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The effect of granule properties on the pore structure of tablets of sucrose and lactose

D. GANDERTON AND A. B. SELKIRK

School of Pharmaceutical Sciences, University of Strathclyde, Glasgow, U.K.

Air permeability and liquid penetration of tablets of sucrose and lactose have been measured. The tablets had been compressed over a wide pressure range from granules which varied in bulk density, size and strength. The degree to which inter- and intra-granular pore structure within the tablet was sustained varied with these properties; low pressure, high density, high strength and large size promoting a more open but less uniform structure. Such structures allowed rapid penetration of liquid through a coarse pore network which isolated a large fraction of the total pore space. Thus tablets of high permeability gave low final degrees of saturation whereas less permeable tablets became fully saturated.

The initial stage in the dissolution of a compressed tablet is the penetration of the structure by the dissolution medium by way of a network of pores. To ensure the effective disruption which is necessary for fast dissolution, penetration should be even and quick.

The pore network of a tablet is exceedingly complex. Capillaries run through in a tortuous random manner, their cross-section varying in both area and shape. Interconnection is profuse and some capillaries may be blind. The network originates in two ways. The first is from the voids present within the granules themselves. These will be referred to as intragranular pores and their size and shape will depend primarily on the size and shape of the particles composing the granules, and the method of granulation. A network of larger, intergranular pores is derived during compression from the spaces between the granules, the size and friability of the granules mainly determining its structure.

The duality of pore structure will be lost, in part at least, during compression when, by the processes of fragmentation and consolidation, granule integrity is progressively lost. These processes will be least effective in tablets prepared from granules which are both large and strong, when resistance to deformation will partly sustain a coarse, intergranular pore network. If, on the other hand, granules are easily deformed, this effect will be absent, the distribution of pore sizes will become more uniform and the properties of the tablet determined by pore structure will not depend upon the properties of the granules.

In this study some aspects of the pore structure of tablets have been examined using air-permeability and liquid-penetration techniques on tablets prepared from sucrose and lactose granules.

Theoretical considerations

One analysis of flow in complex pore systems originates with the work of Kozeny (1927) and Carman (1937). Viscous flow in a capillary of non-circular cross-section was evaluated by means of an hydraulic radius, m, this radius being the ratio of the cross-sectional area of the capillary to its perimeter. The equation describing flow is then

$$u = \frac{m^2}{k_0 \eta} \frac{dP}{dL} \quad \ldots \quad (1)$$

where u is the flow velocity, η is the viscosity of the fluid and dP/dL is the pressure gradient, k_0 is a constant depending on the shape of the section. If it is circular, for example, $k_0 = 2$ and equation (1) becomes Poiseuille's Law.

If the pore space of a tablet is regarded as a bundle of capillaries, it too may be characterized by an hydraulic radius which will be determined by the total cross-section of the pores, their total perimeter and their size distribution. If the pore structure is reasonably uniform, this radius is equal to the ratio of the porosity and the specific surface. If, on the other hand, a wide distribution of pore sizes is present, the contribution of the fine pores, which give much of the internal surface, to flow within the tablet is negligible. A quite disproportionate amount of fluid passes through the coarse pores and experimental values of the mean hydraulic radius derived from equation (1) greatly exceed those calculated from porosity and specific surface.

The permeability of tablets. The volumetric flow rate Q of a fluid passing through a tablet of area A and thickness L is given by the equation

$$Q = \frac{V}{t} = -\frac{B_0 A}{\eta} \frac{dP}{dL} \quad \ldots \quad (2)$$

where η is the viscosity of the fluid and dP/dL is the pressure gradient within the tablet. The constant B_0 is the permeability coefficient. Since Q is related to the velocity of flow by $Q = uA\epsilon$, A being the area of the tablet and ϵ its porosity, equation (2) can be written

$$u = -\frac{B_0}{\eta\epsilon} \frac{dP}{dL}$$

Comparison with equation (1) shows that

$$B_0 = \frac{\epsilon m^2}{k_0} \quad \ldots \quad (3)$$

In measuring this coefficient by gas permeation, the flow rate varies from point to point within the tablet due to expansion of the gas as it moves from high to low pressure. Since the volume V of a gas is inversely proportional to the pressure, P:

$$Q = \frac{V}{t} = \frac{k}{Pt}$$

Substitution and rearrangement of equation (1) gives

$$\int_{P_1}^{P_2} P\,dP = -\frac{k\eta}{B_0 t A} \int_{O}^{L} dL$$

from which we derive the equation:

$$Q = \frac{B_0 A}{2L\eta} \cdot \frac{(P_1^2 - P_2^2)}{P_1} \quad \ldots \quad (4)$$

where Q is the flow rate measured at the upstream pressure P_1, and P_2 is the downstream pressure.

