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GRANULATION OF LACTOSE IN A RECORDING HIGH-SPEED MIXER, DIOSNA P25

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ABSTRACT

When the conditions involved in the granulation process — inter alia liquid flow rate, atomization conditions, impeller and chopper speed, and amount of powder — were fixed, it was possible to determine the end-point of the graulation of lactose with a gelatin solution on the basis of rotation-rate changes affecting the main impeller shaft.

INTRODUCTION

Record (1) has described practical experiences of granulation with high-speed mixers in pharmaceutical production, using an instrumental method for determining the end-point. An automatic system, intended to shut off the addition of granulating liquid in planetary mixers (2), also worked well with other types of mixers, including high-speed mixers (3). Lactose was granulated in a Diosna P25, instrumented for measuring the electric power input to the impeller and chopper motors (4).

The use of an instrumental method, based on the measuring of the rotation rate of the impeller motor

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shaft (5), for determining the end-point of granulation will be studied during granulation experiments with lactose. This means that the effects of impeller and chopper speed, fluid addition rate and method of fluid addition on granule growth and rotation rate of the impeller motor shaft will be examined during the agglomeration process.

EXPERIMENTAL

Materials

Lactose 350 mesh[1] with the following characteristics: geometric mean diameter by weight[2] 34.5 μm (geometric standard deviation 2.14), apparent density[3] 550 kg/m^3 and tap density[4] 800 kg/m^3.

Gelatin was dissolved in warm water. The concentration was 8.6 w/w %, which would correspond to a proper gelatin concentration in the tablet granulation when the lactose was suitably wetted. The gelatin solution was kept at 45 - 50° C. In this temperature range, the density of the solution was 1010 kg/m^3. When atomized, the droplet size of the gelatin solution was mainly 20 - 100 μm. A slide with a layer of viscous oil[5] was passed across the spray cone at a distance corresponding to the distance between nozzle opening and powder bed. The droplet size was immediately determined in a microscope.

In some experiments water at a temperature of 20 or 45 - 50° C was used as a granulating liquid. In most of these experiments, liquid pressure nozzles[6] and a powerful peristaltic pump[7] were employed. When atomized, the droplet size was mainly 20 - 100 μm at 250 ml/min and 20 - 200 μm at 1000 ml/min.

Granulation

7.0 kg lactose was granulated with the gelatin solution, or with water in a recording Diosna P25 (5) at different combinations of main impeller and chopper speed. Most of the experiments were performed at a high chopper speed. The gelatin solution was atomized. Tests with water were performed with or without atomization. The analogue equipment was used for the experiments.

The solution or water was added until the mass was overwetted in some experiments. In some experiments the volume of gelatin solution added per mass of lactose corresponded to 5.4 or 8.9 v/w %. An extra wet massing of 2 or 4 min was performed in the latter cases.

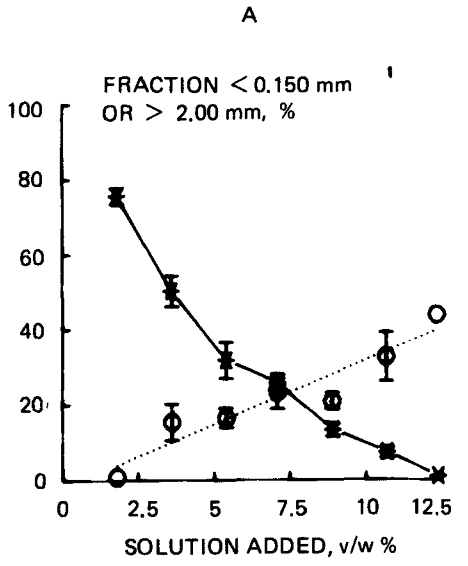
At suitable times during the granulation process, samples were withdrawn from the granule stream in the vicinity of the chopper by a scoop holding about 15 - 30 g dry granules. The samples were immediately dried in a hot air oven at 60° C.

Sieve analysis of the samples were performed with 2 min sieving time (6) through sieves 2.00, 1.50, 1.00, 0.750, 0.500, 0.250 and 0.150 mm[8].

