ELSEVIER

International Journal of Pharmaceutics 127 (1996) 95–102

international journal of pharmaceutics

Relationship between breaking force and pore structure of lactose, glucose and mannitol tablets

Anne Mari Juppo*

University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division, P.O. Box 56, Helsinki FIN-00014, Finland

Received 9 December 1994; revised 19 June 1995; accepted 6 July 1995

Abstract

The aim of this study was to determine the relationship between the breaking force of lactose, glucose and mannitol tablets and the pore structure characterised by numeric porosity parameters: total pore volume, total pore surface area, mean pore diameter, median pore diameter and volume-size distribution of pores, obtained by mercury porosimetry. A clear overall relationship was found between breaking force of tablets and the median of the cumulative pore volume-pore diameter curve and pore volume-size distribution. The dependence of the breaking force on total surface area of pores was less evident. Fragmentation of granules contributes to the creation of large intergranular and intragranular pores, and further fragmentation and plastic deformation of the primary particles contributes to their reduction in number and size. According to pore volume-size distributions, the decrease in the volume of large pores and the shift of the maximum for volume-size distribution towards smaller pore diameter were related to the increased breaking force of tablets.

Keywords: Lactose; Glucose; Dextrose; Mannitol; Tablet; Pore structure; Breaking force

1. Introduction

Theories presented for the relationship between breaking force and microstructure of tablets presume that a tablet is a suspension of solid particles in the air (Hiestand, 1985, Leuenberger et al., 1989). Another well-known extreme is the continuum model of tablets, where the tablet is considered to be a solid entity with holes in it. Obviously, the truth lies somewhere between these two extremes. None of the theories can predict with any certainty the breaking force of a tablet on the basis of the particle diameters. Thus, due to the complexity of the system, the dependence of the breaking force on the microstructure of tablet must be examined empirically.

Crack propagation has been utilised in the characterisation of the mechanical properties of materials (Mashadi and Newton, 1987, York et al., 1990, Rowe and Roberts, 1994). However, as

* Tel.: + 358 0 4294186; Fax: + 358 0 4292024.

SSDI 0378-5173(95)04203-M

concluded by Rowe and Roberts (1994), this theory is based on an assumption that the material studied is a continuous phase. For tablets compressed from very brittle material like granules, this is not true.

The relationship between the pore structure and breaking force has been studied in several ways. Ryshkewitch (1953) and Pitt et al. (1990) have found a linear relationship between porosity and logarithm of strength of the tablets, whereas Selmeczi (1974) and de Jong (1991) reported a linear inverse dependence of tablet strength on porosity. So, it appears, that porosity or total pore volume alone cannot be used to predict the breaking force of tablets. Total pore surface area determined with mercury porosimetry (Vromans et al., 1985, de Boer et al., 1986) and specific surface area (Riepma et al., 1990, 1991, 1992) have been found to be directly proportional to the breaking force of lactose tablets compressed from powder. The pore structure of tablets compressed from granules is, however, much more complicated and can be expected to have a different effect on the breaking force of the tablets. Riepma et al. (1993) have reported that the breaking force of tablets decreases with increasing average pore diameter of lactose tablets compressed from dry-granulated slugs. A relationship between the average pore size and breaking force has also been found for tablets compressed from lactose granules prepared by wet granulation (Zuurman et al., 1994). On the other hand, Riepma et al. (1993) have claimed that lactose tablets with identical pore size distributions had remarkably different breaking forces. The relationship between breaking force characterising mechanical strength and microstructure of tablets is worth studying with materials other than lactose.

The objective of this study was to investigate the relationship between the breaking force of lactose, glucose and mannitol tablets, compressed from granules, and the porosity parameters, i.e. numeric values obtained from mercury porosimetry data: total pore volume, total pore surface area, mean pore size, median pore size of the pore volume-diameter curve and pore volume-size distribution, dV/dd, which are used to characterise the pore structure of tablets.

