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Compression of Lactose, Glucose and Mannitol Granules

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Abstract

The effect of the amount of granulation liquid, compression speed and maximum compression force on the compressibility and compactibility of lactose, glucose and mannitol granules was studied. The porosity based on the geometrical shape and the uniformity of weight of tablets was also studied.

Lactose and mannitol granules showed a greater compressibility than glucose granules. Mannitol granules produced the hardest tablets and lactose and glucose the weakest. The change in the amount of granulation liquid caused changes both in the granule porosity and in the amount of binder; this was attributed to differences in tablet strength. All parameters studied were relatively insensitive to changing speeds of compression in the range used, except for the breaking force of mannitol tablets, which was greatest with the lowest speed of compression. All granule masses showed a relatively good continuous flow suitable for tablet production. Tablets compressed from lactose granules had the best uniformity of weight of the tablets studied.

In compression studies, the behaviour of powders in compression has been extensively studied. Lactose, one of the most common diluents, has been a popular subject (Fell & Newton 1971; Cole et al 1975; Vromans et al 1985; de Boer et al 1986; Riepma et al 1991). Compression of glucose (Duvall et al 1965; Henderson & Bruno 1970; Danielson et al 1983) and mannitol powders (Krycer et al 1982; Roberts & Rowe 1985; Bassam et al 1990) has also been investigated. Consolidation of lactose monohydrate powder has been shown to occur mainly by fragmentation (Hersey et al 1973). Mannitol powder has been characterized as moderately hard and ductile, and the compression has been reported to involve less fragmentation and more plastic deformation. Lactose monohydrate has been found to be a moderately hard, brittle and ductile material: its consolidation includes fragmentation and some plastic flow at contact points (Roberts & Rowe 1987). According to Bolhuis & Lerk (1973), glucose monohydrate tablets are harder than lactose tablets.

Several studies have been made on the compression of lactose, glucose and mannitol powders, but few studies deal with the compression of granules. However, granulation is a frequently used process in tablet production. Tablets compressed from granules are known to be stronger than those compressed from powders. Further advantages, resulting from granulation, are the better flowability and the homogeneity of tablet mass. Granulation also prevents segregation and minimizes dust. One probable reason for the lack of granule compression studies is the complexity of the granule system. In compression, granules rearrange and fragment into primary particles, and the resulting particles rearrange, fragment or deform plastically or elastically. These consolidation mechanisms may coexist. Thus, the properties of both the material and the granules play a role in compression of granules, and the effects of these two are indistinguishable.

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The compression behaviour of lactose granules has been studied (Higuchi et al 1954; Jarosz & Parrott 1983), especially the correlation between porosity of lactose granules and the compressibility and strength of tablets. According to Veillard et al (1982), the hardest lactose monohydrate tablets were produced from granules with a low total porosity. Contradictory results have been presented by Wikberg & Alderborn (1991), who stated that lactose granulation with a higher porosity had a higher fragmentation propensity, which resulted in higher mechanical strength of tablets. A similar response has also been detected by Zuurman et al (1994), who have studied the relationship between bulk density and compactibility of lactose granules. On the other hand, the differences in physical properties of lactose granules, such as porosity and strength have been found to be eliminated during compression, when granules produced by dry granulation were used (Riepma et al 1993).

Few papers have been published on the compression of glucose or mannitol granules. Krycer et al (1982) compared the compressibility of lactose and mannitol crystals and directly compressible granules prepared by irreversible agglomeration of ground particles in a rotary ball mill. Armstrong & Griffiths (1970) studied the effect of moisture on the compressibility of glucose monohydrate granules. No extensive comparative evaluation of lactose, glucose and mannitol granules in compression has been reported.

The objective of this study was to evaluate the compressibility and the compactibility of lactose, glucose and mannitol granules.

Materials and Methods

Granules

Tablets were compressed from granules prepared from

α-lactose monohydrate, anhydrous glucose and D-(−)-mannitol using 20% polyvinylpyrrolidone solution (90 or 120 mL kg^{-1}). Granulation was in a high-shear granulator (Fielder PMA 25/2G, T.K. Fielder Ltd, UK). The granulation process and resulting granule size distribution determined by sieving and granule porosities and pore size distribution determined by mercury intrusion porosimetry have been described previously (Juppo et al 1992; Juppo & Yliruusi 1994).

