J. Pharm. Pharmac., 1970, 22, Suppl., 86 S–94 S Received March 3, 1970

The influence of wet and dry granulation methods on the pore structure of lactose tablets

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The conditions of wet granulation influenced the pore structure of lactose tablets, prepared over a wide range of tabletting pressures. Dry granulation, on the other hand, only influenced pore structure when slugging pressures were high, the granules were coarse and tabletting pressures were low. Mercury porosimetry revealed intense granule fragmentation when dry granulated materials were compressed. The effect of the change of pore size distribution on liquid penetration into tablets is discussed.

Granulation exerts a considerable influence on many properties of a tablet, such as dissolution (Solvang & Finholt, 1970), compressibility (Gray, 1968), weight and dose uniformity (Hersey, 1965) and strength (Raff, Robinson & Svedres, 1961). One mechanism by which granulation may affect the properties of a tablet is by its influence on pore structure. Ganderton & Selkirk (1970) have shown that binder concentration and granule size affect pore structure.

The present study examines two fundamentally different methods of granulation: a dry method in which the granules are produced by compression causing cohesion of the particles (slugging) and a wet method in which the particles are linked by solid bridges, formed during drying of the wetted powder mix (wet massing and screening). The influence of these granulation methods on pore structure has been investigated by measuring porosity, air permeability and the penetration of wetting and non-wetting liquids into a tablet.

EXPERIMENTAL

Wet granulation

Finely powdered lactose was mixed with water in a Z-blade mixer (Duplex Model OO, Morton Machines Ltd., Wishaw, Scotland) for 5 min and forced through a coarse screen. The granules were dried to a constant weight at 70° and rescreened. Sieve fractions $-8+16$, $-16+22$, $-30+44$ and $-60+85$ were collected. The granules were made with a mass containing 13 or 25% v/w of water. The lower massing water concentration represented the minimum amount of water necessary to form coherent granules and the higher massing water concentration, the wettest conditions allowing satisfactory movement of the mass through the screen.

Dry granulation

Lactose powder was compressed, in a large punch and die set, at pressures of 50, 150 and 270 MNm^{-2} to form cylindrical slugs 38·1 mm in diameter. The slugs were removed from the die, broken down on a reciprocating granulator (Model 6, Jackson

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and Crockatt Ltd., Glasgow) and the granules sieved. The sieve fractions −8 + 16, −16 + 22, −30 + 44, −60 + 85 were collected.

Compression

A weighed quantity of granules was placed in a lubricated die sealed at one end by a spigot. The upper punch was inserted and the assembly compressed over a pressure range of 7 to 140 MNm^{-2} between the platens of a hydraulic press. The compaction force was measured in the manner described by Shotton & Ganderton (1960) by means of strain gauges affixed to the shank of the punch.

Porosity, permeability and liquid penetration tests

The porosity of a tablet was calculated from its volume, weight and the density of the material.

The permeability was measured by the method of Lea & Nurse (1939) and the results are expressed as the permeability coefficient previously described (Ganderton & Selkirk, 1970).

The rate of penetration of cyclohexane into a tablet under the influence of capillary forces was measured by the method of Ganderton & Selkirk (1969).

Measurement of the penetration of mercury into tablets was made with a Mercury Penetration Porosimeter (Model 905-1, Coulter Electronics Ltd., Dunstable, Bedfordshire). Five tablets were placed in the sampler holder. The pressure was reduced to 2·7 Nm^{-2} and the holder completely filled with mercury. The penetration pressure was increased incrementally from 3·5 kNm^{-2} to a maximum of 350 MNm^{-2} and for each increase the volume of mercury penetrating the pores was noted.

The distribution of the size of the pores within the tablet was derived from the data by the method of Ritter & Drake (1945).

RESULTS

Dry granulation

The decrease in porosity of lactose slugs with increasing slugging pressure is given in Table 1. When these slugs are broken up to form granules, the pore space within the granules (intragranular porosity) will show similar variation.