2. Materials and methods

2.1. Granulation and compression

The granules were prepared in a high shear granulator (Fielder PMA 25/2G, T.K. Fielder Ltd, UK) from α-lactose monohydrate (EP D 80, Meggle Milchindustrie GmbH, Germany), anhydrous α-glucose (Suomen Xyrofin Ltd, Finland), and D-(−)-mannitol (Merck, Germany) using two amounts of 20% polyvinylpyrrolidone (PVP, Kollidon® K25) solution: 90 and 120 ml/kg, corresponding to 1.8 and 2.4% of PVP in dry granules, respectively. The batch size was 5 kg. Before tableting, the granules were mixed with 1% magnesium stearate in a Turbula mixer (T10B, Willy A Bachofen AG. Maschinenfabrik, Switzerland) for 12 min at a speed of 33 rpm. Tablets were compressed in an instrumented rotary press (Kilian RU-24 II, Kilian & Co. GmbH, Germany) using bevel-edged punches 9 mm in diameter at speeds of 30, 47 and 64 rpm. The target values for the maximum force of the upper punch were 4, 8, 12 and 16 kN for lactose and glucose granules, and 4, 8 and 12 kN for mannitol granules. Granulation, the size distributions and porosity parameters of granules, and compression have been described previously in more detail (Juppo et al., 1992, Juppo and Yliruusi, 1994, Juppo et al., 1995).

2.2. Porosity parameters and breaking force of tablets

Porosity parameters were determined by a high-pressure porosimeter (Autoscan 33, Quantachrome Corp., Syosset, USA) according to a method described previously (Juppo, 1995a). The pressure range of the high-pressure porosimeter was 0.1–227 MPa and corresponded to pores of 6.5 nm to 14 μm in diameter. Porosimeter tests were made in triplicate. Total intruded volume of mercury, total pore surface area, mean and median pore diameters and pore volume-size distribution function, $D_v(d)$, were calculated from the intrusion data with Quantachrome Autoscan PORO2PC Software, Version 2.17, as described in a previous study (Juppo, 1995b). The tablets were

packed in tight glass containers immediately after compression and they were stored in ambient temperature protected from light. The diametric breaking force (Erweka TBH 28, Erweka Apparatebau, Germany) was determined 7 days after compression (n = 20).

3. Results and discussion

3.1. Total pore volume

The dependence of the breaking force of tablets on pore volume is different for each material, and even for different amounts of granulation liquid, especially for glucose tablets (Fig. 1). Mannitol tablets are clearly stronger than other tablets, even when the total pore volume is high. The smaller the empty space between the solid parts of tablet, the stronger the attractive forces between these units. However, no unique relationship between total pore volume and breaking force of tablets was observed (Fig. 1). This means that total pore volume solely cannot be used to predict the breaking force of tablets. Thus, the size of pores has a greater role in bond formation than total pore volume. This is in good agreement with the study presented by Rowe and Roberts (1994),

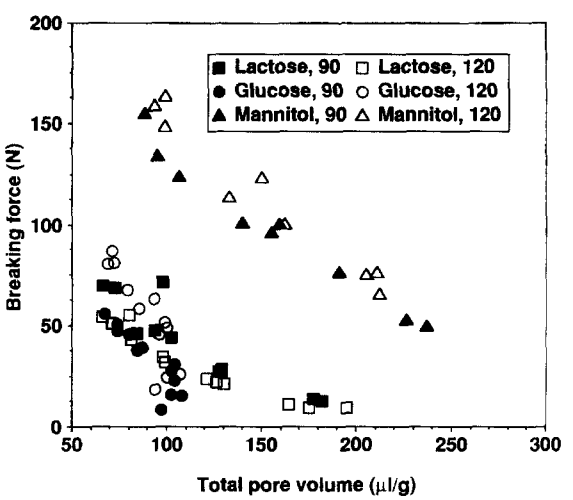

Fig. 1. Breaking force (n = 20) vs. total pore volume (n = 3) of lactose, glucose and mannitol tablets with two amounts of granulation liquid (ml/kg).

where the average pore diameter had a marked influence on crack propagation in addition to porosity.

