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A comparison of granules prepared by pan granulation and by massing and screening

D. GANDERTON AND B. M. HUNTER

Department of Pharmacy, University of Manchester, Manchester, M13 9PL, U.K.

Granules of lactose and calcium phosphate were prepared by pan granulation and by massing and screening. Capillary forces and the gentle action of tumbling in the pan were inadequate to compact the fine cohesive calcium phosphate but were highly effective with the less cohesive lactose where the absence of shear gave very high densification. Whereas massing and screening provided the necessary forces for consolidating calcium phosphate, with lactose a more open structure resulted which further dilated during screening. Increase in both moisture content and time of mixing increased granule density but the degree varied with both method and material as did granule shape, strength and compressibility.

The manifold physical advantages of a large powder aggregate or granule over the component particles has led to the adoption of granulation by many industries. Development of these methods, empirical until 1958, has attracted little systematic study although important scientific contributions have been made in the field of fertilizers by Newitt & Conway-Jones (1958), Capes & Dankwerts (1965) and ores by Kapur & Fuerstenau (1964), using pan granulation. The method used, together with large granule size and high liquid–solid ratio employed, renders the application of findings to a granulation produced by massing and screening somewhat uncertain. Although granulation by this last method has been somewhat neglected Neff & Morris (1968) studied the effect of granulation conditions on the dispersibility, bulk density and porosity of 'instantized' dried milk and demonstrated the susceptibility of these properties to liquid–solid ratio. Fonner, Banker & Swarbrick (1966) prepared granules by five different methods but variation in the binder concentration from method to method reduced the value of this work as a comparative study.

Little information is available on the influence of time of mixing, type of mixer, solid–liquid ratio or particle properties on the properties of granules or the tablets made from the granules, although inferences are often drawn from the behaviour of powder–liquid systems in pans (Pilpel, 1969).

A comparison of the pan granulation process and the conventional pharmaceutical method, using simple powder–liquid systems is therefore a first step in establishing the relation between granulation theory and pharmaceutical practice. Restricting the investigation to variation in solid–liquid ratio and mixing time, an examination of both process and product is made below.

MATERIALS AND METHODS

Materials

Lactose B.P. (Grade 350 A. Whey Products Ltd. Mean particle size 20 μm) was granulated using water as binder over the range 15–34% v/v.*

Calcium phosphate B.P.C. (Tricalcium phosphate. Albright and Wilson Ltd. Mean particle size 4 μm) was granulated with 10% w/v dextrose monohydrate B.P. solution, the quantity of binder varying between 117–191% v/v.

Pan granulation

A hemispherical pan, 40 cm in diameter inclined at 30° to the horizontal and rotated at 32 rev/min, was used. A charge of 2 kg of powder was placed into the rotating pan and the binding liquid sprayed onto the powder surface, at 5 ml s^{-1}, by means of a small atomizer. The pan was closed with a Perspex lid and after the prescribed process time the wet granules were discharged and tray dried, for 4 h at 70°, in a hot air oven.

Granulation by massing and screening

One kg of powder was massed in a z-blade mixer (Duplex Model 00, Morton Machine Co. Ltd., Wishaw, Scotland) with blades operating at 65 and 103 rev/min. The binding liquid was added as a continuous stream and after the specified time of mixing, half the mass was discharged through an oscillating granulator (Jackson Crockatt Model 6) equipped with a 16 mesh screen and the granules tray dried at 70°. The other half of the mass was dried unscreened. Both batches were dry granulated using a 12 mesh screen.

Characterization of granules

Particle size analysis. The particle size distribution of the granules was established by sampling and sieve analysis (B.S. 410 test sieves).

Tapped density. The tapped density of −12 +16 mesh granules was measured according to Neumann (1967). The measuring tube, 38·5 mm in diameter, was filled with 100 g of granules and dropped 200 times through a height of one centimetre.

Intragranular porosity. The internal porosity of the −12 +16 mesh granules was measured by the pycnometric method of Strickland, Busse & Higuchi (1956), the volume of mercury in the pycnometer being measured at intrusion pressures between 25 and 120 cm Hg.

Granule strength. The resistance of granules to fracture was measured by placing a −14 +16 mesh granule between the platens of a miniature press. The lower platen was driven upwards at 0·08 mm s^{-1} and the reaction of the granule measured by a sensitive load cell attached to the fixed upper platen. Electrical output from the load cell was fed to an ultraviolet recording galvanometer to give a continuous record of the signal. The test was repeated 20 times for each batch.

