International Journal of Pharmaceutics, 97 (1993) 29–38

IJP 03085

The effect of dry granulation on the consolidation and compaction of crystalline lactose

K.A. Riepma [a], H. Vromans [b], K. Zuurman [a] and C.F. Lerk [a]

[a] *Department of Pharmaceutical Technology and Biopharmacy, University of Groningen (The Netherlands) and* [b] *Organon International B.V., Oss (The Netherlands)*

(Received 27 August 1992)
(Accepted 13 October 1992)

Key words: Dry granulation; Slugging; Tablet surface area; Consolidation; Compaction; Lactose

Summary

The consolidation and compaction properties of granule fractions prepared by dry granulation (slugging) of α-lactose monohydrate and roller dried β-lactose, respectively, were studied. The results showed that the compactibility of the granule fractions was determined by the type of lactose used and the granule size. The tablets compacted from the granule fractions show a lower compressibility resulting into almost equal crushing strength but a higher specific BET-surface area as compared to the surface area of the slugs. Influence of granule size on tablet strength points to a relation between outside surface area of granules and tablet strength. Obviously, granule particles sustain their integrity to some extent during compaction. Air permeability and mercury porosimetry showed that in tablets with equal strength different pore systems can exist. Generally, tablets compacted from fine granule size fractions exhibited finer pore sizes and higher strengths compared to the tablets compacted from coarse size fractions. Furthermore, mercury porosimetry revealed that the whole pore system determines tablet strength. This means that granule particles deform during consolidation. The influence of the starting materials on tablet strength can not be explained by permeametry surface area measurements and mercury porosimetry. It is suggested that differences in the internal structure between the granules of the two lactose types are responsible.

Introduction

The many advantages of tablets as oral pharmaceutical dosage forms have resulted in a widespread use. Tablets can be compacted by direct compression or after a granulation step. Direct compression involves the mixing of the several ingredients of the powder mass before compaction. By the process of wet or dry granulation the several ingredients are agglomerated prior to tabletting. Granulation is designed to improve the tabletting properties, including fluidity, compressibility and compactibility of the blend of ingredients. The various steps involved in the process of granulation have a significant effect on the particulate characteristics of the resulting granulation. However, relatively few studies, as compared to the great number of studies on direct compression, have been performed concerning the relation between the primary properties of the ingredients, the characteristics of the granulation and the properties of the final tablets.

Correspondence to: C.F. Lerk, Dept of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

Next to the primary properties of the ingredients (drug(s) and excipients like filler-binders and disintegrants) the incorporation of a wet-binder is an important factor for increasing the compactibility of a granulate. This effect is largely determined by the type of wet-binder used (Krycer et al., 1983), the concentration within the granulate and the method of incorporation (Rue et al., 1980; Reading and Spring, 1984). Highest tablet strengths were obtained from granules produced with a high amount of binder solution distributed thoroughly throughout the powder mass.

The physical characteristics of granules, such as porosity, diameter and strength, are of interest as they can affect the compactibility of the particulate mass.

Several papers reported the effect of granule porosity on tablet strength. Increasing tablet strengths were found at increasing porosities of granule particles (Krycer et al., 1982; Wikberg and Alderborn, 1991). In contrast to this, Healey et al., (1973) reported that intra-granular porosity had no effect on tablet strength, whereas Veillard et al. (1982) found that strongest tablets were compacted from granules with lowest total (intra- and inter-granular) porosity.

A number of studies were engaged with the effect of granule size on their compaction properties. Higuchi et al. (1953) and Rubinstein and Blane (1977) reported no obvious relationship between granule size and tablet crushing strength, while other authors (Wells and Walker, 1983; Li and Peck, 1990; Wikberg and Alderborn, 1990c) found stronger tablets with decreasing sizes of granule particles.

Next to porosity and size, granule strength can influence tablet strength. Doelker and Shotton (1977) reported that for some granulations the weakest granules produced the strongest tablets while for an other formulation the opposite result was found. Jarosz and Parrott (1983) found that for granule particles with increasing strength stronger tablets were produced. However, it appeared that compressional force and concentration of a binder contributed more than granule strength to tablet tensile strength.

In conclusion, the compactibility of a granulate is dictated by both formulation and process variables involved in the granulation step, all of these affecting the particulate characteristics of the granulate and the properties of the final tablet.

The aim of the present paper has been to investigate the effect of physical granule properties, such as porosity, internal structure and size, on the compressibility and compactibility of crystalline lactose. In this study the effect of wet binding was excluded by preparing the granules by dry granulation (slugging) and milling. The slugs were compacted from pure sieve fractions of two types of crystalline lactose: α-lactose monohydrate and roller dried β-lactose.

