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INFLUENCE OF TECHNOLOGICAL FACTORS ON THE OPTIMAL GRANULATION LIQUID REQUIREMENT MEASURED BY POWER CONSUMPTION

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SUMMARY

The optimal liquid requirement for wet granulation can be investigated by recording the power consumption of the mixer during liquid addition. In this work it was tried to use this technique on a small laboratory scale (one kg or less) for lactose wet granulation with water. The validity of the power consumption method could be confirmed by granule size analysis. Different factors were studied : kind of mixer, powder quantity, mixer speed, liquid addition speed, granulator screen size, mixing time.

1 - INTRODUCTION

In spite of many advances in the last decade, drugs and excipients which can be used as such for direct tabletting are not the general rule.

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Often a granulation is required to improve the flow of powders as well as the mechanical properties of resulting tablets.

Usually the granules are obtained by adding liquids (binder solutions, or liquids acting as partial solvent). The optimal quantity of liquid needed to get a given granule size at the end of the operation should be known accurately, in order to keep a good reproducibility from batch to batch. Unfortunately only few techniques allow such a good manufacture (for example fluid bed granulation). In the classical granulation process (wet massing and screening) the optimal volume is often fixed empirically.

The aim of this work was to study, on the laboratory scale, a scientific method for the determination of optimal liquid requirement. The technique, previously described by LEUENBERGER and al. (1,2,5)has been applied to 3 mixers, and various experimental conditions have been studied.

2 - PREVIOUS WORKS

Several studies have been undertaken for a better knowledge of wet granulation. Some are related to the kind of bonding between particles ; others try to explain the bonding and size increase of granules ; others specifically investigate the liquid volume required to produce granules.

2.1. Bonding between particles

The first studies were published by RUMPF (10) in 1958. This author showed that different kind of bonding can occur :

- attractive forces between solid particles ;
- adhesive and cohesive forces in binders ;
- solid bridges ;
- interfacial and capillary pressure forces in liquid surfaces.

It was also shown that only solid bridges and interfacial forces take place in wet granulation.

The solid bridges are formed between two particles by mean of a third solid called "binder". These kind of bridges are obtained during drying by cristallisation or hardening of a dissolved substance, or by a layer of colloïdal sediment. In some cases the binder can be the active drug itself, partially dissolved by the granulation fluid.

When the bridges are formed by interfacial forces and capillary pressure, the name of the bridges is "liquid bridges" in which the active drug can be dissolved.

These forces create the primary attraction between particles, and allow the creation of a nucleus.

RUMPF showed that, in function of the quantity of liquid added to the powder bed, there are 3 steps during the agglomeration :

- pendulary state : small liquid lamellas are formed between particles ; big air holes between particles still exist
- funicular state : the air is progressively removed when liquid is added
- capillary state : there are no more void spaces between particles, and if the optimal quantity of liquid is exceeded, even a very few, a kind of droplet is produced.

Several authors tried to quantify the various phenomenons which allow to reach this granular structure (8,11). The studies were especially made on interfacial tension and capillary pressure in the liquid located between particles. The resulting force is a cohesive force H_F which depends on particles spacial packing (cubic, rhomboedric, ...) (6). The cohesive force is given by the equation (fig. 1) :

$$(I) \ldots \quad H_F = \alpha \pi \sin \beta x \left(\sin(\beta + \delta) + \left(\frac{1}{R_1} - \frac{1}{R_2}\right).\frac{x}{4}.\sin \beta\right)$$

where

- α is the granulation liquid surface tension
- x the particle diameter
- β the center angle
- δ the wetting angle
- R_1 the arc radius of the circle described by the concave surface of the liquid bridge
- R_2 the half-least-width of the bridge.

2.2. Granule size increase

The theory of granule size increase has first been established by Newitt and Conway-Jones (8) during a study of silica granulation in a coating pan. This theory has been confirmed later (3,11). In this theory, the granulation occurs in 3 steps (fig. 2).

- nucleus formation : this step is characterized by the appearing of small agglomerates resulting of the joining of several individual particles (pendulary bridges)