Table 1. *The effect of compression on the porosity of lactose slugs*

Slugging pressure MNm^{-2}	Porosity %
50	22·0
150	14·4
270	10·5

When these materials were tabletted, granules of −8 + 16 mesh size, prepared at high slugging pressures, gave the most permeable tablets (Fig. 1A). However, the influence of slugging pressure decreased as the degree of tablet compression increased. With tablets made from −60 + 85 mesh granules (Fig. 1B), slugging pressure only influenced permeability when the porosity of the tablets was 20% or more.

The effect of slugging pressure on the pore size distribution of tablets, prepared from −8 + 16 mesh granules is shown in Fig. 2A and the corresponding results for tablets made from −60 + 85 mesh granules in Fig. 2B.

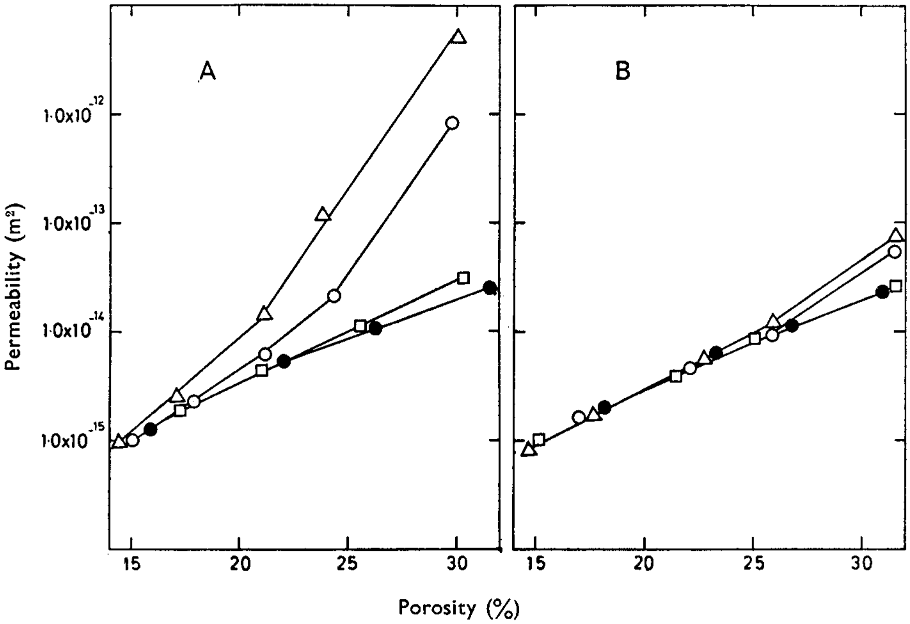

FIG. 1. The effect of slugging pressure on the permeability of lactose tablets made from (A) —8 + 16 sieve granules and from the ungranulated powder and (B) from —60 + 85 sieve granules and ungranulated powder. △ 270 MNm^{-2}. ○ 150 MNm^{-2}. □ 50 MNm^{-2}. ● Ungranulated powder.