The flowability of granules was determined by an automatic flowability recorder (constructed at Orion Corporation, Orion-Farmos, Finland, but not commercially available) as the time (s) for 50 g of granules to flow through a standard orifice with a diameter of 10 mm. The test was performed in triplicate.

Before tableting, granules were sieved through a 2-mm sieve and mixed with 1% magnesium stearate (Breyer Chemie BV, The Netherlands) in a Turbula mixer (T10B, Willy A. Bachofen Ag. Maschinenfabrik, Switzerland) for 12 min at a speed of 33 rev min^{-1}.

Compression

The tablets were compressed with an instrumented rotary press (Kilian RU-24 II, Kilian & Co. GmbH, Germany) without a feeder, using bevel-edged flat punches 9 mm in diameter. Only two pairs of punches and no pre-compression were used. The target weight of tablets was 225 mg and the compression speeds used were 30, 47 and 64 rev min^{-1} and corresponded to the main compression time of approximately 65, 40 and 30 ms. The target values of maximum compression force were 4, 8, 12 and 16 kN for lactose and glucose tablets and 4, 8 and 12 kN for mannitol tablets. During tableting, the relative humidity varied from 17 to 27% and temperature from 23 to 26°C. The instrumentation and the software for the Kilian pilot-size rotary press were developed at Orion-Farmos, Finland. The force sensors were attached to the upper and the lower roll axis. The lower sensor was a strain gauge and the upper sensor a piezoelectric transducer. During compression, 500 data points were collected per turret revolution. The time interval between data points varied from 1 to 2 ms depending on the compression speed. The data collected from 40 compression events per batch was used for data analysis. The maximum values of compression force were calculated by the SAS system (SAS VAX/VMS Version 6.07, SAS Institute Inc., USA).

Tablet properties

The breaking force of tablets was used as a measure of compactibility of the granules compressed. The diametric breaking force (Erweka TBH 28, Erweka Apparatebau, Germany) was determined at least seven days after compression. Measurements were made from 20 tablets. The tablet weight was determined from 100 tablets (Mettler LV 10 Automatic Feeder, Mettler AE 200, Switzerland) and average tablet weight and weight variation were calculated. The porosity of the tablet (ϵ_1) based on the geometrical shape was calculated from the mean tablet weight (m), tablet volume (V) calculated from measured tablet diameter, and height and true density of granules (ρ_h) according to equation 1:

$$\epsilon_1 = \left(1 - \frac{\frac{m}{V}}{\rho_h}\right) \cdot 100\% \quad (1)$$

The diameter and the height of tablets for calculation of tablet volume were measured in triplicate with a micrometer (Micro 2000, M2025, Moore & Wright, UK). The true densities of the granules have been determined by helium pycnometry previously (Juppo & Yliruusi 1994).

The porosity of the granule bed before compression (ϵ_2) was calculated from bulk (ρ_b) and true densities (ρ_h) by equation 2:

$$\epsilon_2 = \left(1 - \frac{\rho_b}{\rho_h}\right) \cdot 100\% \quad (2)$$

Bulk density of granite bed was determined in a graduated cylinder in triplicate. The decrease in porosity of the granule bed ($\Delta\epsilon$) during compression was used to describe the compressibility of granules:

$$\Delta\epsilon = \epsilon_2 - \epsilon_1 \quad (3)$$

Error estimates for porosity of the granule bed and the tablet and for decrease in porosity were calculated according to Lyons (1991).

Statistical analysis

Analysis of variance and Fisher's protected least significant difference test as a post-hoc test were determined with the StatView statistical program for the Macintosh computer (Abascus Concepts, Inc., USA).