Materials and Methods

Coarse (250–300 μm) and fine (< 63 μm) fractions of both α-lactose monohydrate and roller dried β-lactose were used, all supplied by DMV, Veghel, The Netherlands.

All tests were performed at constant temperature (20 ± 1°C) and constant relative humidity (45 ± 5%). The ungranulated powder fractions and granule fractions were stored under these conditions for at least 1 day before use, unless stated otherwise.

The compacts (slugs and tablets) were prepared by compaction of powder and granulate fractions, respectively, into 500 mg flat-faced tablets with a diameter of 13 mm using a programmable hydraulic press (ESH Testing, Brierley Hill, U.K.). If necessary the die was prelubricated with magnesium stearate.

The dry granulate fractions were produced by hand grinding of the slugs in a mortar with subsequent hand sieving.

Compact strength and compact dimensions were determined 30 min after compaction with a Schleuniger 4M tester (Dr Schleuniger Production AG, Solothurn, Switzerland) and an electronic micrometer (Mitutoyo, Tokyo, Japan), respectively. The presented data are the means of at least five compacts.

Compact porosities were calculated from the weight and the dimensions of the compacts, applying true densities of 1.54 g/cm^3 for α-lactose monohydrate and 1.59 g/cm^3 for roller dried

β-lactose. Granule densities were calculated from the dimensions and the weight of the original slugs.

The specific BET-surface areas of the compacts were measured with a Quantasorb gas adsorption apparatus (Quantachrome Corp., Syosset, U.S.A.) using nitrogen as adsorbate in single point determinations. The compacts were stored 'immediately' after compaction in a nitrogen atmosphere to suppress sorption of moisture and subsequently transported to the apparatus. No outgassing procedures were applied. The data are the means of at least four compacts.

Permeametry measurements were performed according to the procedure described by Alderborn et al. (1985). The specific permeametry surface area was calculated with the Kozeny-Carman equation corrected for slip flow. The permeability coefficient was calculated from the air flow through the compact and compact thickness using the procedure described by Wikberg et al. (1990a). The data are the means of at least two compacts.

Mercury porosimetry was performed with a Carlo Erba series 2000 porosimeter. The compacts were evacuated at about 10 Pa prior to the measurements for 30 min. The values are the mean of at least two compacts.

Results and Discussion

Table 1 presents the strength and the porosity of 'slugs' and of 'tablets' compacted from α-lactose monohydrate and roller dried β-lactose, respectively. The slugs were compressed from coarse (250–300 μm) and fine (< 63 μm) ungranulated powder fractions, respectively, of the two lactose powders. Next, tablets were compacted from a sieve fraction (212–425 μm) of 'granules', which were made from the slugs by grinding and sieving. The results show, as expected, increasing crushing strengths and decreasing porosities with increasing compaction forces, for the slugs of both α-lactose monohydrate and β-lactose. Unexpected was the observation of almost equal crushing strengths and porosities of the tablets compacted from the different granules of α-lactose monohydrate and β-lactose, respectively.

TABLE 1

Strength and porosity of slugs compacted from coarse (250–300 μm) and fine (< 63 μm) fractions, respectively, of α-lactose monohydrate and roller dried β-lactose, and of tablets compacted from a granule fraction (212–425 μm) prepared from the slugs

Fraction (μm)		C_f (kN)	C_s (N)	ϵ
α-Lactose monohydrate				
Slugs				
250–300	A	5	6(1)	0.23
	B	20	40(2)	0.12
	C	40	65(9)	0.08
< 63	D	5	5(1)	0.25
	E	40	100(9)	0.10
Tablets				
From	A	20	32(1)	0.12
	B	20	35(4)	0.13
	C	20	33(6)	0.13
	D	20	44(2)	0.15
	E	20	45(4)	0.15
Roller dried β-lactose				
Slugs				
250–300	F	5	17(1)	0.29
	G	20	96(4)	0.17
	H	40	210(9)	0.11
	I	100	–	–
< 63	J	5	19(2)	0.28
	K	40	–	0.11
Tablets				
From	F	20	95(6)	0.16
	G	20	93(4)	0.16
	H	20	76(3)	0.16
	I	20	73(3)	0.16
	J	20	107(10)	0.17
	K	20	86(4)	0.16

C_f, compression force; C_s, crushing strength; ϵ, porosity of slugs and tablets.

This implies that strength and porosity of the granules seem to have almost no effect on the strength and porosity of the tablets compressed from these granules. Moreover, it should be noted that almost equal crushing strengths and porosities were obtained for both the slugs and the tablets, compressed at the same compaction force from the powder and the granules, respectively. Thus, the compactibility of crystalline lactose powders is primarily affected by the applied compaction force and the type of lactose used.

