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A Study on the Preparation of Granules by Mixer Granulation

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Abstract □ A first systematic approach on new and simple preparation method of spherical granules in the system using organic granulating solution was carried out. Mixer granulation required narrow range of moisture content but gentle action of tumbling in the mixer and capillary forces were adequate to compact the porous mass and also were highly effective to produce granules close to sphere. Whereas the granules by massing and screening provided the more open structure, its pore distribution lied between 71 and 16 μm by above 50%, and on the contrary, that of the mixer granulated granules showed only below 25%. Increase in retention time in the mixer decreased the intragranular porosity of granules produced, and in comparison with granular particles produced by conventional wet granulation, those from the mixer granulation had the advantages of flow properties, packing characteristics and definite spherocity. They also had extremely low friability resulting in few fines.

Keyphrases □ Mixer granulation-spheronization process-spherical granule-effect of process variable on granule.

Granulation, the process of "making big ones of little ones", has been with us for a long time and now this processing became a key process in the production of many dosage forms in the pharmaceutical industry.

Moreover, with the development of the many new processing methods designed to produce granular particles as either finished or intermediate products, the need to apply physical characteristics to pharmaceutical granulation to achieve a rational selection of a particular process or piece of equipment is greater than ever any previous time.

Along with this trend, study of the solid spherical particles has been a topic, on which many investigation were reported,[1,2,3] comparing this spherical particles with the irregular ones produced by conventional wet granulation.

Solid spherical products present several potential advantages to the pharmaceutical industry.

They are attractive in appearance; flow freely to alleviate material handling problems; are easily mixed when combined products are desired; and relieve dust problems.

Various techniques and equipments have been applied to obtain spherical granules.

Among them, extrusion-spheronization processing[1,2,4,5] and pan granulation[3] are known to be the familiar ones to achieve this purpose, but both methods are of concern mainly to the system using an aqueous binding solution and have a significant limitation in the system using organic ones.

The purpose of this report is to present a new and simple procedure, mixer granulation, which few information is available on and could be applied to produce a solid spherical granules in the system using an organic binding solution, and to compare the mixer granulation process and the conventional pharmaceutical method. Restricting the investigation to variation in solid-liquid ratio including concentration of binding solution, massing time, and rentention time on mixer granulation, an examination of both process and product is made over the characteristics of granules; shape factor, repose angle, porosities, and friability.

MATERIALS AND METHODS

Materials and Formulation

The materials used were lactose K.P.III, microcrystalline cellulose N.F.XVI, hydroxypropyl cellulose and isopropanol. The mixed power of both lactose and microcrystalline cellulose (8:2) used as basic formulation was granulated with hydroxypropyl cellulose solution in isopropanol, the concentration of binder varying 1–5w/v%, over the range 25.5–32.4w/w%.

Granulation by Massing and Screening

A charge of 1.2 kg of mixed powder of both lactose and microcrystalline cellulose (8:2) was massed in a laboratory kneader (Erweka model).

The binding solution was added as a continuous stream and after the specified time of massing, the mass was discharged through on oscillating granulator (Erweka model) equipped with a 16 mesh screen and the granules were dried for 4 hours at 60°C in a hot air oven and then dry granulated using a 12 mesh screen.

Unless otherwise stated, a standard batch was made from the formulation given, granulated with 29.0w/w% of a 3.0w/v% hydroxypropyl cellulose solution in isopropanol, and massing time 10 minutes.

Mixer Granulation

A charge of 1.2 kg of wet granules massed and charged through on oscillating granulator as same above was placed into a V– shaped mixer and rotated at 30 rev/min.

After the prescribed process time the produced granules were discharged and dried for 4 hours at 60°C in a hot air oven. A standard batch was the same of that of massed and screened but additional 20 minutes of retention in V-shaped mixer.

Characterization of Granules

1) Tapped density: The tapped density of -14 +18 mesh granules was measured.