Results and Discussion

Compressibility of granules

A decrease in porosity of the granule bed in compression describes the ability of granules to consolidate. Reduction in porosity is due to rearrangement and fragmentation of granules and further rearrangement, fragmentation and possible plastic deformation of primary particles. According to Fig. 1, the compressibility of the lactose and mannitol granules is clearly greater than that of the glucose granules. Lactose granules and particles fragment easily. Good compressibility of mannitol granules is obviously caused by plastic deformation of porous granules in addition to fragmentation of granules. As reported previously (Juppo & Yliruusi 1994), the total volume of small (6·5 nm–14 μm) pores is extremely large in mannitol granules. The total volumes of small and large (14–220 μm) pores are nearly equal in mannitol and lactose granules, whereas the total pore volume of glucose granules is clearly smaller. Glucose granules have the largest granule size (Table 1) and largest bulk density (Juppo & Yliruusi 1994). Thus, the porosity of the glucose granule bed before compression is small. During compression, the glucose granule bed has less voids to be filled; hence the ability of granules to deform is smaller. The glucose granules consist of primary particles attached to each other. It is most probable, that these strong glucose granules break into primary particles during compression.

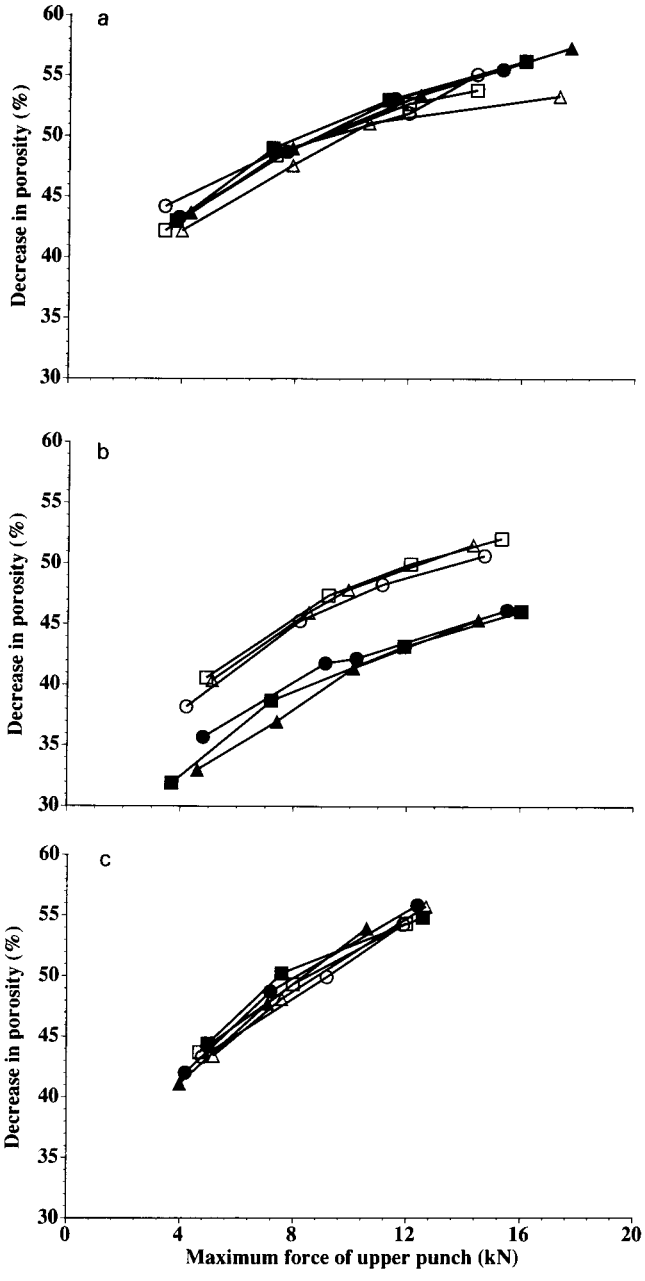

FIG. 1. Decrease in porosity of the granule bed according to compression force. a. Lactose, b. glucose, c. mannitol tablets. ■, ●, ▲, 90 mL kg^{-1}; □, ○, △, 120 mL kg^{-1}; □, ■, 30 rev min^{-1}; ○, ●, 47 rev min^{-1}; △, ▲, 64 rev min^{-1}. Relative errors are smaller than 3%.

