DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(1), 45-56 (1984)



# GRANULATION OF LACTOSE IN A DOMESTIC-TYPE MIXER

N.-O. Lindberg
Research & Development Laboratories,
AB Draco*, Box 1707, S-221 01 Lund, Sweden

## ABSTRACT

When process variables controlling the droplet size and the distribution of the granulating liquid in the powder, i.e. the liquid flow rate, the way of adding the liquid and the wet massing time, are controlled during the granulation of lactose 350 mesh with water in a recording laboratory mixer, the amount of water added determines the torque of the mixing bowl. The torque value can be used as an indication of the granule size.

## INTRODUCTION

In the moist agglomeration process, liquid bridges are formed between the solid particles (1). The cohesive force between solid particles originates from these liquid bridges.

When measuring the electric power consumption of the mixer motor, or the torque applied to the mixing arm, changes in torque and power consumption occur as a result of a change in the cohesive force or the tensile strength of the agglomerates in the moistened powder bed (2).

* Subsidiary to AB Astra, Sweden



 0363-9045/84/1001-0045$3.50/0

The influence of the amount of binder added, and of the wet massing time, on the granule properties was studied in the case of lactose (3). With regard to sucrose, the influence of the fluid-addition rate was studied during wet massing (4).

The granulation behaviour of lactose in a recording laboratory mixer was the subject of this study, where particular attention was given to the influence of the amount of liquid added, the fluid-addition rate, the way of adding the fluid and the wet massing.

## EXPERIMENTAL

### Equipment

A domestic-type planetary mixer, Kenwood 707A with a bowl capacity of about 7 l, reconstructed and equipped with a torque transducer (5).

The granulating solution was added from a gear pump with variable flow rate through a nozzle of the two-fluid type (5).

### Materials

Lactose 350 mesh[1] with a geometric mean diameter by weight of 34 µm (geometric standard deviation 1.79), apparent density 470 kg/m$^3$ and tap density 780 kg/m$^3$.

Water of 20 - 22° C as granulating liquid.

In some experiments, a saturated aqueous lactose solution of 20 - 23° C with a density of 1090 kg/m$^3$, a surface tension of $59.7 \cdot 10^{-3}$ N/m and an apparent viscosity amounting to 5.0 mPas was used as granulating solution.

### Granulation

1.0 kg lactose was granulated with water added at a flow rate of 19 or 76 ml/min, without atomization or with atomization, at an air-flow rate of 14 l/min, the droplet size being mainly 20 - 100 µm. With the lower water-flow rate, there was no extra wet massing.

However, with the higher flow rate experiments were performed both with and without wet massing. In the former case the total time for addition and wet massing was the same as the addition time when the low flow rate was used.

Granulations were performed with the lactose solution at a fluid-flow rate of 76 ml/min, involving atomization both with and without wet massing. The air-flow rate was 14 l/min, and the droplet size was mainly 20 - 200 µm.

The granulations were dried immediately at 70° C in a hot-air oven.

The dried granulations were divided by coning and quartering, as the spinning riffler technique was impossible owing to the funnel being blocked by lumps. The dried granulations of the variants with water contents corresponding to 3.8, 5.7, 7.6, 9.5, 13.3, 17.1 and 20.4 v/w %[2] in undried condition were sieved for 2 min without preceding milling through 2.00, 1.50, 1.00, 0.750, 0.500, 0.250 and 0.150 mm sieves[3]. About 250 g granulation was sieved each time. The whole granulation was sieved, and the particle-size distribution was calculated for the total sample.

10 g samples of the fraction < 0.150 mm was sifted in an air-jet sieve[4] through 45 and 71 µm for 2 min.

To examine the resistance towards abrasion during sieving, some of the experiments at low, medium and high levels of granulating liquid, 5.7, 9.5 and 17.1 v/w % respectively, were compared after 2 and 3 min of sieving. Tests were performed both with water and lactose solution.

## RESULTS AND DISCUSSION

### Sieve analysis

The dominating fractions, < 0.150 mm and > 2.00 mm, were suitable indicators of the agglomeration process.