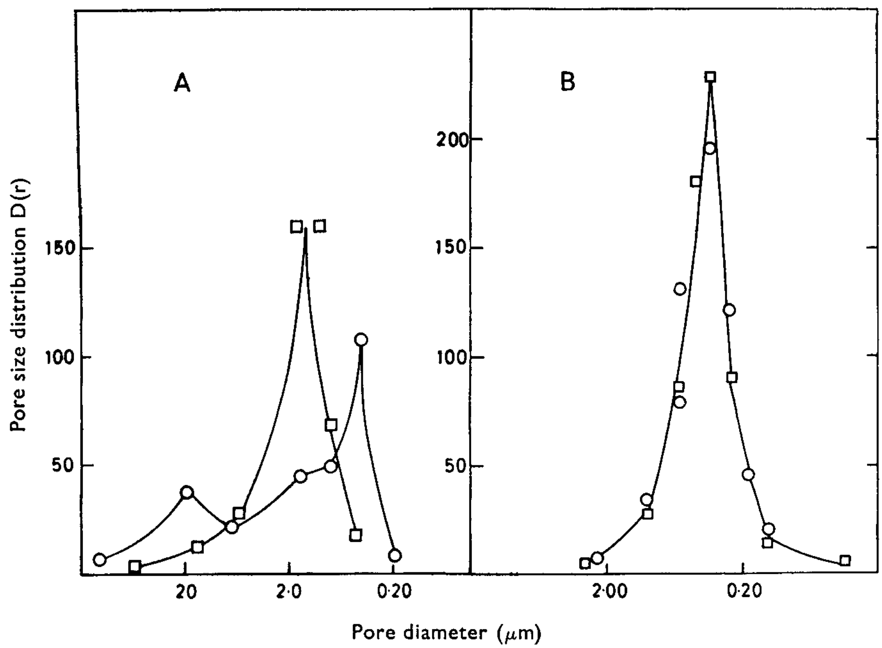

FIG. 2. The effect of slugging pressure on the pore size distribution of lactose tablets of porosity 26·5%, made from (A) —8 + 16 mesh (B) —60 + 85 mesh granules. ○ 270 MNm^{-2}. □ 50 MNm^{-2}.

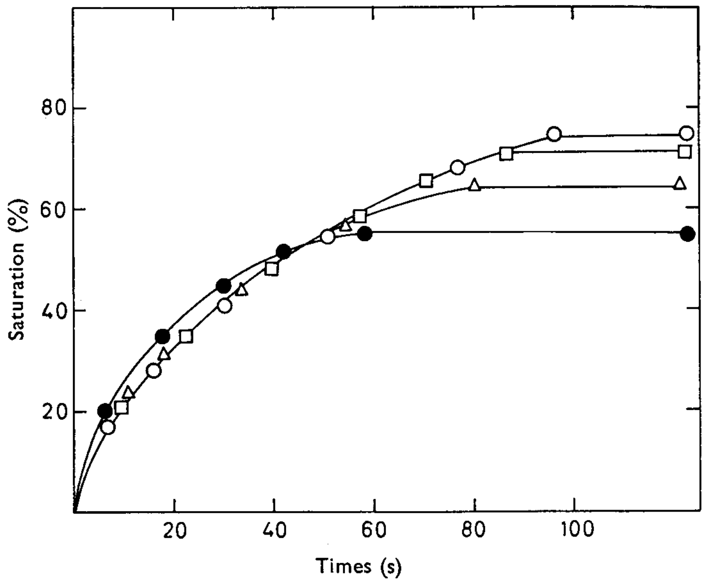

FIG. 3. The effect of granule size on the rate of cyclohexane penetration into lactose tablets made from granules slugged at 270 MNm^{-2}. ● —8 + 16 sieve fraction. △ —16 + 22 sieve fraction. □ —30 + 44 sieve fraction. ○ —60 + 85 sieve fraction.

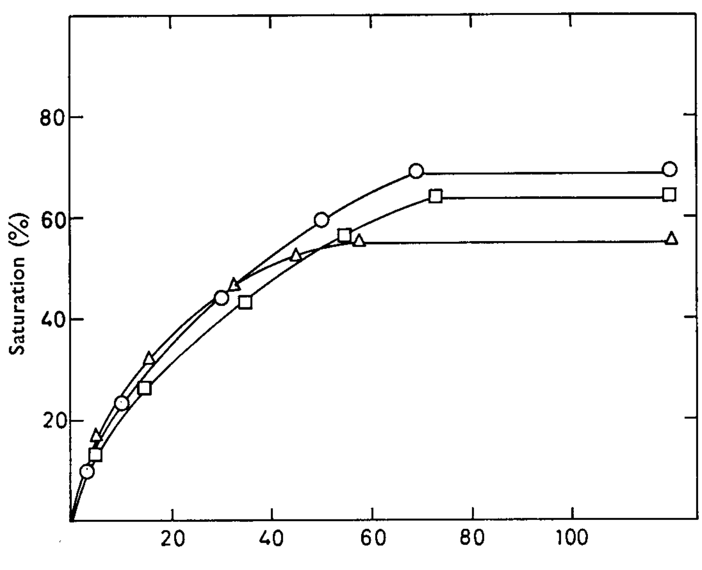

FIG. 4. The effect of slugging pressure on the rate of penetration of cyclohexane into lactose tablets prepared from —8 + 16 mesh granules. ○ 50 MNm^{-2}. □ 150 MNm^{-2}. △270 MNm^{-2}.