The breaking of the dense structure of primary particles requires very high pressures. Therefore, glucose granules or resulting particles are also forced to deform plastically at their contact points.

The amount of granulation liquid has no evident influence on the compressibility of lactose and mannitol granules (Fig. 1a, c). Thus, the differences in bulk densities and porosities of granules prepared with these two amounts of liquid are eliminated in compression. However, the compression behaviour of glucose granules is highly dependent on the amount of liquid used in granulation (Fig. 1b). With increased amount of liquid, the average granule size increases and the size distribution of glucose granules becomes narrower (Table 1). The shape of the granules also becomes more cluster-like (Juppo et al 1992). This results in a lower bulk density (Juppo & Yliruusi 1994). Therefore, the glucose granule bed prepared with 120 mL kg^{-1} granulation liquid has larger voids to be filled during compression. This is why the decrease in porosity is greater in granules prepared with the larger amount of liquid.

Table 1. Granule size distribution of lactose, glucose and mannitol granules determined by sieve analysis (n = 3).

Diluent	Amount of granulation liquid (mL kg^{-1})	Size (%)		
		< 106 μm	< 300 μm	< 1000 μm
Lactose	90	22·4	86·8	95·6
	120	5·9	52·0	96·0
Glucose	90	0·3	53·9	96·6
	120	0·0	12·6	94·0
Mannitol	90	35·4	54·4	76·2
	120	25·7	43·1	67·8

Compression speed had no effect on the decrease in porosity with any granules in the range of speed studied. The decrease in porosity shows a linear relationship with compression force, especially for mannitol granules (Fig. 1c). A slight decrease in the slope for lactose and glucose granules is seen in Fig. 1a, b when tablets are compressed with a force of 12 kN or greater. When compressed with great forces, tablets become so near zero porosity that further densification requires still greater forces.

Porosity of tablets calculated from tablet dimensions

The porosity of mannitol tablets is clearly highest from the tablets compressed with the two lowest compression forces. When maximum compression force increases from 4 to 12 kN the porosity of the mannitol tablets decreases from 27 to 12%, whereas the corresponding decrease for lactose tablets is from 22 to 13% and for glucose tablets from 21 to 11% (Fig. 2). Compressed with a maximum force greater than 8 kN, glucose tablets are slightly more dense than lactose tablets. The glucose tablets compressed from the granules with two different amounts of binder solution have equal porosities. This supports the statement above that the difference in the magnitude of decrease in porosity is caused by the different original porosity of the glucose granule bed.

On the basis of this porosity parameter, no indisputable conclusion can be drawn on the effect of different granule properties resulting from the different amounts of granulation liquid on the porosity of tablets (Fig. 2). Also the effect of compression speed is undetectable in the speed range used in this study. Armstrong & Palfrey (1989) have found that with increasing speed the porosity calculated from tablet dimensions increased for directly compressed lactose tablets. This was not observed in this study for lactose granules. The explanation for the decrease in the slope of graphs at 12 kN in Fig. 2a, b is the same as in the case of decrease in porosity.

Breaking force of tablets

In this study, the relationship between breaking force of tablets and the maximum force of upper punch used in