There was a continuous decrease of < 0.150 mm and increase of > 2.00 mm during the agglomeration; Table 1. The fluid additions without atomization and wet massing were exceptions during the granule formation stage.

No binder was dissolved in the water, the purpose being to avoid influence on its properties. Anyhow, there was a dissolution of lactose in the water during the granulation. Thus lactose functioned as binder in the granules.

A short sieving time was used throughout, in order to reduce the abrasion of the granules. 2 min was a suitable sieving time for this study. When the sieving time was increased from 2 to 3 min, there was a decrease of > 2.00 mm and an increase of < 0.150 mm; Table 2. In general the changes of the different fractions seemed to be independent of liquid level, fluid addition rate, water or lactose solution, and wet massing. However, there was a tendency towards less friable lumps for the higher water levels. The results indicated, inter alia, that lactose dissolved rapidly when water was added and that it functioned as a binder. In that way the resistance against the abrasion of the dried granules was increased. The changes were reproducible. As the wet granules were immediately dried, and the dried granules were not milled before the sieve analysis, the wet granule size can be represented by the dry granule size.

The results of the sieve analysis indicated that smaller fractions had their maximal proportions when small amounts of water were added, while coarser fractions had their maximal proportions when larger amounts were involved; see Table 3. Accordingly the coarser fractions were formed from the smaller fractions when more water was added. There were no principal differences in the occurrence of the maximal proportion with

TABLE 1

Distribution of < 0.150 mm and > 2.00 mm fractions versus volume of water added expressed as a percentage.

| Flow rate, ml/min | Atomi-zation | Extra wet massing | Water level, v/w %: | 3.8 | | 5.7 | | 7.6 | | 9.5 | | 13.3 | | 17.1 | | 20.4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Distribution of fractions, % | | | | | | | | | | | | | |
| | | | Fraction: | F | C | F | C | F | C | F | C | F | C | F | C | F | C |
| 19 | Yes | No | | 64 | 16 | 56 | 20 | 39 | 32 | 26 | 35 | 8 | 46 | 4 | 54 | 1 | 84 |
| 19 | No | No | | 39 | 37 | 42 | 33 | 40 | 31 | 29 | 38 | 10 | 42 | 3 | 59 | 0 | 97 |
| 76 | Yes | No | | 45 | 17 | 41 | 24 | 33 | 29 | 19 | 33 | 8 | 43 | 4 | 49 | 1 | 67 |
| 76 | Yes | Yes | | 47 | 11 | 44 | 15 | 30 | 25 | 16 | 33 | 6 | 48 | 2 | 58 | - | - |
| 76 | No | No | | 47 | 42 | 33 | 41 | 28 | 44 | 23 | 45 | 10 | 46 | 3 | 55 | 1 | 82 |
| 76 | No | Yes | | 52 | 21 | 53 | 18 | 31 | 26 | 18 | 30 | 6 | 45 | 2 | 61 | - | - |

F means < 0.150 mm and C means > 2.00 mm

TABLE 2

Changes of granule fractions, after increasing the sieving time from 2 to 3 min, calculated as a percentage of the composition at 2 min sieving time.

| Granule fraction, | Fluid-addition rate, ml/min: | Water | | | | | Lactose solution | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 76[a] | | | | 19[b] | 76[a] | | | |
| mm | Fluid level, v/w % : | 5.7 | 9.5 | 9.5[c] | 17.1 | 5.7 | 5.7 | 9.5 | 9.5[c] | 17.1 |
| > 2.00 | | 83 | 89 | 85 | 96 | 89 | 83 | 88 | 84 | 96 |
| 1.50 - 2.00 | | 93 | 105 | 102 | 104 | 95 | 100 | 102 | 101 | 106 |
| 1.00 - 1.50 | | 103 | 103 | 104 | 100 | 99 | 100 | 103 | 103 | 101 |
| 0.750 - 1.00 | | 104 | 105 | 101 | 99 | 100 | 107 | 102 | 97 | 103 |
| 0.500 - 0.750 | | 103 | 103 | 101 | 101 | 101 | 105 | 102 | 108 | 100 |
| 0.250 - 0.500 | | 103 | 99 | 99 | 102 | 100 | 98 | 97 | 94 | 101 |
| 0.150 - 0.250 | | 83 | 98 | 97 | 107 | 101 | 87 | 93 | 92 | 109 |
| < 0.150 | | 113 | 116 | 116 | 116 | 109 | 116 | 116 | 120 | 118 |

a atomization
b no atomization
c wet massing

TABLE 3

Added amount of water required for the occurrence of maximal proportions with regard to different size fractions.