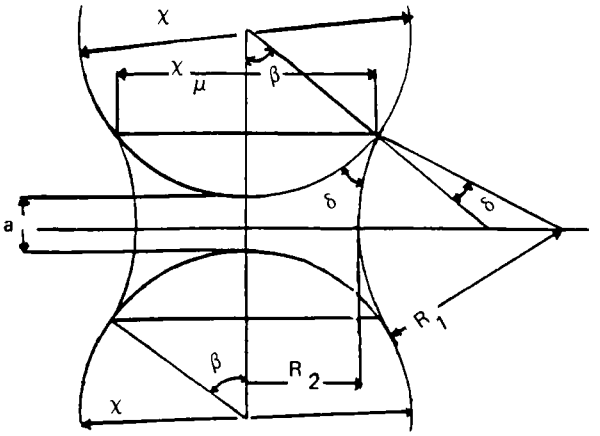


FIG : 1 - MODEL OF A LIQUID BRIDGE FOR SPHERICAL PARTICLE

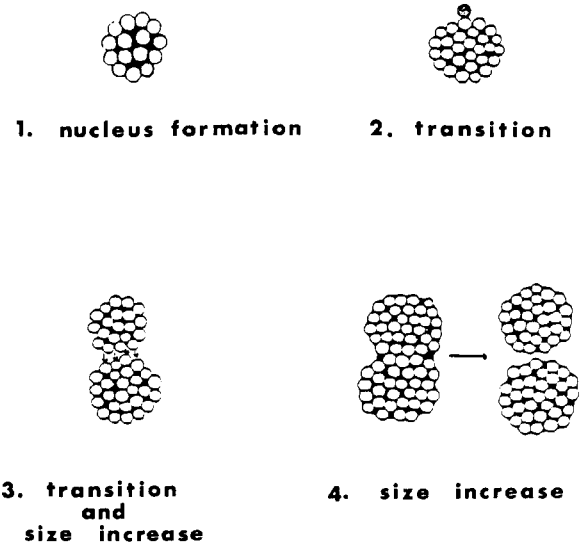


FIG : 2 - STEPS DURING GRANULE FORMATION

- transition : the second stage is the creation of small spheres of irregular size
- size increase : the last step leads to spheres which are regular in shape and size, either by bonding of several spheres or breaking of big spheres under mixing.

At each stage an other kind of bonding takes place (fig. 3) : during nucleation, the pendular forces are the most important ; during transition, funicular forces, and during size increase, capillary forces.

2.3. Evaluation of the required granulation fluid quantity

Some authors have tried to calculate the quantity of liquid required to give good granules. RUMPF (9) was the first to describe, by an equation, the volume of liquid in a powder bed, based on a cubic packing of particles (fig. 4) :

$$(II) \ldots V_{zw} = 2\pi \left[(R_1^2 + b^2) R_1 \cos(\beta + \delta) - \frac{R_1^3 \cos^3(\beta + \delta)}{2} - b \left(R_1^2 \cos(\beta + \delta) . \sin(\beta + \delta)^2 + R_1^2 . \left(\frac{\pi}{2} - (\beta + \delta)\right) \right) - \frac{1}{24} x^3 (2 + \cos\beta) . (1 - \cos\beta)^2 \right]$$

where R_1, β, δ and x have the same meaning as in the equation I, b represents the distance between the center of the particle and system axis.

This interesting theoretical equation seems, however, too complex to have a real use in the practice.

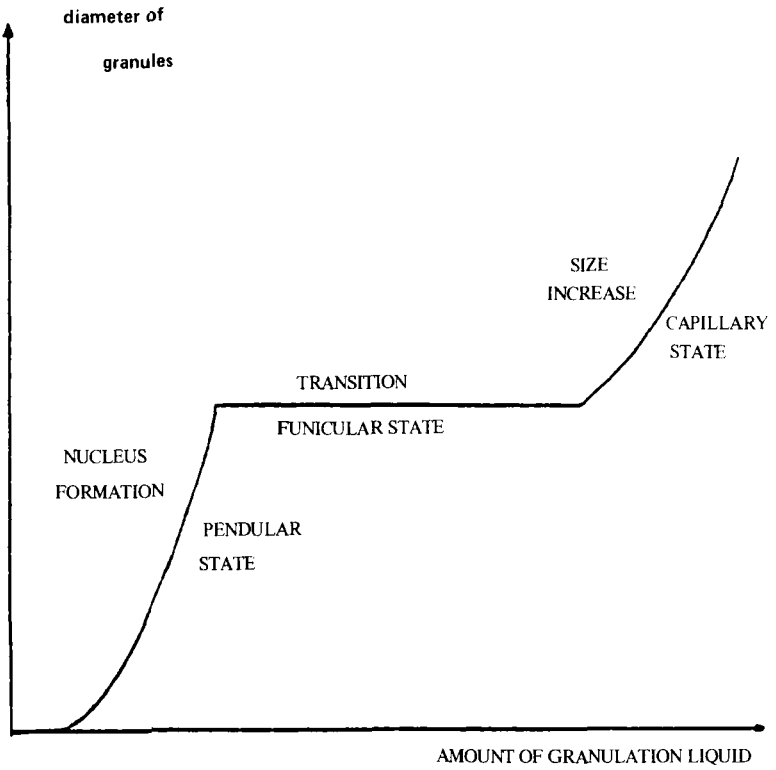


FIG : 3 - STEPS DURING GRANULATION

An other theoretical approach has been given in the litterature (3,5) :