Penetration of liquids into a tablet. The force driving a liquid into a tablet is derived from the pressure differential ΔP associated with the curved liquid meniscus formed as the liquid enters the capillary. This force is determined by the capillary size, the contact angle θ between liquid and solid and the surface tension of the liquid, γ. The rate of penetration is dictated by the balance of this force and the opposing viscous resistance as the liquid moves through the capillary. Since the latter increases with penetration whereas the former remains fairly constant, penetration rate will fall as saturation proceeds. The capillary pressure developed in the tablet is given by Carman (1941)

$$\Delta P = \frac{\gamma \cos \theta}{m} \quad \ldots \quad (5)$$

At some time t, the liquid has penetrated a distance L. The velocity of penetration u, is given by equation (1).

$$u = \frac{dL}{dt} = \frac{m^2}{k_0 \eta} \frac{\Delta P}{L}$$

Substituting for ΔP by means of equation (5)

$$\frac{dL}{dt} = \frac{m\gamma \cos \theta.}{k_0 \eta L} \quad \text{At } t = 0, L = 0: \int_0^L L dL = \frac{m\gamma \cos \theta}{k_0 \eta} \int_o^t dt$$

Therefore

$$L^2 = \frac{2m\gamma \cos \theta}{k_0 \eta} t \quad \ldots \quad (6)$$

Since the total cross-sectional area of the capillaries does not vary with L, the volume of liquid taken up will be proportional to the length of penetration. Hence, as first shown by Washburn (1921), there is a linear relation between the square of the volumetric uptake and the time.

EXPERIMENTAL

Granulation

Lactose and sucrose, both as fine powders, were massed with water in a Z-blade mixer and then forced through coarse screens. The granules were dried to constant weight at 70° and rescreened. The amount of water used during massing was varied. Four lactose batches were prepared with the water content varying in four equal steps from 13 to 25% of the dry powder weight. With sucrose, the water content was 5, 7 or 9%. The granules were sieved and the mesh fractions: −8 + 16, −16 + 22, −30 + 44 and −60 + 85 selected for study.

Compression

The tapped bulk density of each fraction was determined in a 50 ml cylinder, the internal diameter of which corresponded approximately to the diameter of the punch and die (19·17 mm) used for compression. A weighed quantity of granules was placed in the lubricated die, sealed at one end by a spigot. The upper punch was inserted and the assembly compressed over a pressure range 9–105 MN m^{-2} between the platens of a hydraulic press. The compaction force was measured in a manner described by Shotton & Ganderton (1960) by means of strain gauges affixed to the shank of the punch. The porosity achieved at any pressure was calculated from the weight and volume of the tablet whilst still retained in the die. Measurements were therefore taken when the tablet was under some radial constraint. These conditions were reproduced in the permeability and penetration studies by testing the tablet in the die. This ensured a good seal between tablet and die in these tests and also allowed very friable tablets to be studied, advantages which outweighed the account of the very slight expansion suffered by the tablet during ejection.

Permeability and penetration tests

The permeability of the tablets was measured with an apparatus similar to that designed by Lea & Nurse (1939). A capillary flowmeter was used to measure the rate at which dry air was drawn through the tablet. Pressures promoting flow varied from 270 N m^{-2} to 65 kN m^{-2} and were measured by manometers containing kerosene or mercury. All manometers were fitted with one wide limb to facilitate reading and the other sloped to increase accuracy. The permeability coefficient was calculated from equation (4).

The rate at which a liquid penetrated the tablet was measured by moving the tablet to a position at which its lower surface was flush with the bottom of the die. This was placed in a cup which formed one arm of liquid-filled U-tube and the rate of uptake measured as the withdrawal from the other arm. Cyclohexane was used in all experiments to avoid the dissolution or disruption of the tablets.