For each of the three types of tablet, the behaviour is logical: with decreasing total pore volume, the force required to break the tablet increases. Ryshkewitch (1953) has reported a linear relationship between the logarithm of tensile strength of aluminium compacts and porosity. Pitt et al. (1990) found similar behaviour for acetylsalicylic acid tablets. A linear dependence has also been found previously (Selmeczi 1974; de Jong 1991). These linear or logarithmic dependencies have been reported previously for single formulations which have been compressed in different ways. If the lactose, glucose and mannitol granulations had been tested separately, the results would have been in a good agreement with the previous results. For example, there is a linear relationship between breaking force and total pore volume of mannitol tablets (Fig. 1, R^2 = 0.927). However, even different granulations cause deviation from the overall relationship between the breaking force and pore volume of tablets.

3.2. Total pore surface area

Previously, a linear relationship between breaking force and the total pore surface area of tablets compressed from the different types of lactose powders has been found by porosimetry (Vromans et al., 1985, de Boer et al., 1986) and by the nitrogen adsorption method (Riepma et al., 1990, 1991, 1992). The results of this study are contradictory with those previously reported, since there was no linear relationship between the total pore surface area and the breaking force of the three different types of tablet (Fig. 2). With increasing maximum compression force, the breaking force of the tablets increased, but compression force had only a slight effect on the total surface area of the pores, and no effect of compression force was found for lactose tablets (Juppo, 1995b). Thus, the breaking force of tablets cannot be explained satisfactorily by total pore surface area. Obviously, there is also some other factor which affects the breaking force of the tablet.

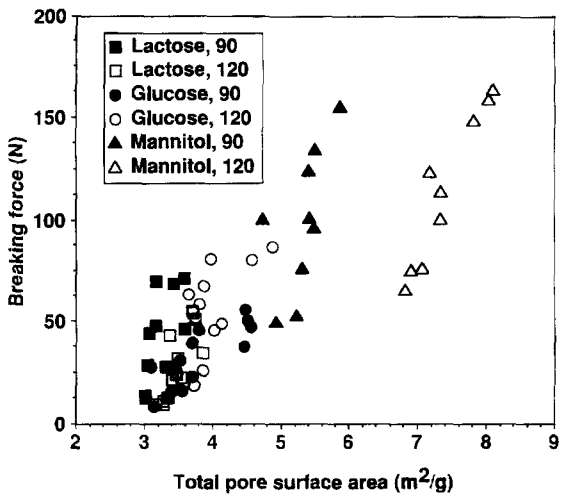

Fig. 2. Breaking force ($n = 20$) vs. total pore surface area ($n = 3$) of lactose, glucose and mannitol tablets with two amounts of granulation liquid (ml/kg).

When powders are compressed, as in the previous studies mentioned above, the pores created are so small in diameter that the changes in their number and size deeply affect the total pore surface area. Therefore, a strong relationship between the total surface area and the breaking force of tablets exists. In the case of compression of granules, the intergranular pores and pores created after granule fragmentation are so large that the changes in their number or size have no great effect on the total pore surface area, but do affect the breaking force of tablets.

Riepma et al. (1993) have found that when different size fractions of dry-granulated slugs, prepared at 40 kN, were compressed into tablets with an equal force, 5 kN, the linear relationship between the breaking force and the permeametric specific surface area was found to be different for α-lactose monohydrate and roller-dried β-lactose tablets. These results are in a good agreement with the results of this study, where different granules from the same material produce different total pore surface area (Fig. 2).

3.3. Mean pore diameter

The relationship between breaking force and mean pore diameter is not unique or unaffected by the material used to make tablets, and thus cannot be the sole factor for prediction of breaking force of tablets (Fig. 3). This behaviour is similar to the case of total pore volume and total pore surface area, from which the mean pore diameter is calculated.

3.4. Median pore diameter

The breaking force of tablets is highly dependent on the median pore diameter of tablets (Fig. 4). This dependence is, however, non-linear, i.e. more like a hyperbolic function or an exponential function. Similar behaviour has also been found previously for the average pore size of lactose tablets (Riepma et al., 1993). With increasing average pore diameter, the breaking force of tablets compressed from dry-granulated lactose slugs decreased non-linearly. This behaviour was, however, different for α-lactose monohydrate and roller-dried β-lactose. In a study reported by Zuurman et al. (1994), the behaviour of the average pore diameters of tablets compressed from α-lactose monohydrate granules prepared by wet-granulation was also consistent with the results of the present study.