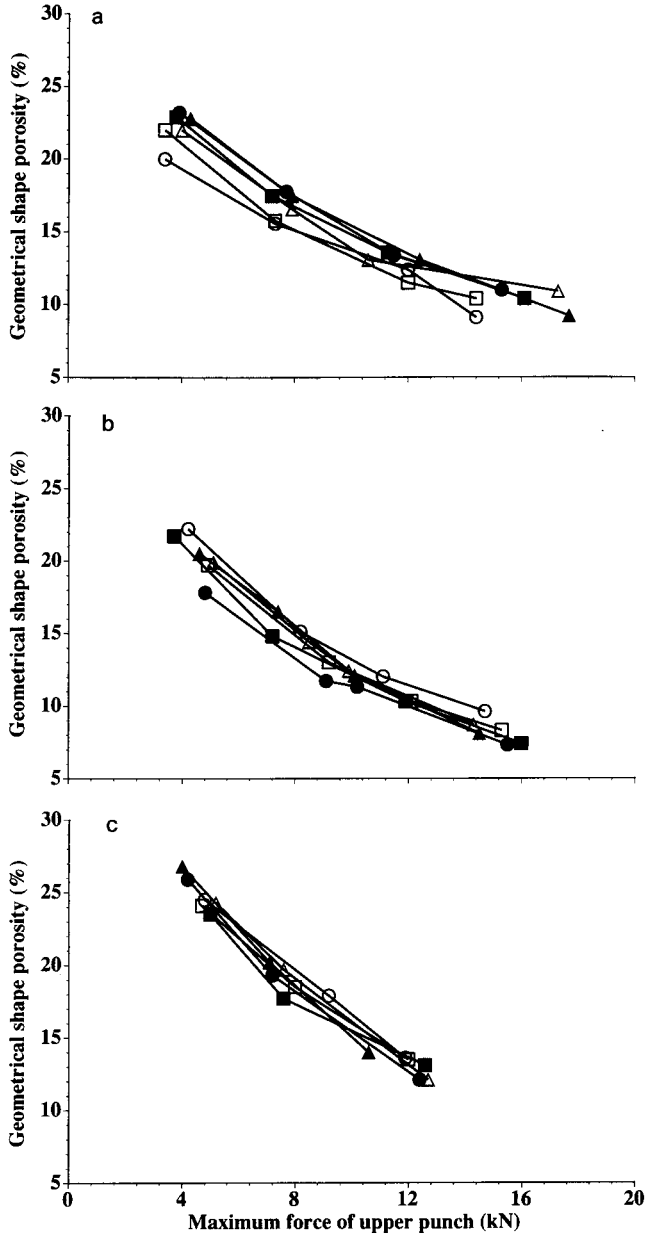

FIG. 2. Porosity of tablets (based on geometrical shape) according to compression force. a. Lactose, b. glucose, c. mannitol tablets. ■, ●, ▲, 90 mL kg^{-1}; □, ○, △, 120 mL kg^{-1}; □, ■, 30 rev min^{-1}; ○, ●, 47 rev min^{-1}; △, ▲, 64 rev min^{-1}. Relative errors are smaller than 4%.