RESULTS

From simple crushing tests with a spatula, it was observed that increase in the amount of the massing liquid increased the strength of the granules. This effect was most marked with the stronger sucrose granules.

The tapped bulk density of the granules varied little with their size, increasing only slightly as the size decreased. On the other hand, increase in the water content during massing markedly increased the bulk density, the porosity changing by up to 6% in the sucrose series and up to 10% in the lactose series.

With lactose, neither granule size nor massing water concentration influenced the relation between porosity and compaction force. The porosity of sucrose tablets produced at any pressure level increased as the size and massing concentration decreased. For example, at 27 MN m^{-2}, the porosity of sucrose tablets prepared from fine granules massed with 9% water was 4% less than the corresponding tablet massed with 5% water.

The relation between permeability and porosity for lactose massed with 13% water is shown in Fig. 1A. A permeability independent of granule size was also found with 17% massed lactose. With 21% massing, however, coarse granules gave more permeable tablets at very low pressures, the effect extending to higher pressures for the lactose massed with 25% water (Fig. 1B).

Data are presented for the coarsest granules in Fig. 2A which shows the extent to which granule strength affected permeability. This factor became less important as the size decreased until, at finest size, no effect could be found.

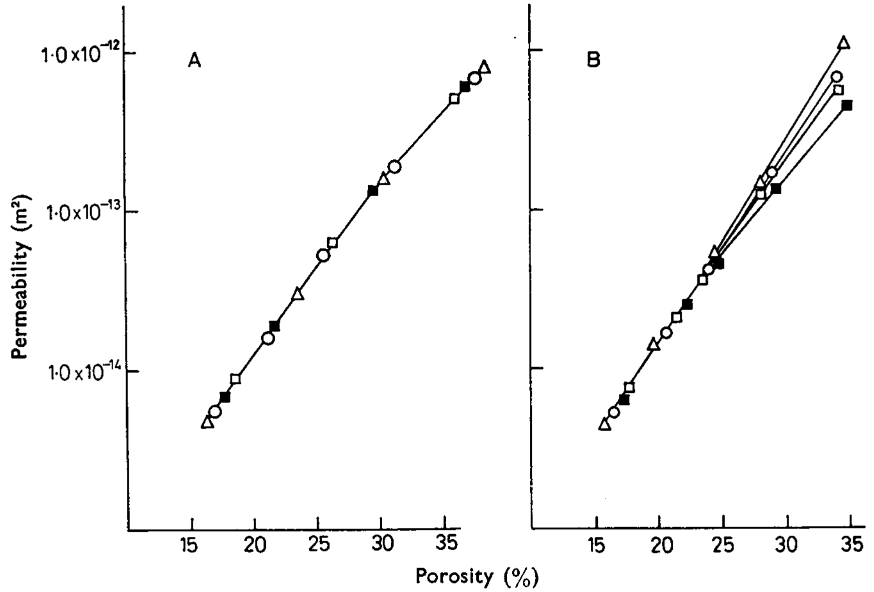

FIG. 1. The effect of granule size on the permeability of lactose tablets massed with A, 13% and B, 25% water. △ 1000–2000 μm. ○ 710–1000 μm. □ 355–500 μm. ■ 180–250 μm.