The greater amount of polyvinylpyrrolidone in the granules (Juppo and Yliruusi, 1994) is obvi-

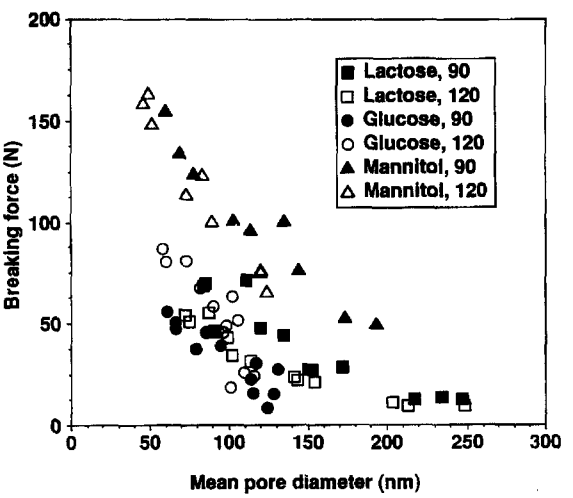

Fig. 3. Breaking force ($n = 20$) vs. mean pore diameter ($n = 3$) of lactose, glucose and mannitol tablets with two amounts of granulation liquid (ml/kg).

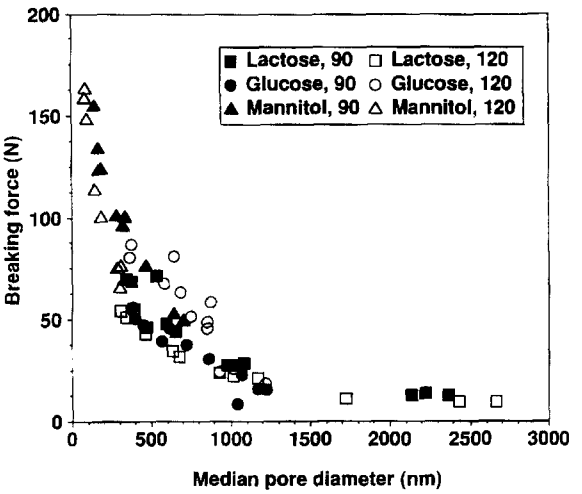

Fig. 4. Breaking force ($n = 20$) vs. median pore diameter ($n = 3$) of lactose, glucose and mannitol tablets with two amounts of granulation liquid (ml/kg).

ously the reason for the greater breaking force of glucose tablets, with 120 ml/kg of granulation liquid. Otherwise, the relationship between the breaking force and median pore diameter appears to be independent of the material.

It has been reported previously that the breaking force of the tablet is closely related to the fragmentation propensity of compressed granules (Wikberg and Alderborn, 1990). A relationship between the porosity of lactose and mannitol granules, and the breaking force of compressed tablets was found in a previous study (Juppo et al., 1995). More porous granules are compressed into tablets with a greater breaking force. The fragmentation tendency of porous granules is high.

According to a idealistic theory presented by Leuenberger et al. (1989), the attractive force is proportional to the particle diameter and inversely proportional to the square of the minimum distance. In the present study, however, it is difficult to make any conclusions from the effect of granule size on the breaking force of tablets, because the amount of binder and the porosity of granules also change with increasing amounts of granulation liquid.

When granules are compressed, the pore structure of tablets consists of intergranular pores, pores created by fragmentation of granules, and intragranular pores changed or unchanged during compression. The intergranular attractions, including van der Waals forces, hydrogen bonding, and even mechanical interlocking, are obviously smaller than the attraction between the primary particles among granules. Therefore, the number and size of large intergranular pores or large pores created by granule fragmentation control the breaking force of the tablet. This is why the median pore diameter, which is mostly affected by the amount of large pores, presents a unique relationship between the breaking force and pore structure of tablets. Apparently, the breaking force of tablets is more dependent on the number of large pores than on the number of small pores. The smaller the number of large pores, the greater the force needed to break the tablet.