(III) ..... $$W = \frac{\varepsilon pe}{\varepsilon pe + (1 - \varepsilon)ps}$$

where - W is the quantity of liquid (in %)

- ε the powder bed porosity
- pe and ps the true densities of liquid and solid

This equation, using simple parameters, seems to be easier to use in production. It can be corrected by a factor indicating

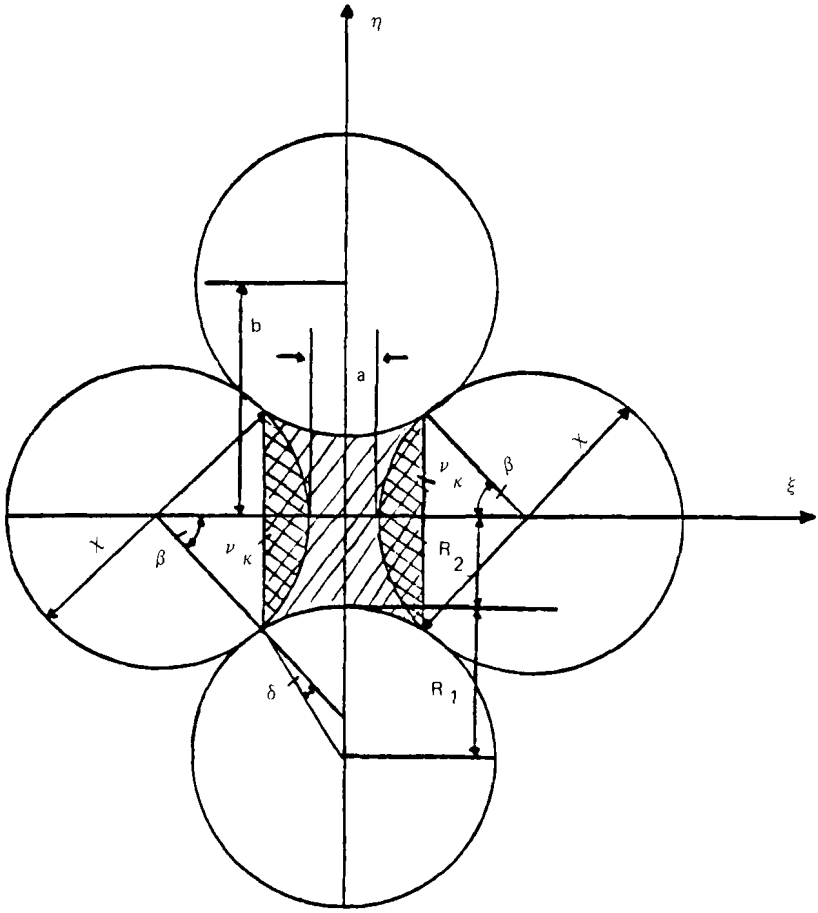


FIG : 4 - VOLUME OF LIQUID IN A POWDER BED

the quantity of liquid sucked up by hygroscopic powders (this liquid is not used to form bonds between particles).

Other authors tried to appreciate the optimal liquid quantity by measuring the energy consumption of the mixer during liquid addition. Two kind of methods were employed :

- strain gauges (7) :

the measurement of power consumption by strain gauges is not

very convenient, because it is often difficult to find a place on the mixer where the strain is high enough to give an accurate record, and low enough to avoid any dammage on the gauges. Usually the gauges are mounted in a Wheatstone bridge, and the resulting signal is recorded.

- wattmeter :

the first trials, in the pharmaceutical field, were published by HUNTER and GANDERTON (4), but the results were not completely satisfactory, due to the recording system. In 1979, LEUENBERGER and al. (1,2) described an apparatus giving much better results : they measured the power consumption by mean of a wattmeter, and the use of electronic filters allowed a good separation between ground noise and the real signal.

The recording obtained by these authors (fig. 7) shows different zones ; they are limited by tangent lines to the different portions of the recorded curve. Each of those zones represent a step in the granule formation.

The step 1 is the liquid saturation of the powder, before any bonding ; the second step is the nucleus formation ; in step 3 is the transition phase and in step 4 the granulate formation is exceeded (droplet formation) and a kind of powder suspension in liquid is formed.

LEUENBERGER and al. (1,2,5) studied the characteristics of tablets obtained with granules at different stages. These authors showed that the optimal value of liquid (Sm) is given by

IV ..... $$Sm = \frac{S_3 + S_4}{2}$$

3 - PERSONAL WORKS

The aim of this work was to study the influence of various technological factors which could modify the optimal granulation liquid requirement, measured by the power consumption technique.