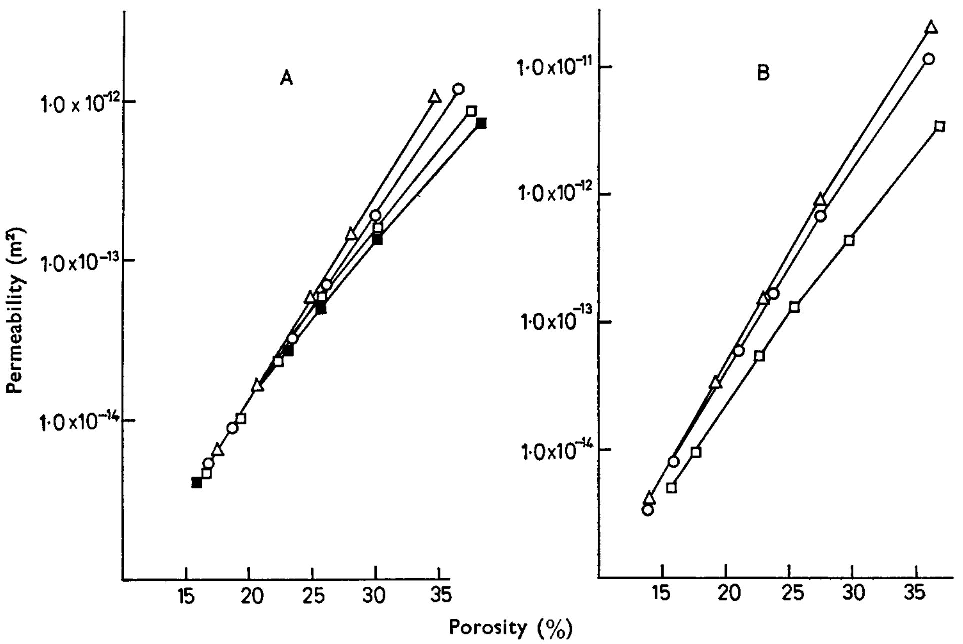

FIG. 2. A. The effect of massing water concentration on the permeability of lactose tablets. ■ 13%. □ 17%. ○ 21%. △ 25%.

B. The effect of massing water concentration on the permeability of sucrose tablets. □ 5%. ○ 7%. △ 9%.

The effects shown by the larger, stronger lactose granules were exhibited to a much higher degree by sucrose. As shown in Fig. 2B, the ability of large granules to maintain an open, permeable structure extended to high compaction pressures as the massing water concentration went up.

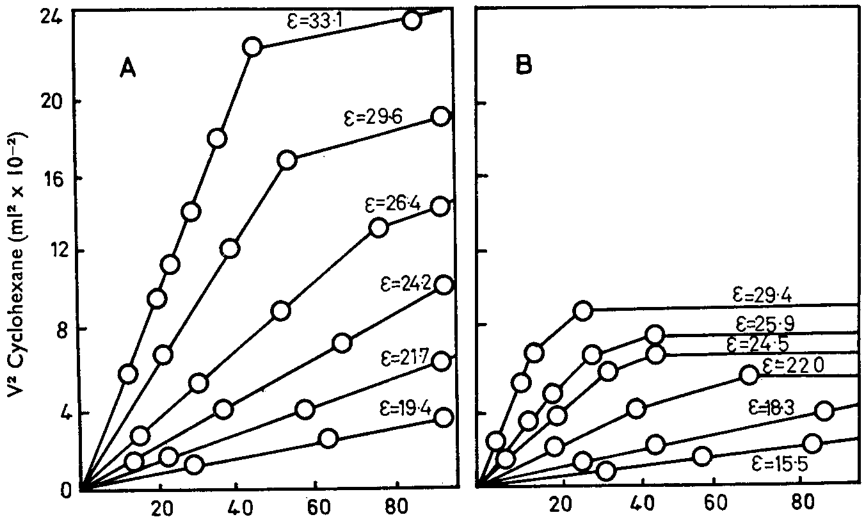

FIG. 3. Uptake of cyclohexane by tablets compressed from $-8 + 16$ granules. A. Lactose massed with 13% water. B. Sucrose massed with 9% water. Porosity values (ϵ%) are shown on the curves.

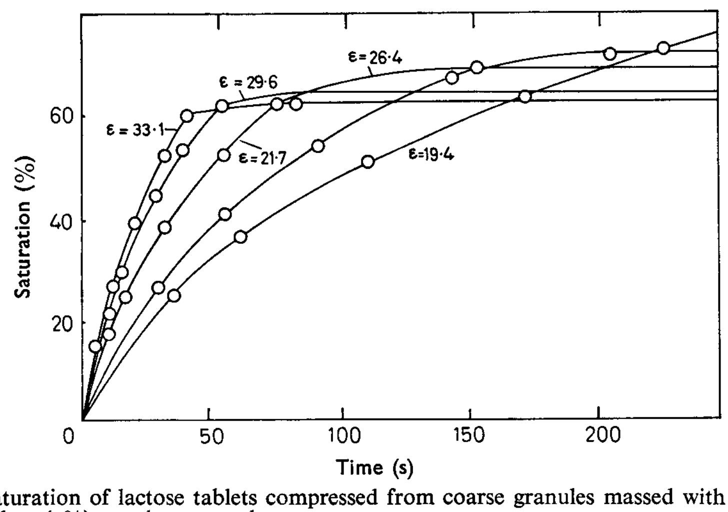

FIG. 4. Saturation of lactose tablets compressed from coarse granules massed with 13% water. Porosity values (ϵ%) are shown on the curves.