3.5. Pore volume size distribution

Riepma et al., 1993 has claimed that equal pore size distributions were found for tablets compressed at 20 kN from dry-granulated slugs prepared with force of 20 kN from α-lactose monohydrate, and those prepared from roller-dried β-lactose, and that these two types of tablet had totally different breaking forces. They also claimed that the influence of starting material on the breaking force of tablets could not be explained with porosimeter results. However, on the basis of their results, when logarithmic scale and the number of columns in the histogram are taken into account, the distributions presented are clearly different, especially in pore diameter range of less than 1 μm. Thus, the entire pore structure may be related to the breaking force of tablets.

In the current study, the pore volume-size distributions of lactose, glucose and mannitol tablets that have the same total pore volume, 0.9 ml/g, show clearly the relationship of pore volume-size distribution to breaking force of tablets (Fig. 5). This supports the assumption that the entire pore size distribution determines the breaking force of tablets. With decreasing number of pores larger than 500 nm and increasing number of pores smaller than 200 nm in diameter, the breaking force of tablets increases. The breaking force of

tablets may also be affected by the material compressed (Fig. 5). Thus, the three materials are also studied separately. A representative example of pore size distributions of lactose tablets having an equal total pore volume, 0.12 ml/g, is presented in Fig. 6. The increase in the volume of pores with a diameter of 50–700 nm, and the shift of the maximum for pore volume-size distribution to the smaller pore diameter are strongly associated with increased breaking force. This is in good agreement with the relationship of median pore diameter and breaking force. The smaller the number of large pores, the greater force needed to break the tablet.

In an example using glucose tablets, the increase in the volume of pores with a diameter of 200–1000 nm, and the decrease in pores with a diameter larger than 1000 nm, appear to be related to large breaking force (Fig. 7). However, it is important to note that this was not always as consistent as the example presented for glucose tablets. The breaking force of glucose tablets is affected more by the amount of PVP than are the other two types of tablet, as was also found for median pore diameter.

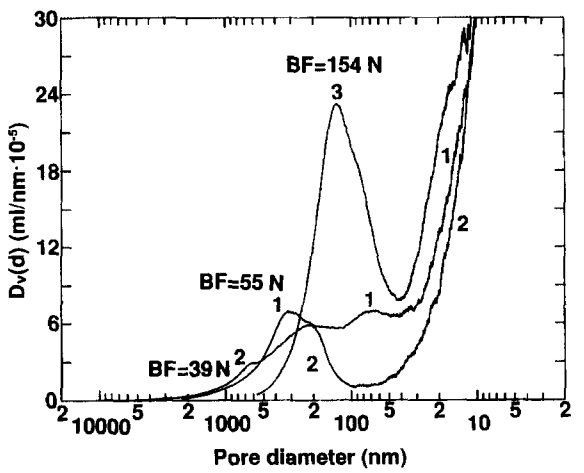

Fig. 5. Pore volume-size distributions of lactose (1), glucose (2) and mannitol (3) tablets having equal total pore volumes: 0.9 ml/g (BF = breaking force of tablets). Lactose tablets: amount of liquid, 120 ml/kg; compression speed, 64 rpm; compression force, 16 kN. Glucose and mannitol tablets: amount of liquid, 90 ml/kg; compression speed, 30 rpm; compression force, 12 kN.

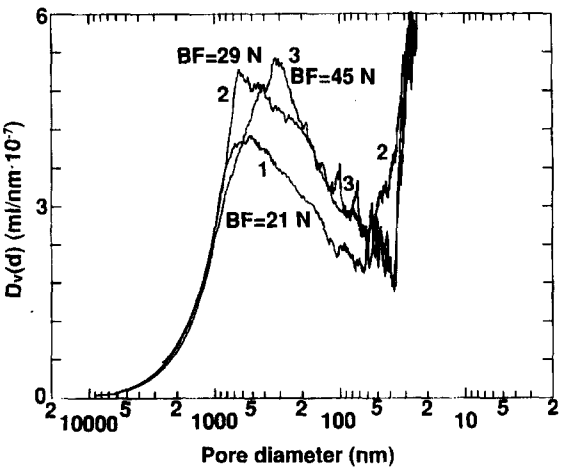

Fig. 6. Pore volume-size distributions of lactose tablets having equal total pore volumes: 0.12 ml/g (BF = breaking force of tablets).(1) Amount of liquid, 120 ml/kg; compression speed, 64 rpm; compression force, 8 kN. (2) Amount of liquid, 90 ml/kg; compression speed, 64 rpm; compression force, 8 kN. (3) Amount of liquid, 90 ml/kg; compression speed, 64 rpm; compression force, 12 kN.