According to the applied Fonner method,[6] 100 g of a granulation was poured into a 200 ml. graduated cylinder and dropped 30 times through a height of 2 centimeters at 2-second intervals and the tapped density was calculated in grams per milliliter.

2) Intragranular porosity: The internal porosity of the -14 +18 mesh granules was measured by the pycnometric method of Strickland,[7] the volume of mercury in the

pycometer being measured at intrusion pressure between 20 and 90 cmHg.

But true density was measured by liquid (benzene) displacement instead of high compression method proposed.[8]

3) Granule shape: The spherocity[3] of the -14 +18 mesh granules was estimated by measuring the ratio of the square of the perimeter to the area of enlarged photographing images, the evaluation procedure involved: a) photographing about 10-20 granules on a calibrated back-ground grid and preparing a transparent slide, b) projecting the particles at about 200 times their actual size, c) tracing the outline dimensions of each granule by means of opisometer, d) the area of each traced granules was determined by means of a planimeter, e) calculating the ratio as mentioned earlier and f) 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.

4) Repose angle: Measurements of repose angle were obtained using an apparatus similar to that described by Kawashima,[9] but the belt feeder proposed was displaced with a standard glass funnel. 60 g of granules was introduced into a standard funnel with a 6 mm diameter orifice.

A holding plate below the orifice was removed, and the material was allowed to fall 10 cm onto a petridish-like plate, 10 cm in diameter and 0.5 cm in edge height.

The height of deposited granular cone was determined using a microcathetometer and the repose angle was calculated as follows;

$$\text{repose angle}(^\circ) = \frac{\text{cone height}}{\text{diameter of plate}/2}$$

5) Friability: Each granulation was subjected to friabilation using the laboratory granular friabilator described by Willis.[10] The samples, their particle size distributions previously classified within -14 +18 mesh, were tumbled for 30 minutes at 90 rpm, after tumbling, each granulation sample was classified with 18 mesh screen.

The friability percent was defined as the relative percent difference in classification before and after friabiliation.

RESULTS AND DISCUSSION

Because of the complex interaction of moisture content, the time for which the materials are in contact and the particular force system excerted on the massing, screening and tumbling in this time, a strict comparison of the data of mixer granulation and granulation by massing and screening is not possible.

Nevertheless, the following statements can

Table I: Effect of varying the volume of granulating solution on the shape factor, repose angle and friability per cent.

	Volume used, w/w%.	shape factor.	repose angle, degree.	friability, %.
Mixer	27.3	0.88	33.7	2.2
	29.0	0.83	34.4	2.7
	30.8	0.82	35.9	1.9
Massed and screened	27.3	0.69	40.8	31.8
	29.0	0.69	40.1	26.4
	30.8	0.67	40.2	18.6

be made over the characteristics of granules produced by both methods.

Shape Factor and Repose Angle

Shape factors and repose angles of massed and screened granules are compared to those of the equivalant mixer granulated material and are presented in Table 1.

Three kinds of new definitions describing the spherocity of particle were reported recently.

Fonner[6] proposed the shape volume factor which estimated by measurement of the ratio of the volume to the cube of the equivalent projected diameter and Ridgway[11] reported the shape coefficient as the shperocity of particle by measuring the ratio of the surface area to the volume of the equivalent particles, in this case, a sphere has a numerical value of 6 and this value increases as the particle shape departs from the spherical.

The last one adopted in this study was described by Ganderton,[3] he measured the ratio of the square of the perimeter to the area of enlarged photographic image as mentioned earlier. Among conditions examined, the effect of varying the volume of granulating solution on the shape factor and repose angle of produced granules was significant, but its absolute value was negligible comparing the differences of data made by both methods. And data obtained from this study also demonstrated that flow property of the spheronized material is superior to those of the massed and screened product, in other words, the repose angle for the different conditions and granulations was found to be dependent of respective granule shape, shape factor. This was brought