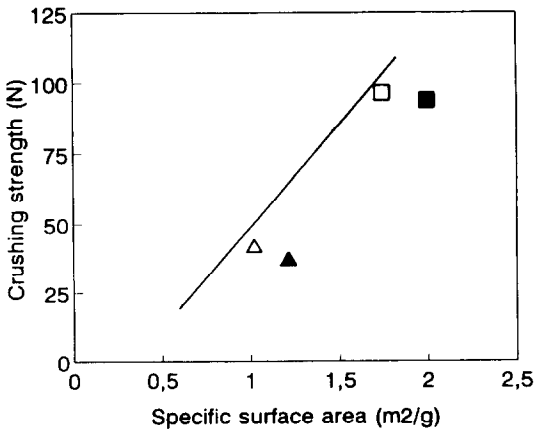

Fig. 1. Crushing strength vs specific (BET-) surface area of compacts compressed at 20 kN from ungranulated powder fractions (250–300 μm) (open symbols) and granule fractions (212–425 μm) (closed symbols) from α-lactose monohydrate (△) and roller dried β-lactose (□), respectively. Granules were prepared from 20 kN slugs. The line is similar to that earlier reported (Riepma et al., 1990).

Vromans et al. (1985, 1987) found for tablets compacted from single sieve fractions of crystalline lactose that one unique relationship exists between strength and specific pore surface area, measured with mercury porosimetry or gas adsorption. This relationship points to an equal bonding mechanism between the particles within the tablets independent of the type of lactose. Fig. 1 shows the strength as a function of the specific BET-surface area of slugs and tablets compacted from α-lactose monohydrate and β-lactose, respectively. The slugs were compacted from ungranulated powder fractions (250–300 μm), while the tablets were compressed from granule fractions (212–425 μm), prepared from the 20 kN slugs. Slugs and tablets were compacted with a force of 20 kN. The line given is equal to that reported earlier by Riepma et al. (1990). As demonstrated, the tablets compacted from the granule fractions showed almost equal crushing strength, but higher surface area as compared to the corresponding slugs. This result points to differences in the consolidation mechanism between ungranulated and granulated crystalline lactose.

Fig. 2 presents crushing strength as a function of compaction load of tablets compacted from two different size fractions (63–106 and 212–425 μm) of ungranulated powder and from granules of α-lactose monohydrate and roller dried β-lactose, respectively. The granules were prepared from 40 kN slugs by grinding and sieving. As seen, the finer sieve fractions yielded stronger tablets. In addition, the tablets exhibited almost equal crushing strengths when compacted at the same compaction load, from the same size fractions of both granules and ungranulated powder. This demonstrates once again that the dry granulation step seems to have little influence on the compactibility of crystalline lactose. Rather, the results indicate a relation between bonding

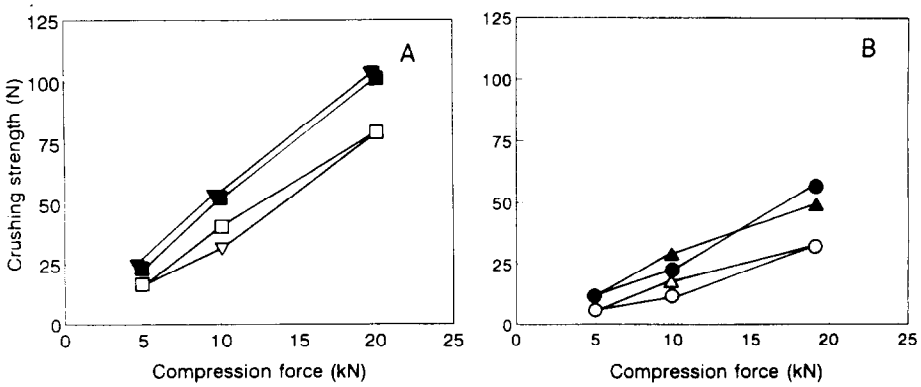

Fig. 2. Crushing strength vs compression force of compacts compacted from ungranulated powder fractions and granule fractions of roller dried β-lactose (a) and α-lactose monohydrate (b), respectively. Granule fractions were prepared from 40 kN slugs. Closed symbols, fine sieve fractions; open symbols, coarse sieve fractions. Roller dried β-lactose: (□) ungranulated fractions, (▽) granule fractions; α-lactose monohydrate: (○) ungranulated fractions, (△) granule fractions.

strength of the tablets and outer surface area of the granules.