The permeability coefficient is related to a hydraulic radius by equation (3). The effect of granule properties on the latter are summarized in Table 1. Definition of the shape constant, k_0, is avoided by expressing values relatively, the hydraulic radius of the least permeable tablet being given the value 1.

Data from some penetration tests are given in Fig. 3. From the origin, the relation between the square of volume taken up and the time was linear as dictated by equation

(6). Before saturation was complete, however, penetration slowed, sometimes very abruptly, an effect most marked with stronger or larger granules.

The percentage of pores saturated when penetration ceased altogether increased with lower porosity (Fig. 4). At any given porosity, for the coarser granules, increase in granular strength reduced the final percentage saturation, although this became less effective at high pressure.

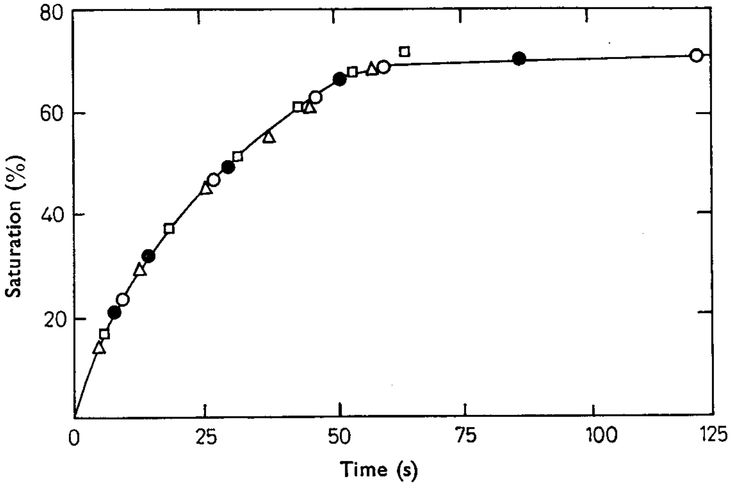

FIG. 5. Saturation of lactose tablets compressed to a porosity of 26% from fine granules massed with varying quantities of water. △ 13%. ○ 17%. ● 21%. □ 25%.

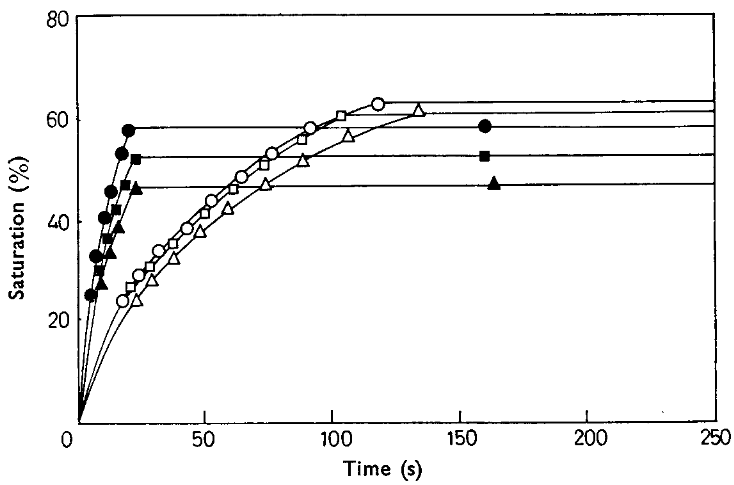

FIG. 6. Saturation of sucrose tablets prepared from fine granules massed with varying quantities of water. Triangles 5%. Squares 7%. Circles 9%. Open symbols represent data from low porosity tablets and closed symbols from high porosity tablets.

For the small lactose granules studied in Fig. 5 no effect of granule strength can be seen, while with the fine sucrose, the final percent saturation increased as the strength of the granules increased, although this effect was only noted at high porosities (Fig. 6).