The influence of granule size on the penetration, by cyclohexane, into tablets made from granules prepared at a slugging pressure of 270 MNm^{-2} is shown in Fig. 3. The fraction of void space saturated, when penetration ceased, was found to decrease with an increase in the size of the granules which had been tabletted. The initial rate of penetration was however unaffected by granule size. The rate of cyclohexane penetration into tablets made from −8 + 16 granules was also independent of slugging pressure but the extent of saturation decreased as the slugging pressure increased (Fig. 4).

Table 2 indicates the role of tabletting pressure on the penetration of cyclohexane into tablets prepared from −8 + 16 mesh granules. As tabletting pressure increased, the rate of cyclohexane penetration decreased but the extent of saturation of the tablets increased. This increase in saturation with increase in tabletting pressure was most marked in those tablets prepared from granules made at a slugging pressure of 270 MNm^{-2}.

Table 2. *The effect of compression on the penetration of cyclohexane in lactose tablets made from coarse slugged granules*

	Time for 30% saturation (s) at Slugging pressures:		
Tabletting pressure	50 MNm^{-2}	150 MNm^{-2}	270 MNm^{-2}
30 MNm^{-2}	15·0 ± 1·0	18·0 ± 1·0	13·0 ± 1·0
50 MNm^{-2}	29·0 ± 2·0	23·0 ± 2·0	20·0 ± 2·0
130 MNm^{-2}	62·0 ± 2·0	58·0 ± 2·0	61·0 ± 2·0

	Final % saturation at Slugging pressures:		
Tabletting pressure	50 MNm^{-2}	150 MNm^{-2}	270 MNm^{-2}
30 MNm^{-2}	69·0 ± 2·0	64·0 ± 2·0	54·5 ± 2·0
50 MNm^{-2}	75·0 ± 1·5	73·5 ± 2·0	60·7 ± 1·5
130 MNm^{-2}	78·5 ± 1·5	80·0 ± 1·0	80·0 ± 1·5

Comparative data for wet and dry granulation

A comparison of the permeability of tablets made from wet granulated and dry granulated materials is made in Fig. 5. Changes in permeability, induced by variation in massing water concentration, are much smaller than those produced by variation in slugging pressure.

Fig. 6 shows the effect of the method of granulation on the cumulative pore size distribution of tablets. Tablets of 29% porosity, made from dry granulated material, showed a coarser pore structure than the corresponding tablets made from wet granulated material. However, for tablets of 15% porosity, the position was reversed, with a coarser pore structure being found with tablets made from the wet granulated materials.

In Table 3, values for the extent of saturation on cessation of penetration of cyclohexane into tablets prepared from wet and dry granulated material are compared with tablets made from the ungranulated powder.

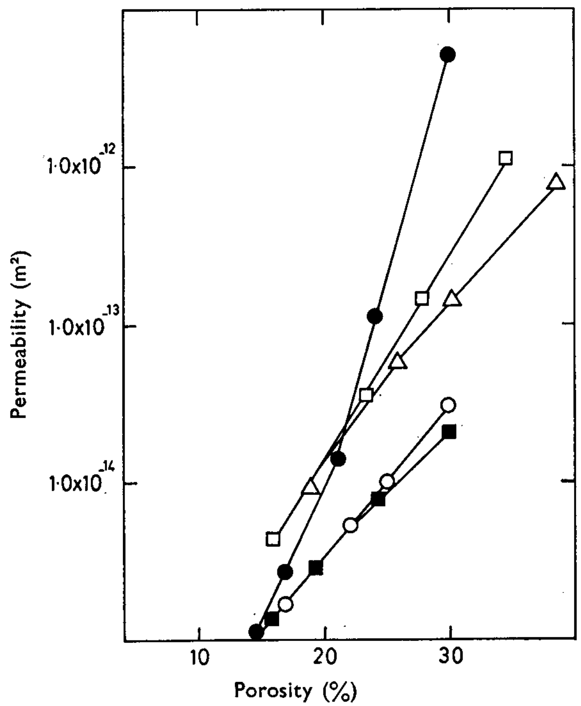

FIG. 5. A comparison of the permeability of lactose tablets made from —8 + 16 mesh granules prepared by wet and dry granulation processes. ● Granules slugged at 270 MNm^{-2}. ○ Granules slugged at 50 MNm^{-2}. □ Granules massed with 25% water. △ Granules massed with 13% water. ■ Ungranulated powder.