For mannitol tablets, the breaking force was greater when the maximum for pore volume-size distribution was at smaller pore diameter, and the volume of pores larger than 200 nm was reduced (Fig. 8). A large amount of small pores (< 200 nm)

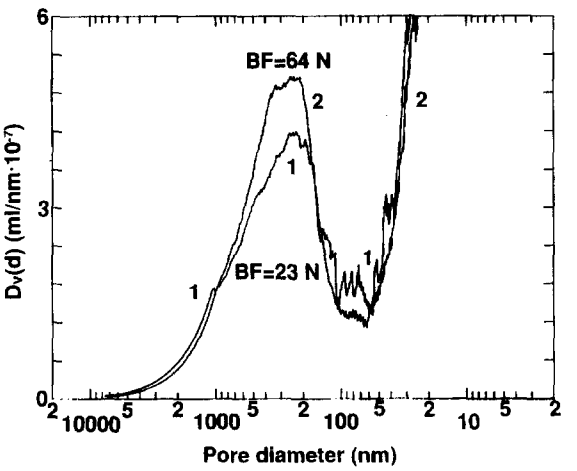

Fig. 7. Pore volume-size distributions of glucose tablets having equal total pore volumes: 0.098 ml/g (BF = breaking force of tablets). (1) Amount of liquid, 90 ml/kg; compression speed, 30 rpm; compression force, 8 kN. (2) Amount of liquid, 120 ml/kg; compression speed, 47 rpm; compression force, 12 kN.

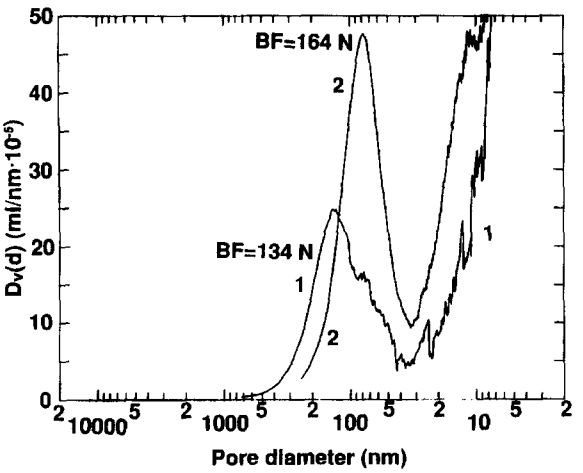

Fig. 8. Pore volume-size distributions of mannitol tablets having equal total pore volumes: 0.093 ml/g (BF = breaking force of tablets). (1) Amount of liquid, 90 ml/kg; compression speed, 47 rpm; compression force, 12 kN. (2) Amount of liquid, 120 ml/kg; compression speed, 30 rpm; compression force, 12 kN.

in mannitol tablets was also related to a high breaking force.

4. Conclusions

As far as compressed granules are concerned, evidently the absence of large pores in the tablet affects the breaking force more than a large number of small pores does. This is indicated by the fact that there is no overall dependence of breaking force on total pore surface area, while there is a dependence on median pore diameter. This is due to the coarse structure of the granules before compression and to extensive fragmentation during compression. Fragmentation and plastic deformation of granules contributes to the reduction in the size and number of large intergranular and intragranular pores. On the basis of pore volume size distributions, it can be concluded that, regardless of the material, the increased breaking force of the tablets is related to the decrease in the volume of large pores and to the shift of the maximum of pore volume size-distribution towards smaller pore diameter.

Acknowledgements

I am grateful to the Foundation for the 350th Anniversary of the University of Helsinki for financial support. I also thank the Orion Corporation, Orion-Farmos for placing the mercury porosimeter at my disposal.