Wikberg and Alderborn (1990a,b) suggested determination of the outside surface area of granules within tablets by air permeability measurement. During this measurement the air is thought to flow mainly through the larger pores, assumed to be located between the granules. For the calculation of the specific permeametry surface area it seemed therefore obvious to use the porosity of the tablet as calculated from the granule density. However, for several granulations they found decreasing surface areas with increasing compaction pressures when calculation of the specific permeametry surface area was performed with the granule density. Therefore, Wikberg and Alderborn decided to use the material density for the calculation of specific permeametry surface areas.

In the present study the difference in densification behaviour of granules with different granule porosities was evaluated by recording the porosity-pressure profiles of granule fractions (212–425 μm) of roller dried β-lactose, prepared from 5 and 40 kN slugs, respectively. When the porosities of the particulate mass are calculated with the granule density before compaction, a profile is obtained which presents the course in inter-granular porosity. Fig. 3a shows a plot of the reciprocal value of this inter-granular porosity vs the compression force of the two granule fractions. Fig. 3a demonstrates a dramatic decrease in inter-granular porosity on compaction of the granules prepared from the 5 kN slugs. However, it is unrealistic to accept that compression results in almost zero inter-granular porosity without affecting the intra-granular porosity. This means that application of a constant granule density for the calculation of specific surface areas of tablets from permeametric measurements will not result in realistic values. If the porosities of the particulate mass are calculated with the material density, the porosity-pressure profiles represent the change in 'total' porosity during compression. Fig. 3b depicts the reciprocal value of this total porosity as a function of the compaction load. The results suggest equal behaviour under compression of the granules made from both the 5 and 40 kN slugs. In this case, it is unrealistic to expect at all compression forces equal air flow patterns through beds of granules with different strength and different initial porosities. It is therefore concluded that application of the material density for the calculation of specific surface areas of tablets from permeametric measurements will also result in unrealistic values.

The effect of both the application of material and granule densities for the calculation of surface areas from permeametry measurements is illustrated in Table 2. Compaction of both powder and granules, the latter produced from 5 and 40 kN slugs, respectively, resulted in tablets with almost equal crushing strength for α-lactose monohydrate and β-lactose, respectively. However, for the specific permeametry surface areas totally different values were calculated for the

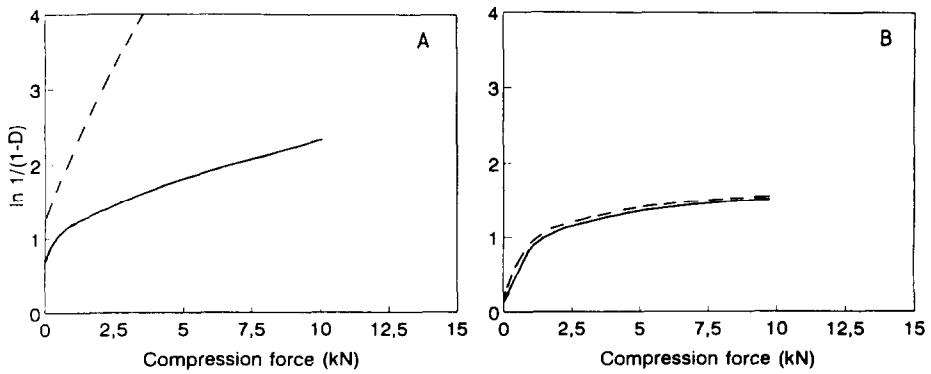

Fig. 3. Heckel plots of granule fractions (212–425 μm) of roller dried β-lactose calculated with granule density (a) and lactose density (b). Broken line: granules prepared from 5 kN slugs; continuous line: granules prepared from 40 kN slugs.

tablets, compressed either from ungranulated powder or from granules, produced from 5 and 40 kN slugs, respectively. Striking are the negative surface areas obtained by application of the granule density. These results again demonstrate that it is meaningless to evaluate specific permeametry surface areas of tablets when compressed from granules with different porosities.

Conversely, it might be assumed that granule densities will not change during compression at low compaction forces if the granules are prepared from slugs which are compacted at high compaction forces. In that case calculation of the specific surface area could be based upon the granule density before compaction. Table 3 lists the crushing strength and specific permeametry surface area of tablets compacted with a force of 5 kN from different size fractions of granules prepared from 40 kN slugs of α-lactose monohydrate and roller dried β-lactose, respectively. The data indicate decreasing compactibilities and decreasing specific permeametry surface areas of the tablets with increasing size fractions of the granules to be compressed. Fig. 4 indeed illustrates a relationship between strength and surface area of the tablets, although different for the two types of lactose. This difference in behaviour is most likely caused by differences in surface texture between the two lactose types. (Vromans et al., 1985).