RESULTS AND DISCUSSION

Sieve analysis

The fractions < 0.150 mm and > 2.00 mm were suitable indicators of the agglomeration process (6). During the addition of liquid, the small fraction decreased while the coarse fraction increased. The relation between volume of gelatin solution added per mass of dry powder, v/w %, and the distribution of fractions < 0.150 mm or > 2.00 mm is seen from Fig. 1A and B. To avoid influences from sampling on the rotation rate, the sample size was deliberatly kept small. Because of the small sample size, the results varied. However, there were significant differences, $P < 0.025$ and $P < 0.005$ using a two-sided Student's t-test, between low and high impeller speed for < 0.150 mm and > 2.00 mm respectively at 8.9 v/w % granulating fluid, i.e. during granule growth. At a lower level, 5.4 v/w % granulating fluid, the differences were not



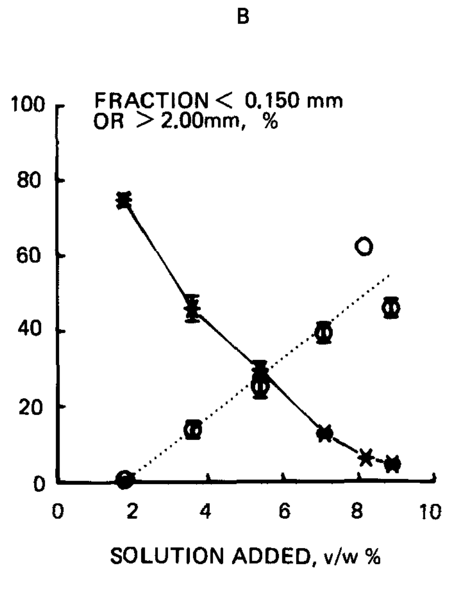


FIGURE 1

A Low impeller speed
B High impeller speed
Fraction < 0.150 mm or > 2.00 mm as a function of volume of gelatin solution added per mass of dry powder, v/w %. Vertical lines indicate standard error. Fraction < 0.150 mm ✱, fraction > 2.00 mm O.

significant. The two levels of granulating fluid corresponded to the range, judged visually, where granules had just started to grow — this applied to both impeller speeds — and just before the mass was overwetted at the high impeller speed. This indicated that the impeller rate, besides the volume of fluid added, had a significant influence on granule growth.

During the wet massing, there was a change of fraction distribution where the two examined fluid levels 5.4 and 8.9 v/w % were concerned. At the low fluid level, there was an abrasion of the coarse fraction at both impeller rates, while the fine fraction increased at a low impeller speed but remained unchanged at the high impeller rate; Table 1. Among the interjacent fractions, there was a decrease at low impeller speed, while there was a decrease or no change at the high impeller rate. At the high liquid level, the fine fraction was unchanged during wet massing where both the impeller speeds were concerned, while the coarse fraction increased at the low impeller rate, decreasing at the high impeller speed. Among the interjacent fractions, an increase of the finer ones and a decrease of the coarser ones were seen at both impeller rates. During wet massing, the impeller rate thus had an influence on granule growth, an influence depending on the fluid level.

Recorder curves, in general

The recorder curve for an experiment at a low impeller and a high chopper rate was compared to data from a similar experiment where the electric power input to impeller and chopper motor was measured (4). The input power was recorded manually every 15 s. The changes on the recorder curve, i.e. changes in the rotation rate of the impeller's motor shaft, were simultaneous with changes in input power to the motors, Fig. 2.

TABLE 1

Wet massing

Fraction, mm	Wet massing time, min	Fraction distribution %: Impeller rate: Low, Liquid level: Low	Impeller rate: Low, Liquid level: High	Impeller rate: High, Liquid level: Low	Impeller rate: High, Liquid level: High
< 0.150	0	13	14	33	6
	2	34	12	29	4
	4	36	13	32	5
> 2.00	0	16	18	27	62
	2	13	26	28	45
	4	13	32	20	38

When the same experiment, with gelatin solution, was repeated 6 - 9 times at a high chopper speed and a low or high impeller speed, a satisfactory agreement of the recorder curves was obtained.

At a high impeller speed, the fluctuations affecting the curves were slight. With a low impeller speed, the fluctuations of the recorder curves were remarkable, especially around S_3 (2); Fig. 3. This indicated a non-uniform distribution of the liquid at the low impeller rate.

Recorder curves, S_3-limit (2) and change of rotation rate

The change on the recorder curve corresponding to S_3 appeared at 3.6 - 4.4 v/w % with the high impeller speed and 3.9 - 5.1 v/w % with the low impeller speed when granulating with the gelatin solution. This difference was not significant. Where the high impeller rate was concerned the difference in rotation speed between dry mixing on the one hand and a rotation rate corresponding to S_3 on the other was 30 - 36 rpm. The corresponding changes at the low impeller speed amounted to 5 - 9 rpm.

It was difficult to find the S_3-limit on some of the curves concerning the low impeller rate.