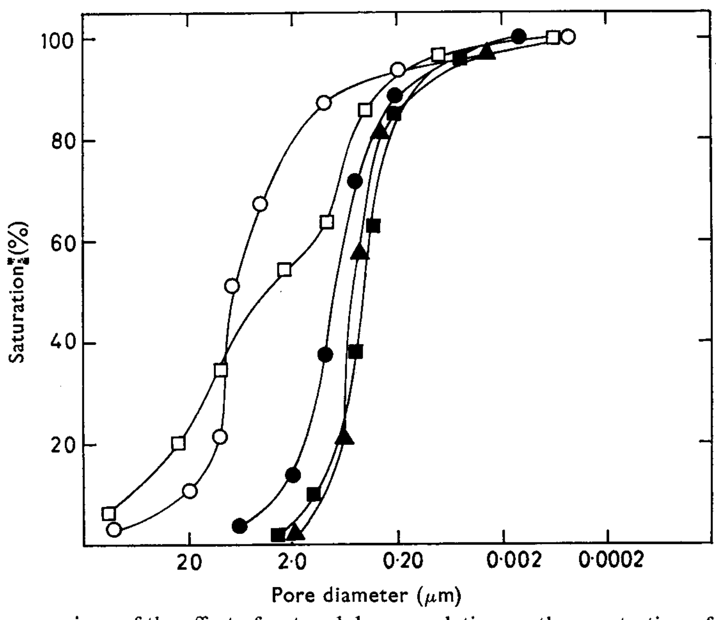

FIG. 6. A comparison of the effect of wet and dry granulation on the penetration of mercury into lactose tablets prepared from —8 + 16 mesh granules. The closed symbols represent results made at 15% porosity and the open symbols at 29% porosity. ○ Granules massed with 25% water. □ Granules slugged at 270 MNm^{-2}. ▲ Ungranulated powder.

Table 3. *A comparison of the saturation of lactose tablets of porosity 26·5%, made from granules prepared by wet and dry granulation methods*

Type of granulation	Granule size (mesh fraction)	Final % saturation
13% force screened	$-8+16$	65·5
13% force screened	$-60+85$	72·0
25% force screened	$-8+16$	58·0
25% force screened	$-60+85$	69·5
270 MNm^{-2} slugged	$-8+16$	54·5
270 MNm^{-2} slugged	$-60+85$	75·0
50 MNm^{-2} slugged	$-8+16$	69·0
50 MNm^{-2} slugged	$-60+85$	76·5
Ungranulated powder	<170	75·0

DISCUSSION

For a given powder, the methods and conditions of granulation interact with tabletting pressure and granule size to determine the pore structure of a tablet. An increase in tabletting pressure produces a finer pore structure for all materials, as shown by their decrease in permeability. Granule size influences that part of the pore structure of a tablet which arises during compression from the spaces between granules (intergranular porosity). The method and conditions of granulation affect both *inter*granular and *intra*granular pore structure by changing the degree of packing within the granules, and the strength of the granules.

The highest slugging pressures used produced a granule with an intragranular porosity of 10·5%. Compression of this material to form a tablet of a given porosity will require less deformation of the granules than a tablet made from dry granulated material of higher intragranular porosity. A coarse intergranular pore system will be more readily sustained, especially when tabletting pressures are low. The discontinuous pore size distribution, shown in Fig. 3, is then obtained. It has a maximum frequency of coarse pores at 17 μm and of fine pores at 0·3 μm. Such a pore size distribution will give rise to the high permeability shown in Fig. 1. This bimodal pore size distribution is absent in tablets made from granules prepared at a slugging pressure of 50 MNm^{-2}. A high intragranular porosity and low granule strength permits extensive granule fragmentation. The pore system is reorganized to give a simple size distribution with a maximum frequency at 1·3 μm. Such a tablet is only slightly more permeable than the corresponding one prepared from ungranulated powder (Fig. 1A).