To circumvent the problem of incorrect porosity calculations by applying either the granule or material density, the air permeability coefficient can be used to gain information about tablet

TABLE 2

Specific permeametry surface area, calculated with granule density and lactose density, respectively, and strength of tablets compacted at 5 kN from an ungranulated powder fraction and from granule fractions, prepared from slugs of α-lactose monohydrate and roller dried β-lactose

Fraction (μm)	S_{v_g} (m^2/g)	S_{v_l} (m^2/g)	C_s (N)
α-Lactose monohydrate			
250–300 (ungranulated)	–	0.22	6
212–425 (from 5 kN slugs)	neg.[a]	0.43	5
212–425 (from 40 kN slugs)	0.39	0.65	6
Roller dried β-lactose			
250–300 (ungranulated)	–	0.50	17
212–425 (from 5 kN slugs)	neg.[a]	0.92	17
212–425 (from 40 kN slugs)	0.26	0.63	16

S_{v_g}, specific permeametry surface area, calculated with granule density; S_{v_l}, specific permeametry surface area, calculated with lactose density; C_s, crushing strength.
[a] Negative value.

TABLE 3

Specific permeametry surface area, calculated with granule density, and strength of tablets compacted at 5 kN from granule fractions prepared from 40 kN slugs of α-lactose monohydrate and roller dried β-lactose, respectively

Fraction (μm)	S_{v_g} (m^2/g)	C_s (N)
α-Lactose monohydrate		
63– 106	0.44	11
106– 212	0.41	10
212– 425	0.39	6
425– 850	0.31	6
850–1400	0.23	5
Roller dried β-lactose		
63– 106	0.62	26
106– 212	0.33	20
212– 425	0.26	16
425– 850	0.18	18
850–1400	0.10	16

S_{v_g}, specific permeametry surface area; C_s, crushing strength.

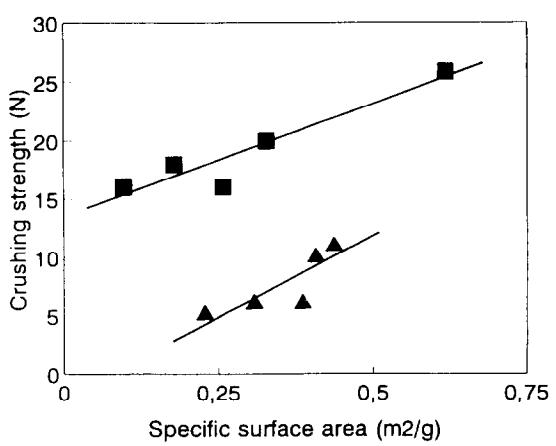

Fig. 4. Crushing strength vs specific (permeametry-) surface area of tablets compressed at 5 kN from granule fractions of α-lactose monohydrate (▲) and roller dried β-lactose (■), respectively. The data were obtained from Table 3.

TABLE 4

Air permeability resistance and strength of tablets compacted at 5 kN from ungranulated powder fractions and granule fractions, respectively, of roller dried β-lactose

Fraction (μm)	R_c ($Nsm^{-4} \times 10^8$)	C_s (N)
212–425 (ungranulated)	3.7	17
Granule fractions		
212–425 (from 5 kN slugs)	18.0	17
212–425 (from 40 kN slugs)	14.3	16

R_c, air permeability resistance; C_s, crushing strength.

structures. Wikberg and Alderborn (1990a) correlated this permeability coefficient with the compactibility of granules. They observed that low values of the coefficient were related to high tablet strengths. Healey et al. (1973) found that differences in physical granule properties caused little variation in the air permeability coefficients of tablets compacted from these granules, indicating similar pore structures.

For the present study the air permeability was determined of β-lactose tablets compacted at 5 kN from ungranulated powder and from granules prepared from slugs compacted at 5 and 40 kN, respectively. Table 4 presents both the crushing strength and the reciprocal value of the air permeability coefficient, called the air permeability resistance (R_c) of the tablets. As shown, all tablets exhibited equal strengths but strongly different air permeability resistances, pointing to differences in tablet pore structure. This result demonstrates again the absence of a relationship between strength and air permeability for tablets compressed from granules.

One may conclude from the results discussed so far that although outer granule surface area is obviously important for compactibility, this is difficult to assess with permeametry techniques because of the densification of the granule particles during the consolidation and the consequent uncertainty towards density and route of flow.