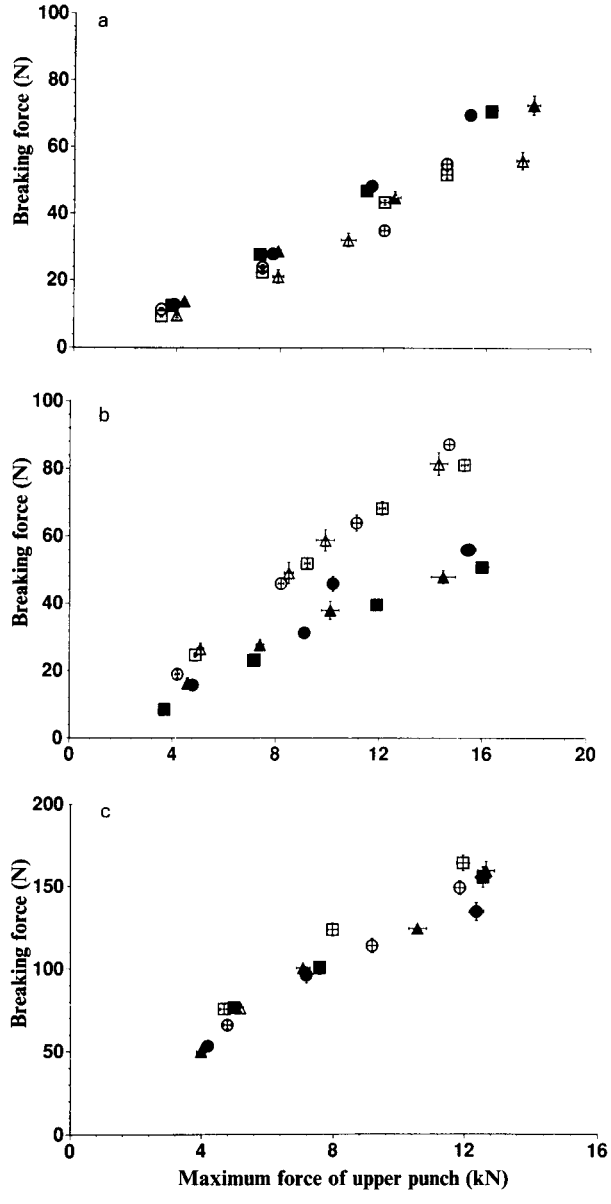

FIG. 3. Mean breaking force (n = 20) of lactose (a), glucose (b) and mannitol (c) tablets according to compression force (n = 40). ■, ●, ▲, 90 mL kg^{-1}; □, ○, △, 120 mL kg^{-1}; □, ■, 30 rev min^{-1}; ○, ●, 47 rev min^{-1}; △, ▲, 64 rev min^{-1}. Error bars represent ± s.e.m. Note: error bars are smaller than the symbol size in some cases.

compression was used as a measure of compactibility of the granules. As seen in Fig. 3, the relationship between upper force maxima and breaking force is approximately linear for all three diluents. Linear dependence of tensile strength on compression force for lactose powder tablets has also been reported by Sheikh-Salem & Fell (1982).

In the range used in this study, compression speed appears to have no clear systematic effect on the breaking force of lactose, glucose and mannitol tablets. In the study of Holman & Leuenberger (1989), all compression parameters for lactose tablets were also essentially insensitive to the changing speeds of compression. On the other hand, Armstrong & Palfrey (1989) reported a decrease in the tensile strength of lactose tablets with increasing speed. Sheikh-Salem & Fell (1982) found that the tensile strength of lactose powder tablets decreases in the order: medium speed > low speed > high speed. In our study, mannitol tablets compressed with the lowest speed of compression (30 rev min^{-1}), have a somewhat greater breaking force than tablets compressed with higher speed (Table 2). Roberts & Rowe (1985) found that mannitol powder has a greater strain-rate sensitivity than lactose. Hence, compression speed has a greater effect on the compression behaviour of mannitol powder than it has on lactose powder. Since plastic deformation is time-dependent, it can be stated that mannitol powder behaves plastically during compression.

Table 2. Statistical analysis (P) for breaking force of lactose, glucose and mannitol tablets.

Diluent	Analysis of variance			Fisher's protected least significant difference		
	Liquid amount	Compression speed	Compression force	30 rev min^{-1}, 47 rev min^{-1}	30 rev min^{-1}, 64 rev min^{-1}	47 rev min^{-1}, 64 rev min^{-1}
Lactose (n = 480)	< 0·001	0·418	< 0·001	0·811	0·214	0·315
Glucose (n = 480)	< 0·001	0·021	< 0·001	0·025	0·761	0·011
Mannitol (n = 360)	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	0·915

Mannitol granules form a more complicated system than powder. In addition to fragmentation, they also densify plastically. This time-dependent phenomenon could probably have been detected more clearly at even lower speeds of compression. The breaking force of glucose tablets prepared with the medium speed (47 rev min^{-1}) appears to be largest (Table 2, Fig. 3b). However, we have no explanation for this phenomenon.

The breaking forces of lactose, glucose and mannitol tablets differ from each other especially with the greatest amount of granulation liquid (Fig. 3). Mannitol tablets are clearly strongest and the effect of compression force is most profound. With the granulation liquid of 90 mL kg^{-1}, the strength of lactose and glucose tablets is similar, but with the 120 mL kg^{-1}, glucose tablets are harder and the effect of compression force is greater than in lactose tablets. The glucose tablets have also been found to be harder in a previous study (Henderson & Bruno 1970). Bolhuis & Lerk (1973) studied the elastic energy of lactose and glucose monohydrates in compression. Glucose represents less elastic energy than lactose in compression, which improves the strength of glucose tablets. In addition to better compactibility, glucose has another advantage over lactose; Duvall et al (1965) observed that glucose tablets produced by direct compression exhibited less browning than lactose tablets in formulations containing no amines. In the presence of amines, browning of glucose tablets was more extensive.