| Granule fraction, mm | Flow rate, ml/min: | Atomization 19 | Atomization 76 | Atomization 76* | No atomization 19 | No atomization 76 | No atomization 76* |
|---|---|---|---|---|---|---|---|
| | > 0.045 | — | 5.7 | 5.7 | — | 7.6 | 5.7 |
| | > 0.071 | 7.6 | 7.6 | 5.7 | 9.5 | 9.5 | 5.7 |
| | < 0.150 | 3.8 | 3.8 | 3.8 | 5.7 | 3.8 | 5.7 |
| 0.150 | - 0.250 | 9.5 | 9.5 | 3.8 | 13.3 | 13.3 | 9.5 |
| 0.250 | - 0.500 | 13.3 | 13.3 | 13.3 | 13.3 | 13.3 | 13.3 |
| 0.500 | - 0.750 | 17.1 | 17.1 | 17.1 | 17.1 | 17.1 | 13.3 |
| 0.750 | - 1.00 | 17.1 | 17.1 | 17.1 | 17.1 | 17.1 | 17.1 |
| 1.00 | - 1.50 | 17.1 | 20.4 | 17.1 | 17.1 | 17.1 | 17.1 |
| 1.50 | - 2.00 | 17.1 | 20.4 | 17.1 | 17.1 | 17.1 | 17.1 |
| | > 2.00 | 20.4 | 20.4 | 17.1 | 20.4 | 20.4 | 17.1 |

Water added, v/w %

* Wet massing. Highest amount of water added 17.1 v/w %

TABLE 4

Fraction distribution as percentage at a water level of 9.5 v/w %, flow rate of 76 ml/min, with and without wet massing. Tests repeated 10 times.

| Granule fraction, mm | | without wet massing: mean, % | without wet massing: coefficient of variation, % | with wet massing: mean, % | with wet massing: coefficient of variation, % |
|---|---|---|---|---|---|
| | > 2.00 | 32.8 | 5.4 | 33.0 | 8.7 |
| 1.50 | - 2.00 | 6.5 | 2.9 | 5.7 | 2.3 |
| 1.00 | - 1.50 | 8.3 | 2.5 | 5.8 | 3.4 |
| 0.750 | - 1.00 | 4.2 | 5.5 | 2.7 | 4.2 |
| 0.500 | - 0.750 | 4.7 | 3.3 | 3.1 | 4.0 |
| 0.250 | - 0.500 | 8.4 | 3.4 | 9.7 | 4.5 |
| 0.150 | - 0.250 | 15.9 | 8.3 | 23.9 | 5.0 |
| | < 0.150 | 19.3 | 12.4 | 16.1 | 10.6 |

Fraction distribution

regard to the fractions between high and low addition rates, although the actual proportions were different. When water was added by means of atomization, the maximal proportion of the smaller fractions, < 0.250 mm, occurred at lower amounts of water, irrespective of the addition rate. For the same fractions without atomization a larger volume of water was needed. This meant that the non-uniform distribution of water at non-atomization delayed the granule formation.

When wet massing was performed, the maximal proportions for the small fractions normally occurred at lower amounts of water. Hence, the small fractions agglomerated more rapidly into coarser granules owing to the wet massing.

Experiments at a normal water level, 9.5 v/w %, with a fluid-addition rate of 76 ml/min and atomization, were repeated 10 times with and without wet massing. The greatest variation with regard to results occurred with the indicator fractions; see Table 4.

A log-normal distribution of granules was not attained until some 17 v/w % water had been employed - a far larger quantity than is normally used in the preparation of tablet granulations.