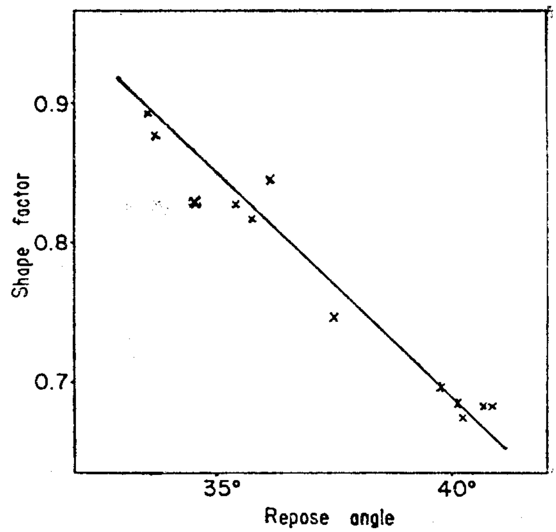

Fig. 1: Shape factor as a function of repose angle for −14 +18 mesh granules.

out in the study of Fig. 1, in which the shape factor was plotted against repose angle to establish the existance of a correlation between these parameters.

These findings are in disagreement with the prediction of Fonner[6] who deduced that the repose angle is independent of paticle shape but reached to the similar conclusion with Ridgway,[11] who inferred their relationship on the close theoretical ground using a close-sized of sand.

Having different definition of the spherocity of particle as mentioned earlier, a strict comparison of these relationship between repose angle and spherocity is not possible but Ganderton's definition could be a method of choice in establishing the correlation between these parameters, as any other definition has been failed to produce a correlationship between these parameters in the light of a satisfactory literature survey.

Porosities

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 granule present.

As the external pressure is increased, mercury first fills the pores between 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 shows that there is a significant difference in the apparent volume of granule between mixer granulated granules and massed and screened ones, when the pressure on the enveloping mercury was increased from 20 to 90 cmHg, this corresponds to a pore diameter range 71 – 16 μm.

With massed and screened granules significant penetration occured over this pressure range from which it can be calculated that 51% of the pores existed between 71 and 16 μm. On the same condition, mixer granulated particles, however, showed 27%, nearly a half of value of massed and screened ones. This figure also demonstrates that most of the pores involved in mixer granulated particles are occupied with below 16 μm ones by above 76% and, on the contrary, only below 50% of pores not greater than 16 μm diameter exist on the massed and screened granules.

In other words, the pore size distribution within the granules was more widened over the range 71 – 16 μm in comparison with the mixer granulated granules.

Mechanism of powder agglomeration are classified roughly as follows; a) binding forces of powder itself, b) capillary forces, c) calcification and d) electrical forces.

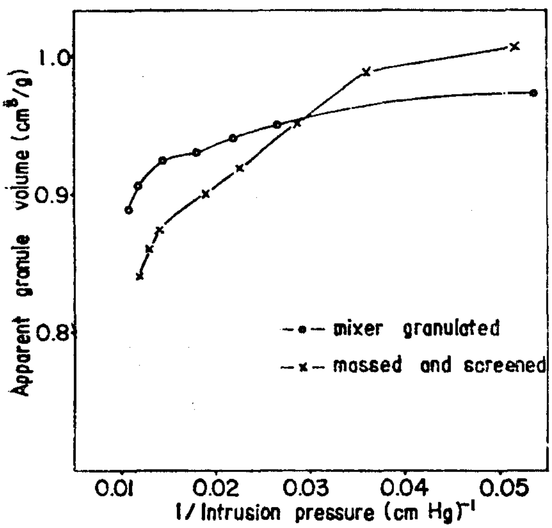

Fig. 2: Change in apparent volume of –14 +18 mesh granules during mercury penetration.