In contrast to the permeability of a tablet, which only presents general information about the pore strucure, more detailed information about the pore size distribution within a compact is obtained with mercury porosimetry (Selkirk and Ganderton, 1970). Fig. 5 shows the pore size distribution of tablets compacted at 5 kN compression force (Fig. 5a) and at 20 kN compression (Fig. 5b) from a coarse (212–425 μm) and a fine (63–106 μm) fraction, respectively, of granules which were prepared from 5 kN slugs of roller dried β-lactose. The results demonstrate at both compaction forces finest pores for the tablets compressed from the fine fraction of granules. Similar differences in pore size distributions were found for α-lactose monohydrate tablets compacted from coarse and fine granules, prepared from slugs compacted at 40 kN compression force (not shown). It is obvious that decreasing granule sizes will yield tablets with finer pore structures

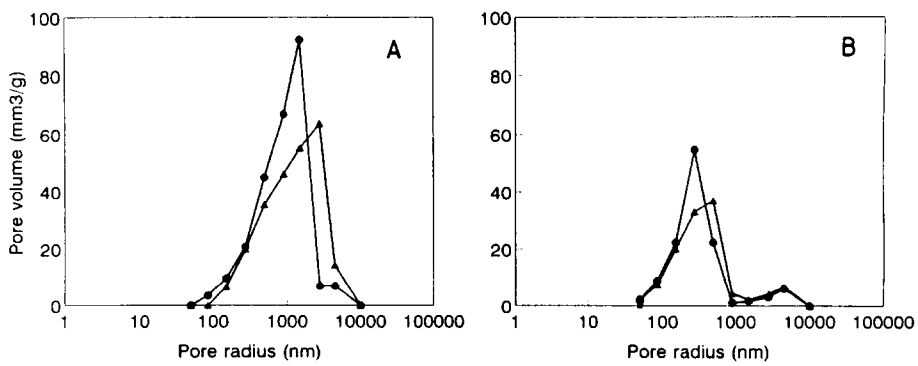

Fig. 5. Pore size distribution, expressed as the volume mercury penetrated, vs pore radius. Tablets were compacted from granule fractions (63–106 and 212–425 μm) compacted at 5 kN (a) and 20 kN (b), respectively, of roller dried β-lactose. The granules were prepared from 5 kN slugs. (●) Fine granule fraction (63–106 μm); (▲) coarse granule fraction (212–425 μm).

and higher strengths. This suggests a relationship between strength and pore size distribution. Fig. 6 compares the pore size distribution of β-lactose tablets with equal strength which were compacted from granules (212–425 μm), prepared from 5 and 40 kN slugs, respectively. The pore size distributions demonstrate that a duality in intra- and inter-granular pore system is sustained for the tablets compressed from the 40 kN slugs, but is lost for the tablets compressed from the 5 kN slugs. Obviously, the properties of the initial granules influence the pore structure of the final tablets, although no direct relationship between pore size distribution and tablet strength is shown. However, when the strength of the tablets is plotted vs the average pore diameter within the tablets (Fig. 7) decreasing tablet strength correlates with increasing average pore diameter. Moreover, it is demonstrated that the two different lactose types show different courses between strength and average pore diameter of the tablets. Conversely, almost equal pore size distributions were found for tablets compressed at 20 kN compaction force from granule fractions (212–425 μm) prepared from 40 kN slugs of α-lactose monohydrate and roller dried β-lactose, respectively, although the tablets exhibited totally different crushing strength (see Fig. 2). This difference in behaviour is consistent with the difference in relationship as found between crushing strength and permeametry surface area (Fig. 4).

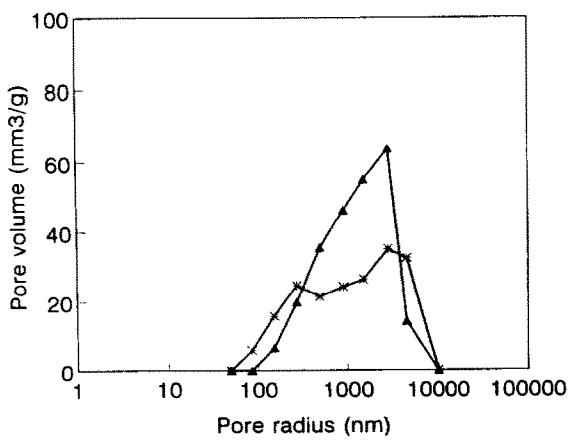

Fig. 6. Pore size distribution, expressed as the volume mercury penetrated, vs pore radius. Tablets were compacted at 5 kN from granule fractions (212–425 μm) of roller dried β-lactose. The granules were prepared from 5 and 40 kN slugs. (▲) Granule fraction prepared from 5 kN slugs; (*) granule fraction prepared from 40 kN slugs.