## Granulation

The volume of water added, the fluid addition rate, and the way of adding the liquid, all influenced the torque at the beginning of the water addition; Fig. 1. With the exception of the high flow rate, without atomization and wet massing, this first part of the curves mainly reflected granule formation, but it also showed a gliding transition to granule growth. High flow rate without atomization and without wet massing, i.e. large water-droplet size and non-uniform distribution of water in the powder, resulted in a deviating curve.

This variant was the only one of similar appearance as the curves of power consumption versus amount of granulating liquid according to Bier et al (6). During the first stage of the curves in Fig. 1. there was an increase especially of the finer fractions. This first stage covered water levels up to about 7 v/w %, but the transition into the granule growth stage was determined by the process variables.

The second part of the curves for torque versus water added did not differ significantly, with the exception of 13.3 v/w % water, high flow rate, and extra wet massing; Fig. 1. The exception was significant, $P < 0.025$ using a two-sided Student's t-test. Anyhow, the main variable during this granule-growth stage was the volume of water added, although high flow rate and extra wet massing did exert a certain degree of influence. Fraction < 0.150 mm decreased and > 2.00 mm increased during this stage; Table 1. The change was complex with regard to all the fractions, but as a rule the small fractions decreased while the coarser fractions increased.

After the addition of water corresponding to a level of about 20 v/w % there was a sudden increase of torque, concomitant with overwetting of the mass; Fig. 1. This was reflected in the disappearance of < 0.150 mm and a steep increase of > 2.00 mm; Table 1.

The coefficient of variation for the torque with regard to the repeated experiments in Table 4 was 1.1 and 1.7 % without and with wet massing respectively.

The curves concerning torque versus volume of lactose solution added were congruent to the corresponding curves for water, with the exception of the first 50 ml or so, when lactose solution resulted in somewhat lower torque. This deviation was caused by the less efficient atomization of the lactose solution.

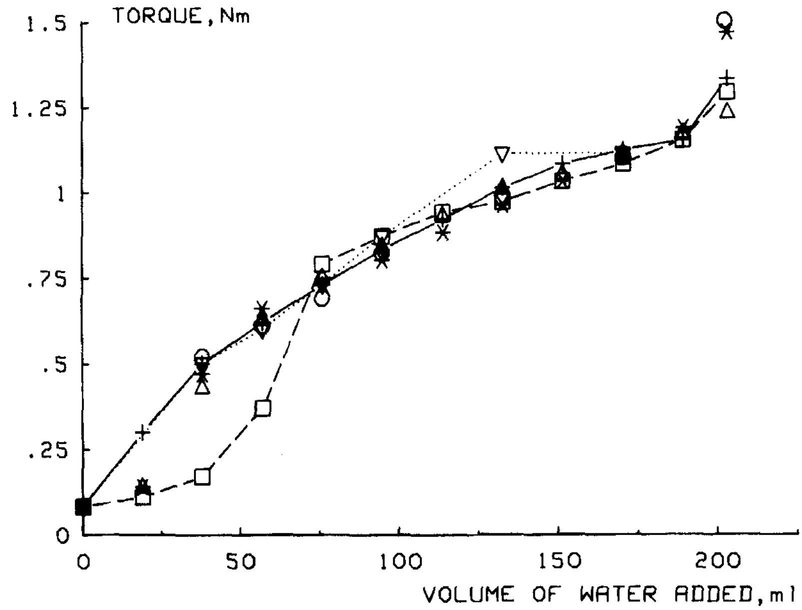
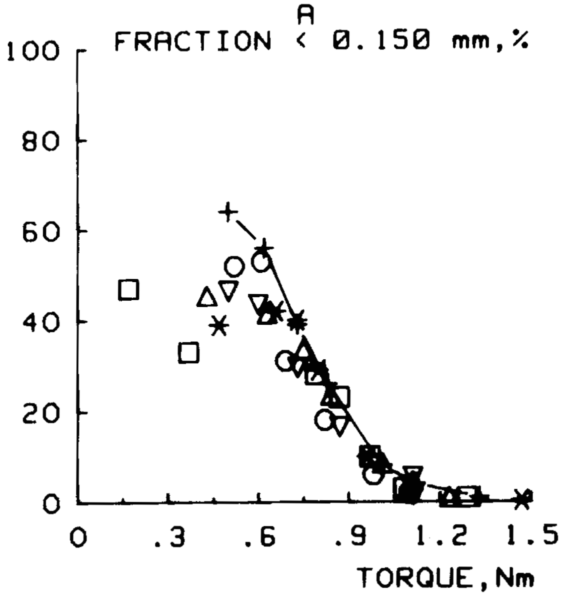