* The percentage moisture content is expressed as

$$\text{M.C. (\% v/v)} = \frac{\text{Vol of liquid}}{\text{Vol of dry solid}} \times 100$$

This method of expressing moisture content enables direct comparison to be made between results for different materials.

Granule shape. The shape of the −12 +16 mesh granules was estimated by measuring the ratio of the square of the perimeter to the area of enlarged photographic images (150×) using an opisometer and planimeter. Division of this value into that obtained for a circle, 12·57, gave a shape factor which approached unity as the granules became more spherical in shape. Measurement was made on five granules from each batch.

Granule compressibility. One g of −12 +16 mesh granules was placed in a die 19·05 mm in diameter closed at the lower end by a spigot. The instrumented upper punch was inserted and the assembly compressed, porosity of the granule mass being recorded as a function of pressure.

RESULTS

The particle size distribution of granules of lactose and calcium phosphate is given in Fig. 1.

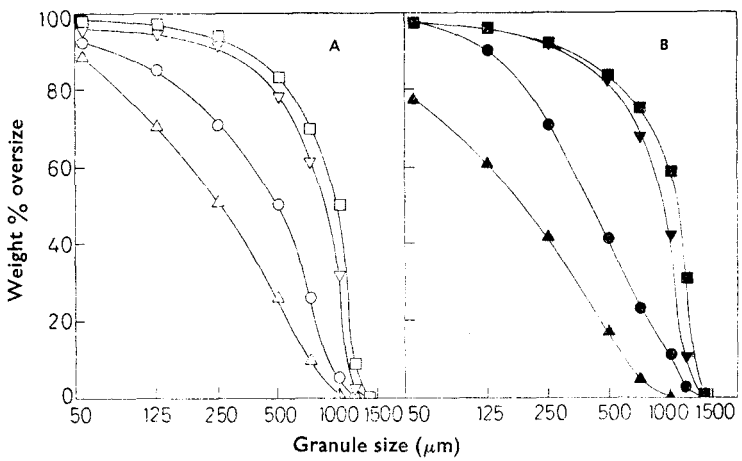

FIG. 1. Sieve analysis of granules prepared by massing and force screening. A. Lactose. Amount of binder added: △ 15·3% v/v, ○ 18·4% v/v, ▽ 23·0% v/v, □ 30·6% v/v. B. Calcium phosphate. Amount of binder added: ▲ 117% v/v, ● 125% v/v, ▼ 141% v/v, ■ 157% v/v.

Shape factors of typical massed and screened granules are compared to those of the equivalent pan granulated material in Table 1. Neither moisture content nor time of mixing had a significant effect on the shape factor.

Table 1. *Shape factors of granules prepared after* 60 *min processing.*

	Pan		Massed and screened	
	Shape factor	Standard deviation	Shape factor	Standard deviation
Calcium phosphate 157% v/v binder ..	0·93	0·04	0·78	0·05
Lactose 30·6% v/v binder ..	0·94	0·03	0·64	0·02

The intragranular porosity is derived from the weight and apparent volume of the granules in the pycnometer. The apparent volume of the material under test is the difference between the volume of the empty pycnometer and the measured

volume of mercury in the chamber with the granules present. As the external pressure is increased, mercury first fills the pores between the granules, completely enveloping the granules and then begins to enter the intragranular pores. The intragranular porosity is calculated from the volume before any internal pores are filled.

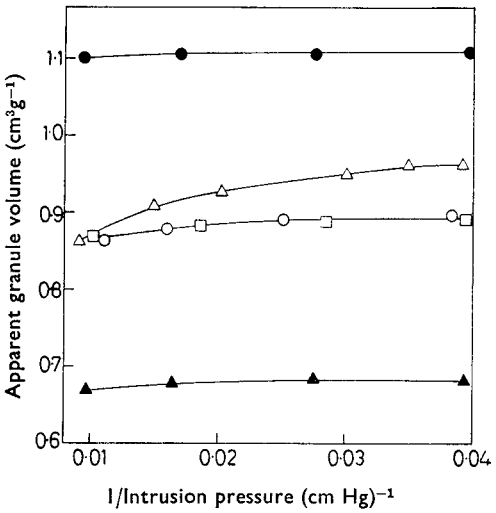

FIG. 2. Change in apparent volume of −12 +16 mesh granules during mercury penetration. Lactose, 30·6% v/v binder: ○ pan granulated, △ massed and screened, □ massed only. Calcium phosphate, 157% v/v binder: ● pan granulated, ▲ massed and screened.