DISCUSSION

The results described show that granule properties can greatly influence the pore structure of tablets. It is probable that the duality of this structure, as described earlier, is sustained in part even when compaction pressures are very high.

Some information on the size of the intragranular pores may be inferred from the bulk density of the uncompacted materials. Increase in the massing water concentration progressively increased bulk density. If we assume that the former has little effect on the shape and surface of the granules, packing to define the intergranular pore space will be much the same. Increase in the bulk density must then be ascribed to a decrease in the intragranular pore space. Compaction to a given overall porosity therefore requires less deformation in those granules massed with the most water.

A coarser intergranular pore structure characterized by a high permeability is more easily sustained in these cases. This is not necessarily related to the strength of the granules but rather to the particle packing within the granules before compression. Thus comparison, at any granule size, of the permeability of the lactose massed with 13% water to that massed with 17% shows that although both granules are very friable, the latter are more permeable. If, on the other hand, granule size is compared at the same particular massing concentration, when the intragranular pore structure before compaction is the same, no effect on permeability can be seen. The coarse intergranular pore structure of the large granules is not sustained in these materials and the overall pore structure, at any porosity level, is the same. Granule size does not, therefore, influence pore structure. This is not true of the lactose massed with higher concentrations of water. Here large granules are able to maintain a coarser intergranular pore structure as shown by their higher permeability, although this effect is limited to lower pressures when deformation is small. With the more robust sucrose granules summarized in Table 1, increase in granule size and strength simultaneously operate to maintain a coarse intergranular pore network which, in the case of the strongest granules, remains influential until almost the lowest porosities.

Inherent in the maintenance of an intergranular pore system is a wide and perhaps discontinuous distribution in the size of the pores. Such a distribution is characteristic of tablets produced from sucrose granules, especially at low pressure. The

Table 1. *Experimental values of relative mean hydraulic radius for sucrose and lactose tablets*

	$\epsilon = 30\%$			$\epsilon = 20\%$		
	Sucrose massing concentration					
Mesh size	5	7	9	5	7	9
8–16	1·34	2·37	2·92	1·14	1·45	1·64
16–22	1·18	2·00	2·28	1·05	1·38	1·52
30–44	1·14	1·70	1·97	1·05	1·34	1·45
60–85	1·00	1·41	1·67	1·0	1·26	1·41

	Lactose massing concentration							
	13	17	21	25	13	17	21	25
8–16	1·00	1·03	1·16	1·35	1·00	1·04	1·04	1·08
16–22	1·00	1·03	1·11	1·25	1·00	1·04	1·04	1·08
30–44	1·00	1·03	1·09	1·17	1·00	1·04	1·04	1·08
60–85	1·00	1·02	1·02	1·02	1·00	1·04	1·04	1·08

large pores will carry a disproportionate amount of fluid and the permeability will be high. Expressing this system in terms of a channel, a threefold increase in hydraulic radius occurred when size, strength and bulk density of the granules were varied in tablets compressed to a porosity of 30%. This factor was still over 1·6 at a porosity of 20%.

With the weaker lactose granules, the pore structure will be relatively uniform and the effect of granule properties on mean hydraulic radius are quite small, as shown in Table 1.

The inferences on pore structure drawn from permeability are supported by liquid penetration. A coarse intergranular pore structure permits a more rapid movement of liquid through the tablet than is found in tablets of the same porosity but with more even pore structure. However, in the former case, rapid penetration isolates other pore areas which cannot then be penetrated because the trapped air cannot escape. The fractional pore space of sucrose tablets which was saturated diminished as the size or strength, or both, of the granules increased. Similarly, destruction of the intergranular pores was shown by increased fractional saturation as the tablet was compressed to lower porosity.

The more even pore structure of the lactose tablets was reflected in the total saturation found with this material. Only at high porosities and with larger, stronger granules was the effect of an intergranular pore structure found.

Early stages of penetration with all materials obeyed a relation of the form given in equation (6). The linearity of this relation and its passage through the origin precludes any constriction at the surface of the tablet. The pore structure at the surface is not, therefore, made atypical by contact with a smooth metal surface during compression.

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