FIGURE 1

Relation between torque of the mixing bowl, Nm, and volume of water added, ml.

| Sign: | Flow rate, ml/min: | Atomization: | Wet massing: |
|---|---|---|---|
| ✳ | 19 | No | No |
| + | 19 | Yes | No |
| □ | 76 | No | No |
| △ | 76 | Yes | No |
| ○ | 76 | No | Yes |
| ▽ | 76 | Yes | Yes |

When fractions < 0.150 mm and > 2.00 mm were plotted versus torque, there were non-linear relations; Fig. 2A and B. When the droplet size was small and the water homogeneously distributed, i.e. low flow rate with atomization, or high flow rate with atomization with or without wet massing, the relations were distinct both during the granule formation and during the growth stages. All curves coincided when overmassing began. This meant that the torque value can be used as an indication of the granule size when process vari-



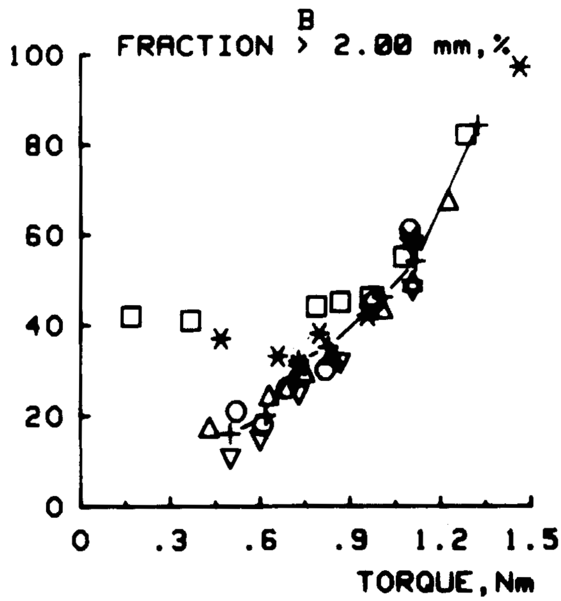




FIGURE 2

A Fraction < 0.150 mm, %, versus torque of the mixing bowl, Nm.

B Fraction > 2.00 mm, %, versus torque of the mixing bowl, Nm.

The same signs as in Fig. 1.

ables such as the liquid flow rate, the way of adding the liquid and the wet massing time were controlled. Under these circumstances the amount of water determined the granule size. In any case, it must be borne in mind that the variation in granule size was larger than the variation in torque.

## CONCLUSION

The torque value of the mixing bowl can be used as an indication of the granule size when lactose is granulated with water under controlled conditions.

## FOOTNOTES

1. DMV, Veghel, The Netherlands
2. v/w % means volume of granulating liquid (ml) per mass of dry powder (g) multiplied by 100
3. Laboratory sieving machine type Vibro, Retsch, Haan b. Düsseldorf, West Germany
4. Type 200, Alpine AG, Augsburg, West Germany

## REFERENCES

1. H. Rumpf, Chem. Ing. Techn. 30,144 (1958)
2. H. Leuenberger, Pharm. Acta Helv. 57,72 (1982)
3. D. Ganderton and B.M. Hunter, J. Pharm. Pharmac. 23,1 S (1971)
4. A. Rogerson, D.N. Travers and T.M. Jones, J. Pharm. Pharmac. 28,63 P (1976)
5. N.-O. Lindberg, L. Leander and B. Reenstierna, Drug Dev. Ind. Pharm. 8,775 (1982)
6. H.P. Bier, H. Leuenberger and H. Sucker, Pharm. Ind. 41,375 (1979)