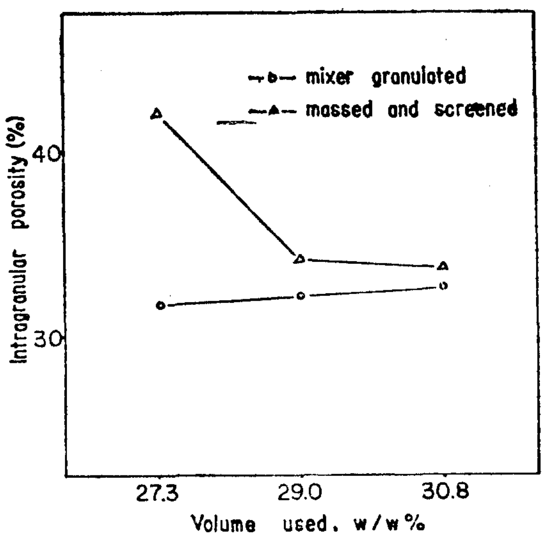

Fig. 3: The effect of moisture content on the porosity of –14 +18 mesh granules.

Nevertheless, in mixer, the force producing densification are mostly capillary forces and the gentle repacking of particles due to rolling.

But as shown in Fig. 3, the predominant factor affected on densification was the repacking of particles if once provided there was a least amount of mobile liquid layer to give capillary cohesion into the system studied.

This case is in disagreement with pan granulation,[3] in which increased moisture content decreased the intragranular porosity, however, in the granulation by massed and screened, both studies made a same conclusion.

Table II: Effect of granulating conditions on the porosities of −14 +18 mesh granules prepared by both methods.

			Intra-granular porosity, %	Extra-granular porosity, %	Total porosity, %
Mixer	Granulating solution				
	– w/w%	1	34.9	49.5	67.1
		3	32.5	49.1	65.6
		5	30.2	48.1	63.9
	– volume of 3% soln., w/w%	27.3	30.3	49.1	64.5
		29.0	32.4	49.1	65.6
		30.8	34.5	49.3	66.8
	Massing time, min.	5	31.4	50.3	65.9
		10	32.4	49.1	65.6
		15	25.3	57.3	68.1
Massed and screened	Granulating solution				
	– w/w%	1	36.6	58.7	73.8
		3	34.1	63.1	75.7
		5	33.0	65.9	77.1
	– volume of 3% soln., w/w%	27.3	42.3	60.3	77.1
		29.0	34.1	63.1	75.7
		30.8	33.3	62.3	74.9
	Massing time, min.	5	33.9	66.2	77.7
		10	34.1	63.1	75.7
		15	25.9	64.2	73.5

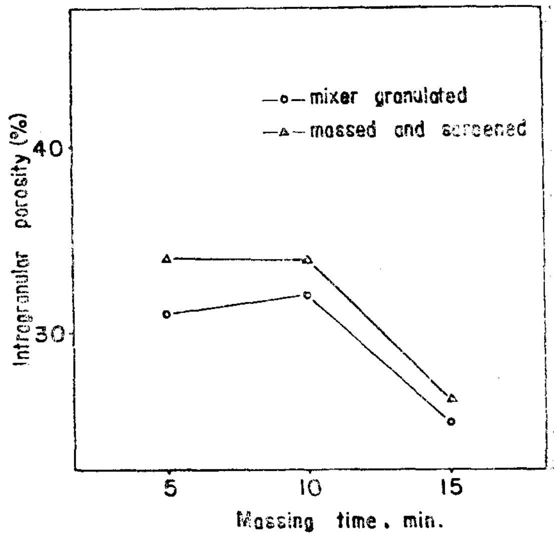

Fig. 4: The effect of massing time on the porosity of −14 +18 mesh granules.

The total extragranular and intragranular porosities were derived from tapped density and pycnometric measurement including granule and true densities and are listed in Table 2.

The effect of massing time on the intragranular porosity was interesting as shown in Fig. 4.

Granules which had been prepared by both methods after 15 minutes massing, respectively, produced similar value of 25% intragranular porosity, from which it can be assumed that densification of plastic mass does not occur in rolling processing within the condition studied but in massing processing, and also the rolling processing in mixer is only of concerns on spheronization, in this case, the shape factors of mixer granulated particle and particle of massed and screened were 0.83 and 0.69, respectively.