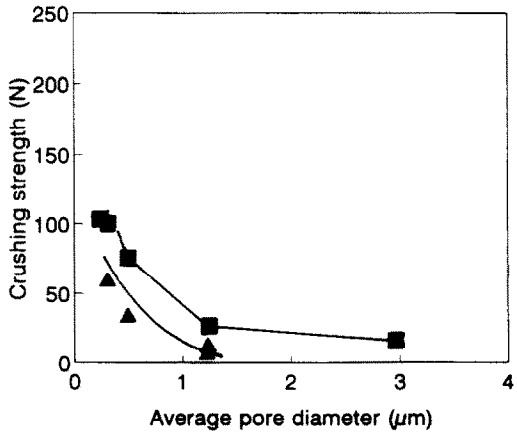

Fig. 7. Crushing strength vs average pore diameter of tablets compacted from granule fractions of roller dried β-lactose (■) and α-lactose monohydrate (▲), respectively.

Considering the results discussed, it is apparent that the compactibility of granules prepared by dry granulation of crystalline lactose is affected by neither the strength nor the porosity of the slugs, but is principally determined by the primary properties of the lactose powders and the size of the granules. The tablets compacted from the granule fractions exhibit higher specific BET-surface areas, at equal strengths, compared to the tablets compacted from the ungranulated powder fractions. From this it is concluded that as a result of the method of dry granulation the compressibility of the crystalline lactose has decreased. In this respect, one can distinguish here on the one hand homogeneous systems, compacted from single crystals, and on the other heterogeneous systems, consisting of composed particles. The observation that tablet strength is affected by granule size is demonstrative of a relation between bonding strength and outside granule surface area. This means that the granule particles sustain their integrity to some extent during compaction, although the intra-granular porosity decreases during consolidation. With gas adsorption no distinction can be made between the outside granular surface area, which is obvi-

ously relevant for bonding, and the intra-granular surface area. This means that the BET-surface area measurement delivers no useful information about the tablets compacted from the granule fractions. In these tablets one can distinguish a packing arrangement with corresponding coordination number of the individual lactose particles within the granules, and a packing arrangement with corresponding coordination number of the granule particles. During compaction the deformability of the granule particles by both fragmentation and particle rearrangement is more important than internal fragmentation within the granule particles. The relation between outside granule surface area and compact strength suggests that inter-granular attraction determines tablet strength. Mercury porosimetry data show, however, that it is the whole pore size distribution which determines compact strength. This reveals that the influence of the intra-granular pore system also cannot be ignored. Moreover, Fig. 7 shows that different relationships exist between strength and average pore diameter of tablets compressed from dry granules of the two lactose types. A similar difference was observed for the relation between permeametry surface area and strength of the tablets (Table 3 and Fig. 4). These differences in behaviour between dry granules of the two types of lactose might be caused by differences in internal structure between the granule particles.

In conclusion, the consolidation and compaction properties of granules prepared by dry granulation from sieve fractions of α-lactose monohydrate and roller dried β-lactose, respectively, are principally determined by the primary properties of the lactose powder, the granule size and the compaction force. Differences in physical properties of the granules, such as porosity and strength, are eliminated during compaction and do not affect the compactibility of the granule particles. The relation between granule size and compact strength indicates that the granule particles sustain their integrity, to some extent, during compaction. However, consolidation of the granules involves both intra- and inter-granular porosity changes. Mercury porosimetry reveals that the whole pore system determines tablet strength.

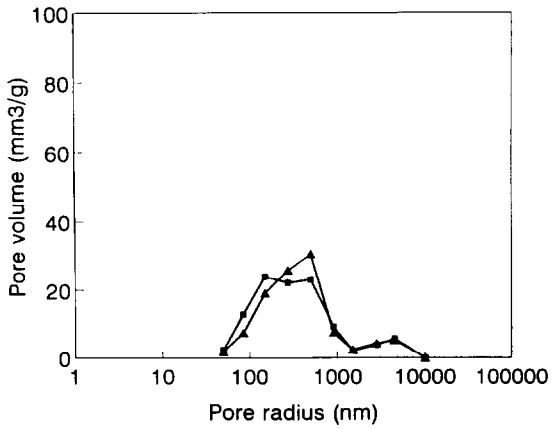

Fig. 8. Pore size distribution, expressed as the volume mercury penetrated, vs pore radius. Tablets were compacted from granule fractions (212–425 μm) of α-lactose monohydrate (▲) and roller dried β-lactose (■), respectively, with a force of 20 kN. Granules were prepared from 40 kN slugs.

The observed differences in compactibility between the granules of the two lactose types are suggested to be caused by differences in the internal granular structure.