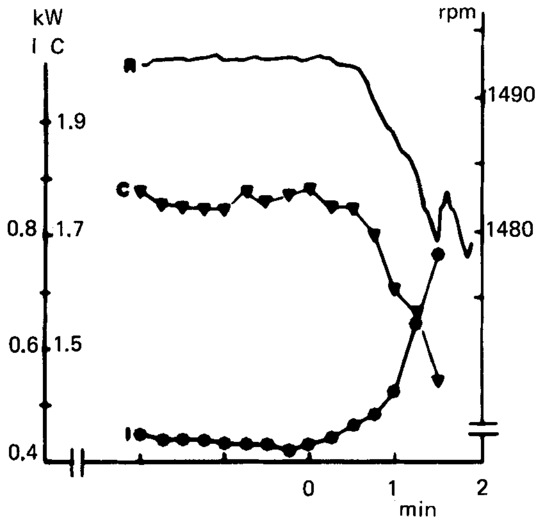


FIGURE 2
Electric power input, kW, of impeller (I) or chopper motor (C) and change of rotation rate, rpm, of impeller motor shaft (R) respectively versus time, min. The fluid addition began at time 0.

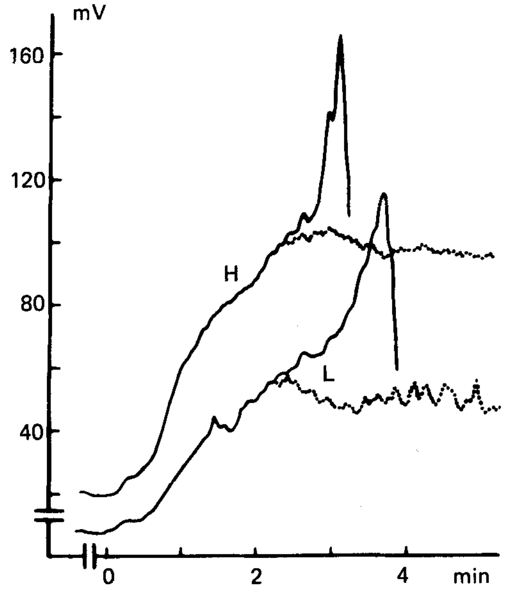


FIGURE 3
Recorder curves for low (L) and high (H) impeller speed respectively. The fluid addition began at time 0. After 2.5 min the addition of liquid was interrupted, dotted curve, or continued, continuous curve. Output signal, mV, versus time, min.

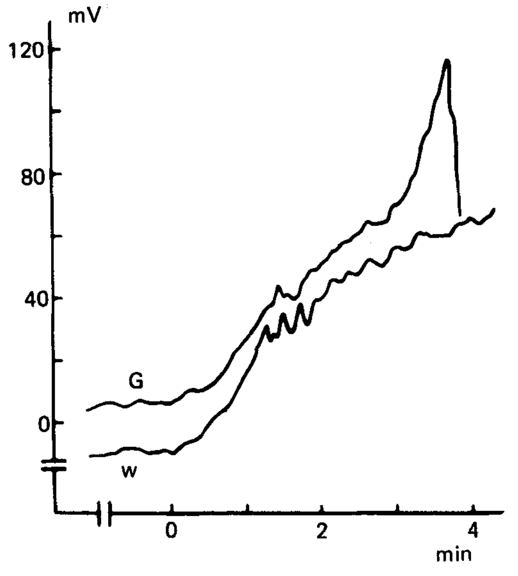


FIGURE 4
Recorder curves for low impeller speed with water (W) and gelatin solution (G) of same temperature as granulating fluids. Output signal, mV, versus time, min. The curve for water is moved along the Y-axis to facilitate the observations. Graduation of Y-axis refers to the gelatin solution. The fluid addition began at time 0.

The differences in S_3 between low and high impeller speed reflected differences in the distribution of the solution.

When water was used as granulating fluid, overwetting occurred later; Fig. 4. This was in accordance with earlier, unpublished, results from agglomeration of lactose with an aqueous solution of Tween 80 in a Kenwood mixer. With the Tween 80 solutions, the overwetting of the lactose occurred at an earlier point in time.

When the granulating liquid was added at a higher flow rate, S_3 appeared after a larger volume. This also reflected a poor distribution in the powder; see Fig. 5.