Friability

Neither of any condition variable in this study had no significant effect on the friability of mixer granulated granules, in which friability per cent was less than 3%.

Granules prepared by massing and screening, on the other hand, produced a broad distribution of friability per cent with variation of conditions studied by the range of 15–35%, indicating at least 5 times more friable than those produced in the mixer, however, failed to find any relationship between them.

Mixer Granulation and Conventional Wet Granulation

The proportion of moisture in the powder to be granulated is said to be important.

But the optimum contents of moisture demonstrated by previous workers couldn't be applied on this study, as their base formulations, granulating solutions and even preparing methods were different from that of this study.

It has been generally known that the very narrow moisture content range is required in pan or drum granulation,[3,12] in which about 18% of water content was recommended.

In mixer granulation, increasing moisture content of base formulation-granulating solution mixes caused a slow but progressive decrease of retention time in mixer to obtain a desirable particle size distribution.

Granulation by this method produced granules over the moisture content range 27.3 – 30.8 w/w %, and 29.0 w/w % of solution made the optimum moisture content.

Below this range the aggregated broke down to fines on tumbling processing and above it a very rapid ball growth suddenly occured within one or two minutes, in this condition, the forward processing became out of control.

For a given moisture content within the range of 27.3 – 30.8 w/w %, the aggregation of powder was accompanied by a slow increase in the packing density of the powder within the granules. Fig. 5 shows that the intragranular porosity is falling slowly from 34.1 to 29.0% by 25 minutes tumbling and falling from 29.0 to 20.0% with further ten minutes processing in mixer, in latter stage it seems to occur the saturation of the mass and organic solvent appears on the surface of the balls, causing an uncontrollable aggregation.

Granulation by massing and screening produced suitable granules over wider moisture content range 25.5 – 32.4 w/w % than that of mixer granulation, above this range 'worms' were formed. From Table II, Figs. 3 and 4, it could be assumed that concentration of granulating solution had a little effect on

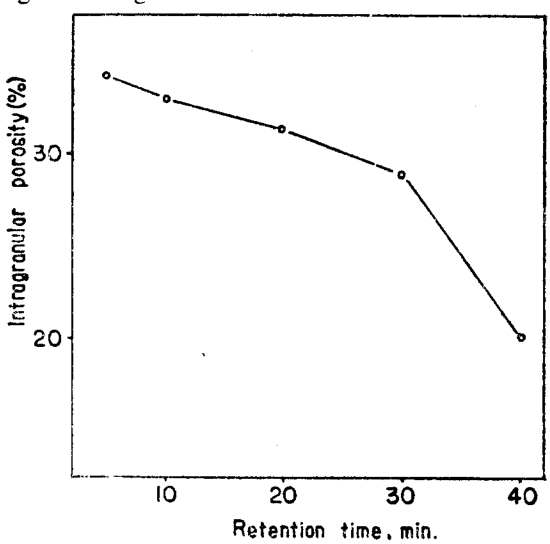

Fig. 5: The effect of retention time in mixer on the porosity of -14 +18 mesh granules.

packing within the granule, on the other hand, both moisture content and massing time made a significant difference on the intragranular porosity, indicating ranges 33.0 – 42.3% and 25.9 – 33.9%, respectively.

Mixer granulated materials were almost spherical with shape factors approaching unity, which led to dense packing with extragranular porosities of 49 – 57%.

Results of this work show that mixer granulation provides a versatile system for producing spherical particles.

In comparison with granular particles produced by conventional wet granulation, those from the mixer granulation have the advantages of flow properties, packing characteristics, and definite spherocity.

They also have extremely low friability resulting in few fines. The application of this process in the pharmaceutical fields could provide a relatively simple means of producing spheres, which can help to overcome many of the problems of powder technology at present encountered in this industry.

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