If small granules are tabletted, the pores between the granules are much finer and the pore size distribution is less complex. At low tabletting pressures, the pore size distribution of tablets made from granules slugged at 50 and 270 MNm^{-2} is very similar, the mode occurring at a little under 1μm.

In a wet granulation process, increase in massing liquid concentration has only a small effect on the intragranular porosity (Hunter, B. M., unpublished observations). The effect on the strength of the granules however, can be marked, so that a coarse structured tablet can be made if coarse, strong granules are used (Ganderton & Selkirk, 1970).

Granules prepared by wet and dry methods behave differently on compression. In the permeability comparisons made in Fig. 5 the coarsest pore structures are found in tablets, produced at low tabletting pressures, from $-8 + 16$ mesh granules made at a slugging pressure of 270 MNm^{-2}.

There is, however, a marked reduction in the permeability of these tablets as tabletting pressure is increased so that, for tablet porosities of less than 20%, the permeability is less than that of the same materials which have been wet granulated and compressed. Thus, although a coarse intergranular network may be envisaged for tablets prepared at low tabletting pressures from dry granulated materials, a period of intense granule fragmentation must occur. This fragmentation is shown by the change in the cumulative pore size distribution given in Fig. 6. At 29% tablet porosity a much wider pore size distribution is exhibited by tablets prepared from coarse granules slugged at 270 MNm^{-2}. A fifth of the void space exists as pores greater than 27·0 μm, whereas the comparable figure for the tablets of wet granulated material is only 9·8 μm. The position is reversed at 15% porosity where the respective values are 0·63 and 1·2 μm. The pore size distribution of tablets made from dry granulated material is then only slightly different from tablets prepared from the ungranulated powder.

Decrease in granule size, or slugging pressure, reduces the influence of the dry granulation process on the pore structure of a tablet. The simultaneous operation of both factors yields tablets with permeabilities little different to compressed powder (Fig. 5). In contrast the permeability of tablets made from the wet granulated fine materials is some four times higher than tablets of ungranulated powder at the highest tabletting pressures used.

On this evidence the influence of granulation by slugging on the pore structure of tablets is destroyed by high tabletting pressures. Granules formed by wet granulation, on the other hand, seem more robust and the influence of granulation in promoting a coarser, wider pore size distribution persists to the highest tabletting pressures used. These conclusions are reached despite the wider variations possible in the conditions of dry granulation. Granulation pressures are only limited by the mechanical aspects of the compressors and, in this study, very high pressures were used. On the other hand, critical limits are placed on the conditions of wet granulation to ensure satisfactory performance during forced screening.

Pore size distribution influences the penetration of a wetting liquid into a tablet. Despite the lower suction potential of a coarse capillary, the rate of advance of a liquid is higher (Carman, 1941). The contribution of such capillaries should give a higher overall penetration rate for structures of wide pore size distributions. Uptake of cyclohexane is not, however, enhanced by formulation variables such as granule size or granule strength which widen pore size distribution (Figs 3 and 4). This may be explained by uneven penetration. A relatively coarse pore structure is produced by the interaction of high slugging pressure, coarse granules and low tabletting pressure. Rapid penetration of the largest capillaries isolates other areas of finer pore structure from which air cannot escape. These areas then make no contribution to the overall uptake of liquid. In tablets of narrower pore size distribution, although the rates of capillary penetration are lower, larger parts of the pore structure participate in liquid uptake. Such a concept is supported by the fraction of the pore space filled when penetration ceases; this falls as the pore size distribution widens. Higher final saturations are therefore found in dry granulated tablets (Table 3). Coarse granules formed at high slugging pressures give tablets of low final saturation when tabletting pressures are low. This provides an exception consistent with its wide pore size distribution. With tablets prepared from granules made by slugging, the erosion of the coarse pore structure with increasing compression provides the high saturation values given in Table 2.

Acknowledgements

The authors would like to express their sincere thanks to Dr. H. Palmer of ICI Dyestuffs Division for his invaluable assistance. They gratefully acknowledge the financial support of the Science Research Council.

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