Fig. 2 shows that there is no change in the apparent volume of granules of calcium phosphate, pan granulated lactose and lactose which had been massed but not screened, when the pressure on the enveloping mercury was increased from 25 to 100 cm Hg; this corresponds to a pore diameter range 56–14 μm. Virtually no pores are therefore present in this range and the distinction between intragranular and extragranular pores is therefore clear. With massed and screened lactose granules however, significant penetration occurred over this pressure range from which it can be calculated that 22% of the pores existed between 56 and 14 μm. The space which existed as voids greater than 50 μm was considered to be extragranular.

The total extragranular and intragranular porosities were derived from tap density and pycnometric measurements and are presented in Table 2.

A typical result of the strength test is given in Fig. 3. The test was considered complete at the last inflexion on the load curve, which corresponded to the last point of brittle failure. Little further work was then done on the plastic powder mass formed, the applied energy being almost completely transmitted to the load cell. The area under the curve represents the work done on the granules during crushing. Results for granules produced by the two methods of granulation are given in Table 3. The decrease in porosity when these granules are compressed in a die is given in Fig. 4.

Pan granulation

Increasing moisture content of calcium phosphate-dextrose solution mixes caused a slow but progressive increase in powder aggregation by layering; an increasing

Table 2. *Effect of moisture content on the porosities of* −12 +16 *mesh granules produced after* 10 *min processing.*

	Moisture content % v/v	Intragranular porosity %	Extragranular porosity %	Total porosity %
Pan				
Calcium phosphate	126	72·8	36·5	82·5
	157	69·7	40·0	82·0
	174	68·4	39·0	81·0
	191	56·8	material too large for test	
Lactose..	23·0	32·6	39·0	58·0
	28·3	29·3	39·5	57·5
	30·6	27·1	41·0	57·0
	32·1	24·8	42·0	56·0
Massed and screened				
Calcium phosphate	117	51·6	45·0	74·5
	125	51·2	47·0	75·0
	157	51·1	42·5	71·5
Lactose..	15·3	38·6	48·5	68·5
	18·4	37·6	49·5	68·5
	27·5	33·1	50·5	67·5
	30·6	32·0	50·0	66·0
	33·7	25·5	50·0	62·5

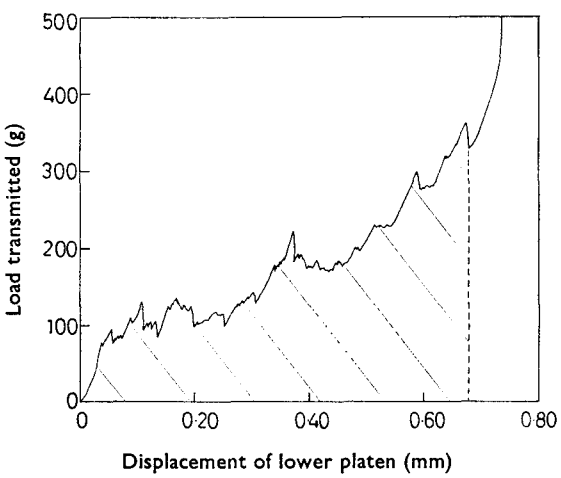

FIG. 3. Typical trace obtained from crushing a −14 +16 mesh granule. The shaded area is measured to calculate the work done.