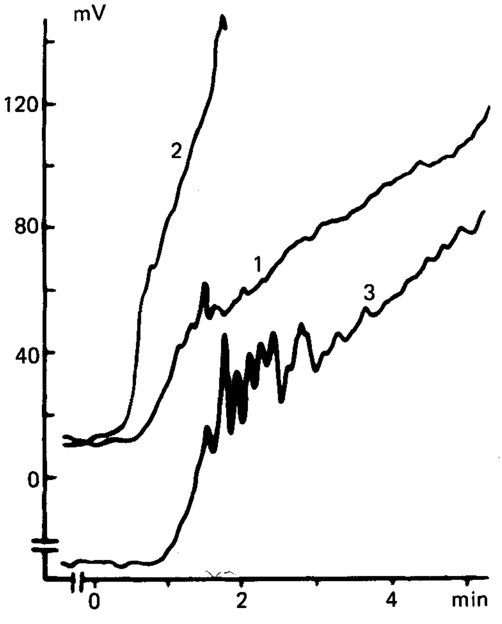
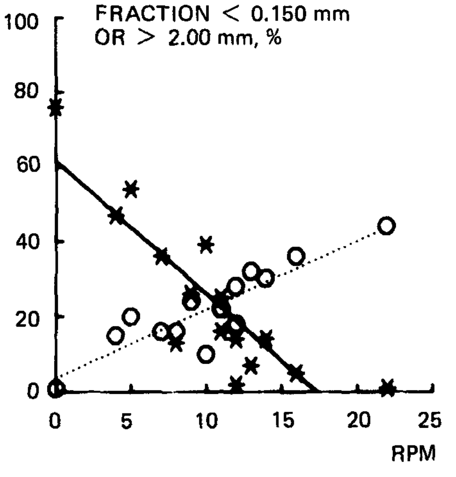


FIGURE 5
Recorder curves for low impeller speed, water of 20° C at flow rate of 250 (1) or 1000 (2) ml/min. Pressure nozzles.
Recorder curve for water at flow rate of 250 ml/min without atomization (3) is moved along the Y-axis to facilitate the observations.
Output signal, mV, versus time, min. Graduation of Y-axis refers to atomization. The water addition began at time 0.

The addition of a solution without atomization resulted in greater fluctuations around S_3; Fig. 5.

When the distribution of fractions < 0.150 mm and > 2.00 mm were plotted versus the speed difference, of the impeller's motor shaft, between dry mixing and the actual sampling time during granulation, distinct relations appeared; Fig. 6A and B. With higher impeller speeds, the relations seemed to be linear, the correlation coefficients being r = 0.98 for < 0.150 mm and r = 0.96 for > 2.00 mm. In the case of the low impeller speed, there also seemed to be a linear relation with r = 0.87 for < 0.150 mm and r = 0.89 for > 2.00 mm. The

A



B

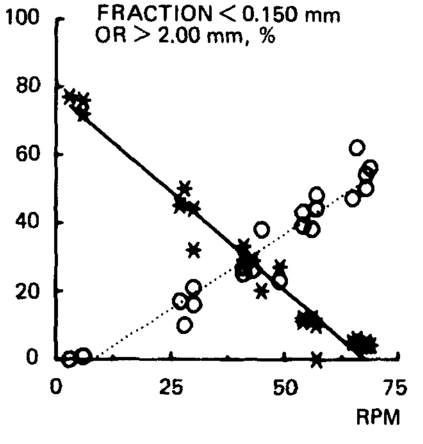


FIGURE 6
Fraction < 0.150 mm or > 2.00 mm, %, versus decrease of rotation rate of impeller shaft, rpm.

A Low impeller speed
B High impeller speed
The same signs as in Fig. 1.

TABLE 2
Change of rotation rate of the main impeller shaft at different stages during granulation.

Stage	Change of rate, rpm Impeller speed: Low	High
Granule formation	2 - 6	20 - 35
Granule growth	7 - 20	35 - 55
Overwetting	> 23	> 60

spreading of points in the figures was due to the smallness of the samples taken for sieve analysis.

These changes in the impeller-shaft rotation rate were compared to visually observed changes of the mass during the process. Stages corresponding to granule formation, growth and overwetting are assorted in Table 2. The lower limit of the interval of rotation-rate changes with regard to granule growth coincided with the changes of rotation rate at S_3.

During wet massing, there was a tendency towards an increased rate of rotation; Fig. 3.

Conclusion

The end-point of the granulation of lactose with gelatin solution can be detected from the changes of rotation rate of the main impeller motor shaft, as there were linear relations between granule fraction distribution and the rate of the impeller shaft. However, this presupposes that the conditions involved in the process, e.g. fluid addition rate, atomization/non-atomization, impeller and chopper speed and the amount of powder, are all being controlled. Another premise is that the granule size distribution is the main quality parameter of the granulation.

Footnotes

1. DMV, Veghel, The Netherlands
2. From sieve analysis data. Test performed with Air jet sieve 200, Alpine AG, Augsburg, West Germany

3. According to DIN 53912
4. According to DIN 53194 with a jolting volumeter JEL ST 2, J. Engelsmann AG, Ludwigshafen, West Germany
5. Omala 680, Shell
6. Nozzle 402.286, 90° spraying angle, Lechler, Fellbach, West Germany
   for approximately 250 ml water/min.
   Nozzle 402.488, 120° spraying angle, Lechler
   for approximately 1000 ml water/min.
7. Flow inducer type HRSV 214, Watson Marlow Ltd, Falmouth, U.K.
8. Laboratory sieving machine type Vibro, Retsch, Haan b. Düsseldorf, West Germany

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