Acknowledgements

The authors wish to express their gratitude to S. Pulici and R. Jager for their help in performing the experiments.

References

Alderborn, G., Duberg, M. and Nyström, C., Studies on direct compression of tablets: X. Measurement of tablet surface area by permeametry. *Powder Technol.*, 41 (1985) 49–56.

Doelker, E. and Shotton, E., The effect of some binding agents on the mechanical properties of granules and their compression characteristics. *J. Pharm. Pharmacol.*, 29 (1977) 193–198.

Healey, J.N.C., Humphreys-Jones, J.F. and Walters, V., The effects of granule porosity and strength on the porosity, air permeability and tensile strength of tablets. *J. Pharm. Pharmacol.*, 25 (1973) 110P.

Higuchi, T., Rao, A.N., Busse, L.W. and Swintosky, J.V., The physics of tablet compression: II. The influence of degree of compression on properties of tablets. *J. Am. Pharm. Assoc. Sci. Ed.*, 42 (1953) 194–200.

Jarosz, P.J. and Parrott, E.L., Comparison of granule strength and tablet tensile strength. *J. Pharm. Sci.*, 72 (1983) 530–535.

Krycer, I., Pope, D.G. and Hersey, J.A., The role of intragranular porosity in powder compaction. *Powder Technol.*, 33 (1982) 101–111.

Krycer, I., Pope, D.G. and Hersey, J.A., An evaluation of tablet binding agents: I. Solution binders. *Powder Technol.*, 34 (1983) 39–51.

Li, L.C. and Peck, G.E., The effect of agglomeration methods on the micromeritic properties of a maltodextrin product, Maltrin 150™. *Drug Dev. Ind. Pharm.*, 16 (1990) 1491–1503.

Reading, S.J. and Spring, M.S., The effects of binder film characteristics on granule and tablet properties. *J. Pharm. Pharmacol.*, 36 (1984) 421–426.

Riepma, K.A., Lerk, C.F., De Boer, A.H., Bolhuis, G.K. and Kussendrager, K.D., Consolidation and compaction of powder mixtures: I. Binary mixtures of same particle size fractions of different types of crystalline lactose. *Int. J. Pharm.*, 66 (1990) 47–52.

Rubinstein, M.H. and Blane, M.C., The effect of granule size on the in vitro and in vivo properties of bendrofluazide tablets 5 mg. *Pharm. Acta Helv.*, 52 (1977) 5–10.

Rue, P.J., Seager, H., Ryder, J. and Burt, I., The relationship between granule structure, process of manufacture and the tabletting properties of a granulated product: II. Compression properties of the granules. *Int. J. Pharm. Tech. Prod. Mfr*, 1 (1980) 2–6.

Selkirk, A.B. and Ganderton, D., An investigation of the pore structure of tablets of sucrose and lactose by mercury porosimetry. *J. Pharm. Pharmacol.*, 22 (1970) 79S–85S.

Veillard, M., Bentejac, R., Puiseux, F. and Duchêne, D., A study of granule structure: Effects of the method of manufacture and effects of granule structure on compressibility into tablet form. *Int. J. Pharm. Tech. Prod. Mfr*, 3 (1982) 100–107.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H. Studies on tabletting properties of lactose: II. Consolidation and compaction of different types of crystalline lactose. *Pharm. Weekbl. Sci. Ed.*, 7 (1985) 186–193.

Vromans, H., Bolhuis, G.K, Lerk, C.F. and Kussendrager, K.D., Studies of tableting properties of lactose: IX. The relationship between particle structure and compactibility of crystalline lactose. *Int. J. Pharm.*, 39 (1987) 207–212.

Wells, J.I. and Walker, C.V., The influence of granulating fluids upon granule and tablet properties: the role of secondary binding. *Int. J. Pharm.*, 15 (1983) 97–111.

Wikberg, M. and Alderborn, G., Compression characteristics of granulated materials: II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements. *Int. J. Pharm.*, 62 (1990a) 229–241.

Wikberg, M. and Alderborn, G., Compression characteristics of granulated materials: III. The relationship between air permeability and mechanical strength of tablets of some lactose granulations. *Int. J. Pharm.*, 63 (1990b) 23–27.

Wikberg, M. and Alderborn, G., Volume reduction behaviour of some lactose granulations and its relation to tablet strength. *Proc. 5th. Int. Conf. Pharm. Technol. A.P.G.I.*, Paris, France, 2 (1990c) 171–179.

Wikberg, M. and Alderborn, G., Compression characteristics of granulated materials: IV. The effect of granule porosity on the fragmentation propensity and the compactibility of some granulations. *Int. J. Pharm.*, 69 (1991) 239–253.