References

de Boer, A.H., Vromans, H., Lerk, C.F., Bolhuis, G.K., Kussendrager, K.D. and Bosch, H., Studies on tableting properties of lactose. Part III. The consolidation behaviour of sieve fractions of crystalline α-lactose monohydrate. *Pharm. Weekblad*, 8 (1986) 145–150.

de Jong, J.A.H., Tablet properties as a function of the properties of granules made in a fluidized bed process. *Powder Technol.*, 65 (1991) 293–303.

Hiestand, E.N., Dispersion forces and plastic deformation in tablet bond. *J. Pharm. Sci.*, 74 (1985) 768 770.

Juppo, A.M., Change in porosity parameters of lactose, glucose, and mannitol granules caused by low compression force. *Int. J. Pharm.*, (1995a) in press.

Juppo, A.M., Porosity parameters of lactose, glucose, and mannitol tablets obtained with mercury porosimetry. *Int. J. Pharm.*, (1995b) in press.

Juppo, A.M. and Yliruusi, J., Effect of amount of granulation liquid on total pore volume and pore size distribution of lactose, glucose, and mannitol granules. *Eur. J. Pharm. Biopharm.*, 40 (1994) 299 308.

Juppo, A.M., Yliruusi, J., Kervinen, L. and Ström, P., Determination of size distribution of lactose, glucose, and mannitol granules by sieve analysis and laser diffractometry. *Int. J. Pharm.*, 88 (1992) 141 149.

Juppo, A.M., Kervinen, L., Yliruusi, J. and Kristoffersson, E., Compression of lactose, glucose, and mannitol granules. *J. Pharm. Pharmacol.*, in press.

Leuenberger, H., Bonny, J.D., Lerk, C.F. and Vromans, H., Relation between crushing strength and internal specific surface area of lactose compacts. *Int. J. Pharm.*, 52 (1989) 91–100.

Mashadi, A.B. and Newton, J.M., The characterisation of the mechanical properties of microcrystalline cellulose: a fracture mechanics approach. *J. Pharm. Pharmacol.*, 39 (1987) 961–965.

Pitt, K.G., Newton, J.M. and Stanley, P., Effects of compaction variables on porosity and material tensile strength of convex-faced aspirin tablets. *J. Pharm. Pharmacol.*, 42 (1990) 219 225.

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.

Riepma, K.A., Veenstra, J., de Boer, A.H., Bolhuis, G.K., Zuurman, K., Lerk, C.F. and Vromans, H., Consolidation and compaction of powder mixtures. II. Binary mixtures of different particle size fractions of α-lactose monohydrate. *Int. J. Pharm.*, 76 (1991) 9–15.

Riepma, K.A., Zuurman, K., Bolhuis, G.K., de Boer, A.H. and Lerk, C.F., Consolidation and compaction of powder mixtures. III. Binary mixtures of different particle size fractions of different types of crystalline lactose. *Int. J. Pharm.*, 85 (1992) 121–128.

Riepma, K.A. Vromans, H., Zuurman, K. and Lerk, C.F., The effect of dry granulation on the consolidation and compaction of crystalline lactose. *Int. J. Pharm.*, 97 (1993) 29-38.

Rowe, R.C. and Roberts, R.J., Simulation of crack propagation in porous compacted specimens of microcrystalline cellulose. *Eur. J. Pharm. Biopharm.*, 40 (1994) 9–13.

Ryshkewitch, E., Compression strength of porous sintered alumina and zirconia. *J. Am. Ceramic Soc.*, 36 (1953) 65–68.

Selmeczi, B., Der Einfluß des Pressdruckes auf die physikalischen Eigenschaften verschieden hergestellter Tabletten. *Arch. Pharm.*, 307 (1974) 755–760.

Vromans, H., Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H., Studies on tableting properties of lactose. Part. 2. Consolidation and compaction of different types of crystalline lactose. *Pharm. Weekblad*, 7 (1985) 186–193.

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 (1990) 23–27.

York, P., Bassam, F., Rowe, R.C. and Roberts, R.J., Fracture mechanics of microcrystalline cellulose powders. *Int. J. Pharm.*, 66 (1990) 143–148.

Zuurman, K., Riepma, K.A., Bolhuis, G.K., Vromans, H. and Lerk, C.F., The relationship between bulk density and compactibility of lactose granulations. *Int. J. Pharm.*, 102 (1994) 1–9.