Granules made from lactose produce the weakest tablets of the diluents studied and mannitol granules the strongest. Mannitol has shown more time-dependent plastic behaviour in compression than lactose. Plastic deformation brings the surfaces in near contact, which is attributable to strong interfacial adhesion. Bonds may also form between granules as a result of the porous and fibrous structure of mannitol granules by mechanical interlocking. According to Krycer et al (1982), the elastic recovery of lactose tablets compressed from crystals and from the granules prepared by irreversible agglomeration of ground particles was higher than that of mannitol tablets, when compressed with a pressure of 120 MPa. The crushing strength of lactose tablets compressed from both crystals and granules was greater than that of mannitol tablets. In our study, however, the porous structure of mannitol granules together with the greater degree of plasticity of mannitol compared with lactose (Roberts & Rowe 1987) resulted in the best compactibility of the diluents studied.

According to Wikberg & Alderborn (1991), the increased porosity of lactose granules increases the tensile strength of compressed tablets. The amount of liquid significantly affects the breaking force of lactose tablets (Table 2, $P < 0·001$) so that with a larger amount of liquid (120 mL kg^{-1}), the breaking force is smaller (Fig. 3a). As presented in a previous paper (Juppo & Yliruusi 1994), the intruded volume of mercury in a pore diameter range of 14–220 μm decreases from 0·63 to 0·40 mL g^{-1}, when the amount of liquid in the granulation of lactose is increased from 90 to 120 mL kg^{-1}. Thus, these results agree with those obtained by Wikberg & Alderborn (1991) and by Zuurman et al (1994), who have also studied the relationship between bulk density and compactibility of lactose granules. Granules with a low bulk density resulted in tablets with a high crushing strength. The granule bed with a low porosity has a low deformation potential. There is a lack of space for deformation of granule particles during compression causing less contact points and weaker tablets. The increase in the amount of binder appeared to have no effect on the breaking force of lactose tablets.

The porosity of glucose granules does not have a similar effect on the measured breaking forces of tablets. With an increased amount of liquid, the total pore volume of the pores in the diameter range mentioned above decreases from 0·13 mL g^{-1} to 0·07 mL g^{-1} (Juppo & Yliruusi 1994), but the breaking force increases (Table 2, $P < 0·001$). The probable reason for the better strength of tablets compressed from larger granules is both the larger amount of binder and the greater degree of fragmentation creating newly unlubricated surfaces for formation of strong bonds. Furthermore, fragmentation is not the only mechanism; plastic deformation apparently takes place at the contact points of primary particles.

The difference in breaking forces of mannitol tablets prepared with two amounts of liquid was found to be significant (Table 2, $P < 0·001$). Mannitol granules produced with 120 mL kg^{-1} liquid have a greater total volume of pores in the diameter range 6·5 nm–14 μm (Juppo & Yliruusi 1994). This, as for lactose granules, together with the larger amount of binder might cause the better compactibility of granules with the larger amount of binder solution. It should be noticed that even if the liquid amount did not affect the compressibility of granules, the compactibility of all granules was highly influenced.

With increasing amount of granulation liquid, the granule size increases (Table 1). When granules are

lubricated, the amount of lubricant on the surface of the granules is dependent on the specific surface area of the granules. The larger the granules, the smaller the amount of lubricant on the granule surface. Magnesium stearate, as a hydrophobic agent, would be presumed to weaken the bonds between granules. The increased amount of granulation liquid, should then cause weaker tablets. However, the glucose and mannitol tablets with 120 mL kg^{-1} liquid are stronger than those prepared with 90 mL kg^{-1}. Thus, other effects caused from the greater amount of granulation liquid overcome the effect of increased amount of lubricant on the granule surface. In the case of lactose tablets, the breaking force is greater for the tablets produced from the granules with the lower amount of liquid. It is impossible to say with certainty if this is due to the higher porosity of granules or to the smaller amount of lubricant per unit area. Furthermore, it is evident that the granules fragment during compression and thereby produce unlubricated surfaces. Because different phenomena affect the system simultaneously, no conclusions can be drawn from the effect of the amount of lubricant at the granule surface on the basis of this study.