Table 3. *Work done in crushing granules produced after* 10 *min processing.*

	Pan		Massed and screened	
	Work done J	s.d. J	Work done J	s.d. J
Calcium phosphate 157% v/v binder ..	$7{\cdot}0 \times 10^{-5}$	$2{\cdot}0 \times 10^{-5}$	$6{\cdot}9 \times 10^{-4}$	$1{\cdot}7 \times 10^{-4}$
Lactose 30·6% v/v binder ..	$5{\cdot}1 \times 10^{-4}$	$2{\cdot}1 \times 10^{-4}$	$7{\cdot}1 \times 10^{-4}$	$1{\cdot}6 \times 10^{-4}$

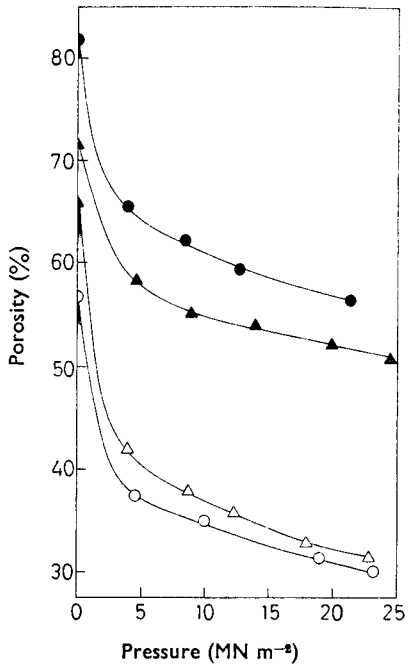

FIG. 4. The effect of pressure on the porosity of −12 +16 mesh granules. Lactose, 30·6% v/v binder: ○ pan granulated, △ massed and screened. Calcium phosphate, 157% v/v binder: ● pan granulated, ▲ massed and screened.

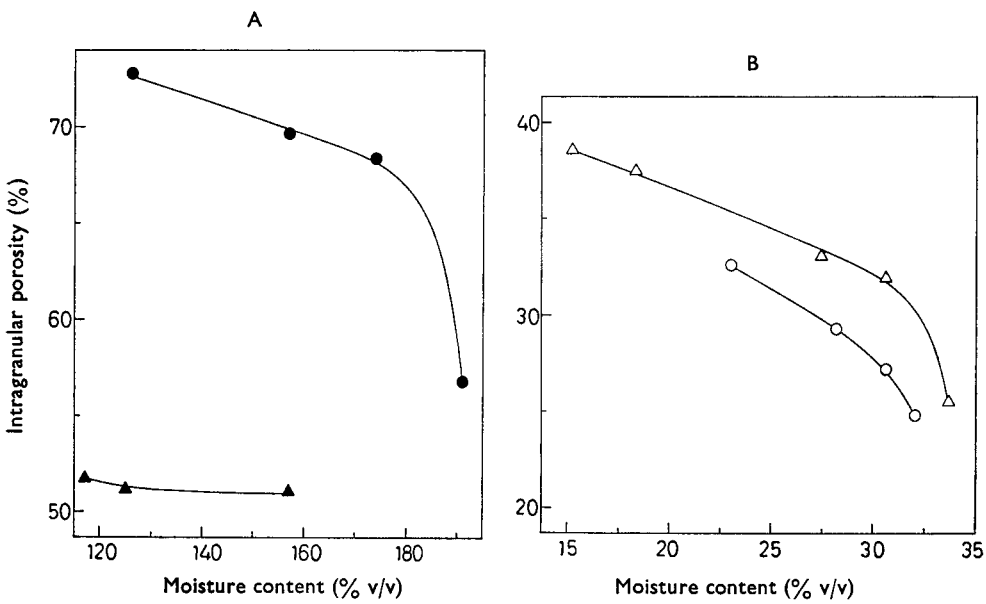

FIG. 5. A. The effect of moisture content on the porosity of −12 + 16 mesh calcium phosphate granules processed for 10 min. ● pan granulated, ▲ massed and screened.

B. The effect of moisture content on the porosity of −12 +16 mesh lactose granules processed for 10 min. ○ pan granulated, △ massed and screened.

percentage of the powder existing as balls with diameters greater than 1 mm until a moisture content of 174% v/v was reached. At this point very rapid ball growth suddenly occurred. This change in growth pattern only existed over a very narrow moisture content range (174–191% v/v). Above 191% v/v uncontrollable ball growth occurred.

Fig. 5A shows that the aggregation of powder over the moisture content range 126–174% v/v is accompanied by a slow increase in the packing density of the powder within the granule, the intragranular porosity falling from 72·8 to 68·4%. Conditions of rapid ball growth are also the conditions for sudden powder densification, the intragranular porosity falling from 68·4–56·8% when a further 17% v/v liquid was added.

