23
	slugging (20 kN)	0.62	0.57	0.12
	slugging (40 kN)	0.58	0.53	0.10
Roller dried β-lactose				
250–300 μm	slugging (5 kN)	0.64	0.49	0.29
	slugging (20 kN)	0.62	0.53	0.17
	slugging (40 kN)	0.59	0.54	0.11
150 mesh	high shear mixer	0.59	0.52	0.15
450 mesh	fluid-bed	0.75	0.60	0.37
	high shear mixer	0.62	0.53	0.17
	slugging (5 kN)	0.66	0.53	0.27
	slugging (20 kN)	0.62	0.55	0.16
	slugging (40 kN)	0.58	0.54	0.09

Granulations were prepared by wet granulation, with water as a binder, or by dry granulation.

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

porosity has little, if any, effect on tablet crushing strength. For roller dried β-lactose, however, it can be seen that an increase in the intragranular porosity leads to an increase in tablet crushing strength. From the right-hand part of Fig. 3 it must be concluded that the intergranular porosity of lactose granules has no marked effect on tablet crushing strength. On comparison of Figs 1 and 3, it is obvious that the compactibility of a granule fraction is related to the total porosity of the granule powder bed. However, differences between bulk densities of granulations are mainly caused by differences in their intragranular porosities.

A previous paper (Riepma et al., 1993) showed a relationship between the pore system of a tablet, determined via mercury porosimetry, and the tablet strength. Tablets were compacted from granule fractions prepared by slugging of various powders of α-lactose monohydrate and roller dried β-lactose, respectively. The results demonstrated that the tablet strength was related to the average pore diameter of the compacts. Generally, with an increase in the average tablet pore diameter, the crushing strength decreased. With respect to these results, Fig. 4 demonstrates the

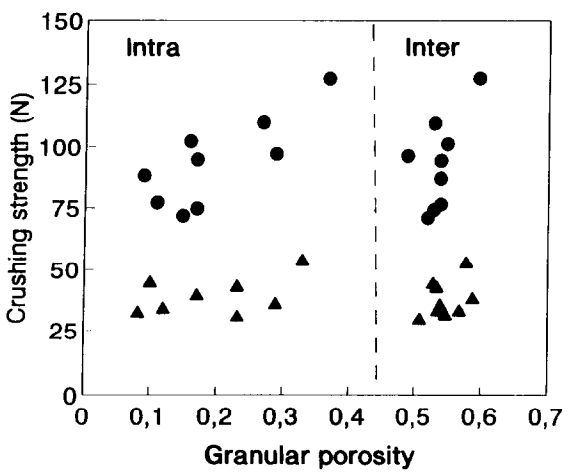

Fig. 3. Strength of tablets compressed from lactose granulations vs both the intragranular porosity (left) and the intergranular porosity (right) of the granule fractions (125–250 μm; 212–425 μm) before compaction. The granulations were prepared by wet or dry granulation from α-lactose monohydrate (▲) and roller dried β-lactose (●) powders, respectively.

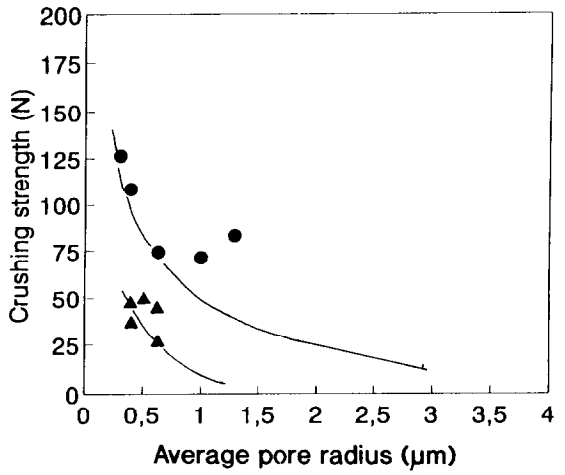

Fig. 4. Crushing strength vs the average pore radius of tablets compressed from granule fractions (212–425 μm) prepared by wet granulation from α-lactose monohydrate (▲) and roller dried β-lactose (●), respectively. The lines represent the relationships as observed for tablets compacted from slugs (Riepma et al., 1993) of α-lactose monohydrate (lower line) and roller dried β-lactose (upper line).