Variation in tablet weight

In addition to good compressibility and compactibility, the compressed mass must flow readily so as to create a small variation in tablet mass. As presented in Table 3, glucose granules have the best flowability of granules studied and mannitol granules the worst. All granules shared a continuous flow behaviour. The relative decrease in volume of the granule bed caused by tapping correlates well with the flow time. With increasing compression speed, the coefficient of variation of tablet weight increases for lactose and glucose tablets, as can be expected (Table 4). The effect of compression speed is highly significant ($P < 0.009$). This effect was

Table 3. Flowability of granules.

Diluent	Granulation liquid (mL kg^{-1})	Flow time (s/50 g)
Lactose	90	4·6 ± 1·3
	120	4·3 ± 0·5
Glucose	90	2·6 ± 0·7
	120	3·6 ± 0·4
Mannitol	90	8·7 ± 0·5
	120	6·7 ± 0·8

Mean ± s.d., n = 3.

Table 4. Mean weights and weight variations of tablets (n = 100).

	Speed of turret (rev min^{-1})	Amount of granulation liquid					
		90 mL kg^{-1}			120 mL kg^{-1}		
		Target value of maximum force of upper punch (kN)	Mean weight (g)	Coefficient of variation (%)	Target value of maximum force of upper punch (kN)	Mean weight (g)	Coefficient of variation (%)
Lactose	30	4	0·219	2·7	4	0·221	2·3
		8	0·224	0·9	8	0·224	0·9
		12	0·225	0·9	12	0·226	1·3
		16	0·225	0·9	16	0·225	1·3
	47	4	0·220	2·3	4	0·232	3·0
		8	0·220	2·3	8	0·228	1·8
		12	0·220	2·3	12	0·230	2·2
		16	0·220	2·3	16	0·227	1·8
	64	4	0·222	1·8	4	0·228	2·6
		8	0·221	2·3	8	0·232	3·9
		12	0·220	2·7	12	0·232	3·4
		16	0·219	3·2	16	0·230	2·6
Glucose	30	4	0·218	3·2	4	0·229	1·7
		8	0·221	1·8	8	0·231	2·6
		12	0·226	1·3	12	0·231	2·6
		16	0·225	1·3	16	0·226	0·9
	47	4	0·230	2·6	4	0·217	4·7
		8	0·231	3·0	8	0·218	3·2
		12	0·230	3·5	12	0.222	2·3
		16	0·235	4·3	16	0·225	1·8
	64	4	0·223	2·7	4	0·220	3·6
		8	0·224	2·2	8	0·230	3·0
		12	0·217	5·1	12	0·228	4·4
		16	0·217	5·5	16	0·227	3·1
Mannitol	30	4	0·237	5·1	4	0·230	2·6
		8	0·231	3·0	8	0·230	2·6
		12	0·226	1·8	12	0·230	2·6
	47	4	0·223	2·2	4	0·222	2·3
		8	0·224	2·2	8	0·222	2·3
		12	0·226	1·8	12	0·220	2·7
	64	4	0·213	6·1	4	0·224	1·8
		8	0·226	3·1	8	0·226	1·8
		12	0·223	3·1	12	0·228	2·2

not observed for mannitol tablets. The difference in flow time of glucose and mannitol tablets does not result in differences in the uniformity of tablet weight (Tables 3, 4). This is probably due to the larger size and narrower size distribution of glucose granules (Table 1) which increase weight variation. Of the tablets studied, lactose tablets have the best uniformity of weight, despite the fact that the flowability of lactose granules is poorer than that of glucose granules. Another reason is the smaller size of lactose granules. All granule masses showed relatively good flow without the feeder, especially at the lowest or medium speeds of compression, enabling tablet production.

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