Similar results were found with lactose. All the powder can be aggregated into granules by adding 8·5% v/v water. Controlled growth of these granules occurred provided the moisture content did not exceed 32% v/v. Above this level sudden ball growth occurred although Fig. 5B shows that the increased rate of densification was not as extensive as found with the calcium phosphate granules.

The effect of time on the density of the granules is shown in Fig. 6A. There is marked densification of the lactose over an hour in the pan and more gradual densification of the calcium phosphate.

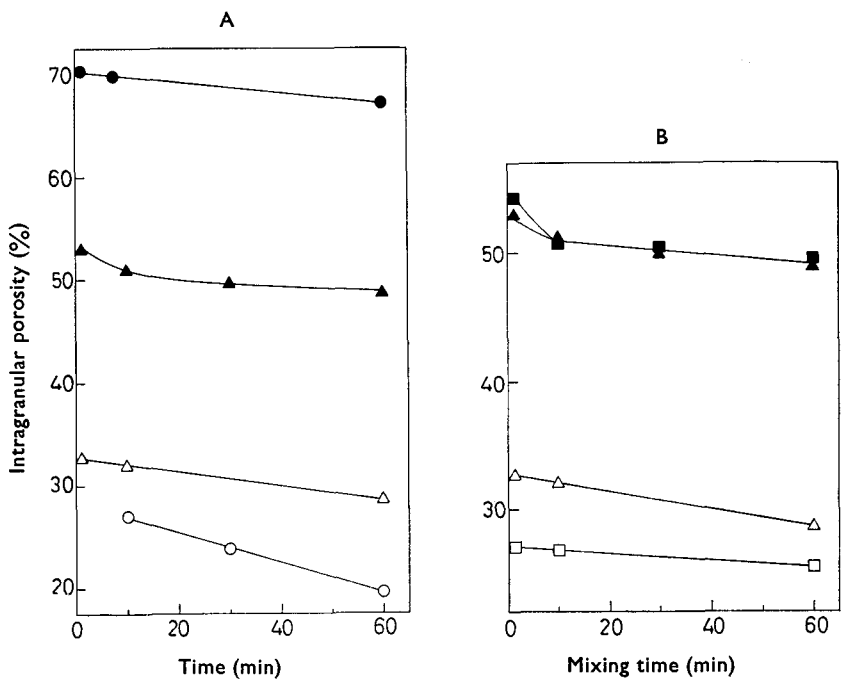

FIG. 6. A. The effect of time of processing on the porosity of −12 +16 mesh granules. Lactose, 30·6% v/v binder: ○ pan granulated, △ massed and screened. Calcium phosphate, 157% v/v binder: ● pan granulated, ▲ massed and screened.

B. The effect of wet screening on the porosity of −12 + 16 mesh granules. Lactose, 30·6% v/v binder: △ massed and screened, □ massed only. Calcium phosphate 157% v/v binder: ▲ massed and screened, ■ massed only.

Granulation by massing and screening

Granulation of calcium phosphate by this method produced suitable granules over a narrow moisture content range (117–157% v/v). Below this range the aggregates broke down to fines on screening and above it 'worms' were formed. Reference to Fig. 5A shows that within this range, moisture content had little effect on packing within the granules, the intragranular porosity in all conditions lying between 51 and 52%. Lactose, on the other hand, could be granulated over a wider range of moisture contents over which the intragranular porosity fell from 38·6 to 25·5% (Fig. 5B).

With both lactose and calcium phosphate, increase in moisture content led to the change in the particle size distribution given in Fig. 1 by elimination of the finer fractions. The limiting distribution reached with the wetter mixes was governed by the mesh used in wet screening.

Increase in the time of massing showed that the density of the wet mass increased over a period of 1 h. For lactose the porosity of the granules decreased from 32·5–28·5% (Fig. 6A).

Determination of the porosity of −12 +16 mesh granules formed with and without wet screening (Fig. 6B) showed that there was little effect on a wet mass of calcium phosphate although material massed for only 1 min was densified. The intragranular porosity of the lactose was increased.

DISCUSSION

A comparison of processes

A strict comparison of the data of pan granulation and granulation by massing and screening is not possible. This is because of the complex interaction of moisture content, the time for which the materials are in contact and the particular force system exerted on the mix during this time. Nevertheless, the following statements can be made.