relationship between the strength and the average pore radius of tablets compacted at 20 kN from granule fractions (212–425 μm) prepared by wet granulation of the two lactose types. The lines in Fig. 4 represent the relationship as shown in a previous paper (Riepma et al., 1993) for tablets compacted from slugs. As can be observed, the data for the tablets compacted from granules prepared by wet granulation show a tendency similar to those found previously. Thus, the strength of tablets compacted from granule fractions prepared by wet granulation or slugging is related to the average tablet pore diameter.

In Fig. 5 the average tablet pore radii from Fig. 4 are plotted vs the bulk density of the granulations from which the tablets were compacted. As can be seen, the average pore diameter increases with an increase in the granule powder bulk density. Clearly, for both lactose types, the total porosity of the granulations affects the porous system within the tablets and hence tablet strength.

The results presented so far demonstrate that the possibility of deforming a granule fraction during compaction, defined as the deformation

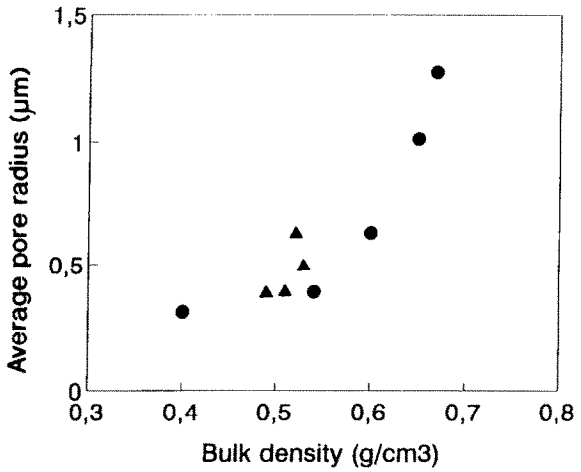

Fig. 5. Average pore radius of tablets compressed from granule fractions (212–425 μm) prepared by wet granulation from α-lactose monohydrate (▲) and roller dried β-lactose (●), respectively, vs the bulk density of the granulations before compression.

potential, increases with an increase in the total porosity of the granule bed. This involves a greater amount of space being available for the process of deformation, independent of the mechanism of deformation. However, from previous work, it is known that during compression the granule particles sustain their integrity to a large extent (Riepma et al., 1993). Therefore, the deformation of the individual granule particles within a granule bed can be considered as a sort of plastic behaviour, in which the internal mechanism involves rearrangement and fragmentation. For a granule powder bed, a high bulk density, i.e., a low porosity, will result in a low deformation potential: there is a lack of space for deformation of the granule particles during compression. As a consequence, less intimate contact between the granule particles within the tablets takes place, which results in weaker tablets. On the other hand, granule particles in a granulation with a low bulk density will deform more readily, resulting in tablets with a smaller average pore diameter and hence a higher crushing strength.

This work reveals that the compactibility of lactose granules, prepared by wet granulation with water as a binder or by dry granulation is, in addition to the type of lactose used and the granule particle size, dependent upon the bulk density of the granule powder bed. An increase in the granule powder bulk density results in a decrease in its compactibility. The bulk density of the granule fractions depends upon the size and shape of the starting materials and the method of granulation. Although the compactibility of a granule fraction is related to the total porosity of the granule powder bed, differences between bulk densities of granulations are mainly caused by differences in their intragranular porosities. Compaction of granules with a high bulk density produced tablets with a high average pore diameter and a low crushing strength. Therefore, for binderless lactose granulations, it is concluded that with an increase in the total porosity of a granule powder bed the deformation potential increases. A high deformation potential, i.e., high compactibility, can be achieved by using a granulation procedure, such as fluid bed granulation, in which granulations with a low bulk density are produced.

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