Lactose

When water was added to lactose tumbling in a pan, granules typical of those used in tabletting processes were formed within the moisture range 15–30% v/v. Similar conditions were reported by Sherrington (1968) for agricultural granulation. A further increase in moisture causes very rapid ball growth and behaviour similar to that described for other materials by Newitt & Conway-Jones (1958), Kapur & Fuerstenau (1964) and Capes & Dankwerts (1965) is observed. The moisture range for ball growth is very limited because of the sudden fall in intragranular porosity. For any given moisture content, this densification will cause a larger proportion of the pores within the granules to become filled. Ultimately all voids become saturated, water appears on the surface of the balls and uncontrollable aggregation occurs These limiting conditions which occurred after 10 min tumbling when 32·1% v/v of water was added, gave dried aggregates with an intragranular porosity of 24·8%. Depending on the amount of lactose dissolved during tumbling and redeposited on drying, this porosity indicated that between 98 and 99% of the intragranular void space had been filled with liquid before drying.

Increased time of tumbling also causes densification of the mass and an increase in the fraction of the intragranular pores filled with liquid. This was most clearly

demonstrated when 31% v/v water was added. Granules were first formed but after 50 min tumbling saturation of the mass occurred and large balls were formed.

In the pan, the forces producing densification are capillary forces and the gentle repacking of particles due to rolling. Increased moisture content decreases the intragranular porosity because the capillary forces increase. Eventually an extremely close packed system is produced (intragranular porosity 20·1%) for material tumbled for 1 h This is far closer than any form of dry packing (tapped porosity 45%). Massing and screening, on the other hand, gave granules of higher intragranular porosity (Fig. 5B). The z-blade mixer employs a force system with a pronounced element of shear. In such a system, the deformation of closely packed aggregates must occur by making them less dense. The granules thus formed allowed slightly higher moisture contents to be tolerated before the mass became saturated. The additional shear encountered by the granules during screening causes further loss of density of the particles within the granules and as shown in Fig. 2 the pore size distribution within the granules is significantly widened over the range studied.

Calcium phosphate

Calcium phosphate is a very fine cohesive powder with a tapped porosity of almost 80%. It required much more liquid for granulation than lactose, and granules formed by tumbling had porosities of 68·4–72·8%. At this stage, the capillary forces appear to be far less effective in consolidating calcium phosphate than the coarser, less cohesive lactose. Even after the sudden densification which occurred when the moisture content exceeded 174% v/v, the limiting intragranular porosity was more than double that found for lactose.

When calcium phosphate was massed in the z-blade mixer and screened, the intragranular porosity of the dried granules was unaffected by change of moisture content.

Provided there was a mobile liquid layer to give capillary cohesion to the mass, mechanical agitation appeared to determine the degree of consolidation and much higher densification was obtained than in the pan. This closer packing limited the moisture content range over which granules could be successfully formed. This is in contrast to the behaviour of lactose where closest packing, and hence restriction of the range in moisture content, was found in the pan. Packing was not close enough, however, to produce the fall in density during additional shear, and screening had little effect on the porosity of the wet mass.

Granule shape, strength and compressibility

Pan granulated materials were almost spherical with shape factors approaching unity. Massed and screened lactose granules were irregular in shape, the calcium phosphate being much smoother with a higher shape factor. The almost spherical shape of the pan granulated material led to dense packing with extragranular porosities of 36–42%. Massed and screened lactose on the other hand packed with an extragranular porosity of 50%.

Massed and screened granules of calcium phosphate were much stronger than the equivalent pan granules. The strength of these aggregates is derived from the dextrose bonds formed at points of contact within the granule. The more dense massed and screened granules (porosity 51%) will have many more point contacts per unit area than the pan granules (porosity 70%).

Although pan granulated lactose was slightly more dense than granules that had been massed and screened, there was little difference in their strengths. Other factors, such as the rate of solution, may affect the strength of the bond formed by recrystallization.

The strength of the granules appears to play no part in the compressibility, and variation in this property is related to the amount of densification achieved in the granulation process. Thus the close packed granules of calcium phosphate formed by massing and screening are highly compressible, the component particles having already been moved to close juxtaposition so that compaction in the region investigated is largely the rearrangement of extragranular space by fragmentation—a relatively easy process. With pan granules, individual particles are less closely packed and more work must be done to achieve a compact of given porosity.

With lactose similar but less pronounced effects are found because intragranular porosities of the granules produced by the two methods differ by only 5%.

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