3.1. Material and methods

Unless otherwise specified, all the studies were made on 1.000 kg of lactose ("impalpable grade" - HMS-NL). This quantity of powder was introduced in a mixer, and progressively wetted with water by mean of a peristaltic pump (10 ml/min.). During the mixing and wetting stage the power consumption was measured as a function of the quantity of liquid added by mean of a wattmeter and the resulting signal recorded. The wet mass was granulated through a screen of 630 µm and the granules dried in thin layer at room temperature.

The method of granulation was evaluated by studying the physical properties of the granulates and not by manufacturing tablets. It was considered that a granulate can be regarded as satisfactory when more than 80 % of particles having the same size are obtained. So the optimal quantity of liquid could be calculated by plotting the percentage of particles of a given size as a function of granulation liquid quantity added.

The particle size distribution has been studied each time on two batches : it has been measured by screening the particles (Erweka vibratory screens type EML, with 1000 µm, 500 µm, 250 µm and 160 µm screens-vibrations during 15 minutes).

3.2. Influence of technological factors

The technological factors which may have an influence on the optimal granulation liquid quantity required can be classified into two categories : those related to the mixer, and those related to the other devices used for granulation (peristaltic pump, granulator ...).

3.2.1. Factors related to the mixer

For this study, three different laboratory mixers have been used :

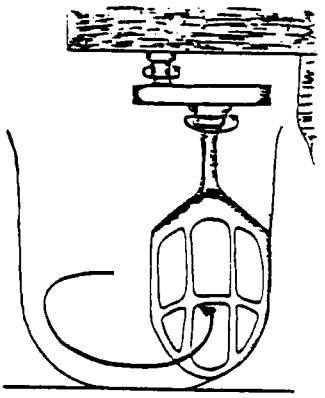
- A planitary mixer with 1 paddle (ERWEKA) (Figure 5).
- A planetary mixer with 2 paddles (PRIMAX) (Figure 5).
- An helicoïdal mixer (BOSCH) (Figure 5).

A comparison between the characteristics of the mixers is given in table 1.

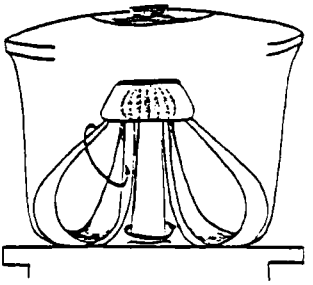
According to the different mechanical criterions, it seems that the Bosch mixer is the most well adapted to small laboratory trials. The power consumption record of the three types of mixers is different : for example the base line (fig. 6) does not have the same shape, and this obtained with the Bosch mixer gives the most precise drawing, and also the lowest variations.

After switching on the mixer, a certain time is needed to reach the consumption steady state : here also the Bosch mixer seems to be the most adequate to give a good drawing.

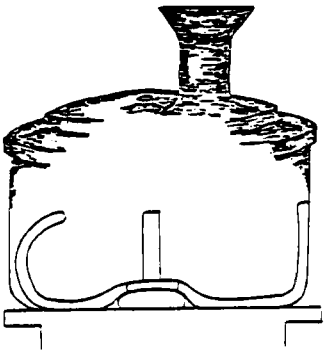
During the record of the power consumption of the empty mixer, the base line shows sometimes unwished variations, but



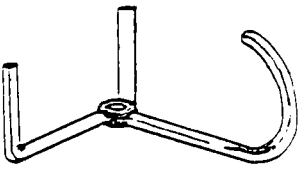
PLANETARY ERWEKA^{R} MIXER



PLANETARY PRIMAX^{R} MIXER



BOSCH^{R} MIXER



PADDLE OF BOSCH^{R} MIXER

FIG : 5 - DIFFERENT KIND OF MIXERS USED

the Bosch mixer was this with the lowest variations. So it seemed to us that the helicoïdal apparatus is the best one to study, on a laboratory scale, the mixing before granulation. This good experimental properties can be related to the mixing paddle of the apparatus (Fig. 5) : the paddle is fixed to the bottom of the mixer, and its particular shape leeds to important frictions

Table 1 : Comparison between the characteristics of the mixers.

MIXER	Planetary ERWEKA	Planetary PRIMAX	Helicoïdal Bosch
Rotation speed	++	++	+++
Efficiency of the mixer	+	++	+++
Kind of closing	0	++	+++
Filling	+	0	+++

along the apparatus walls as soon as a small quantity of powder is put into the mixer.

For these mechanical and electrical reasons the Bosch mixer was choosen to undertake this study.

3.2.1.2. Verification of the validity of the method

With the described material it was tried to verify the data published by LEUENBERGER and al. (1,2,5).

The record obtained with our apparatus shows some similarities with the record published by LEUEUNBERGER (fig. 7) ; this similarity does however not signify that the optimal liquid quantity is equal to $\frac{S_3 + S_4}{2}$

For this reason the quantity of liquid corresponding to the different steps was measured :

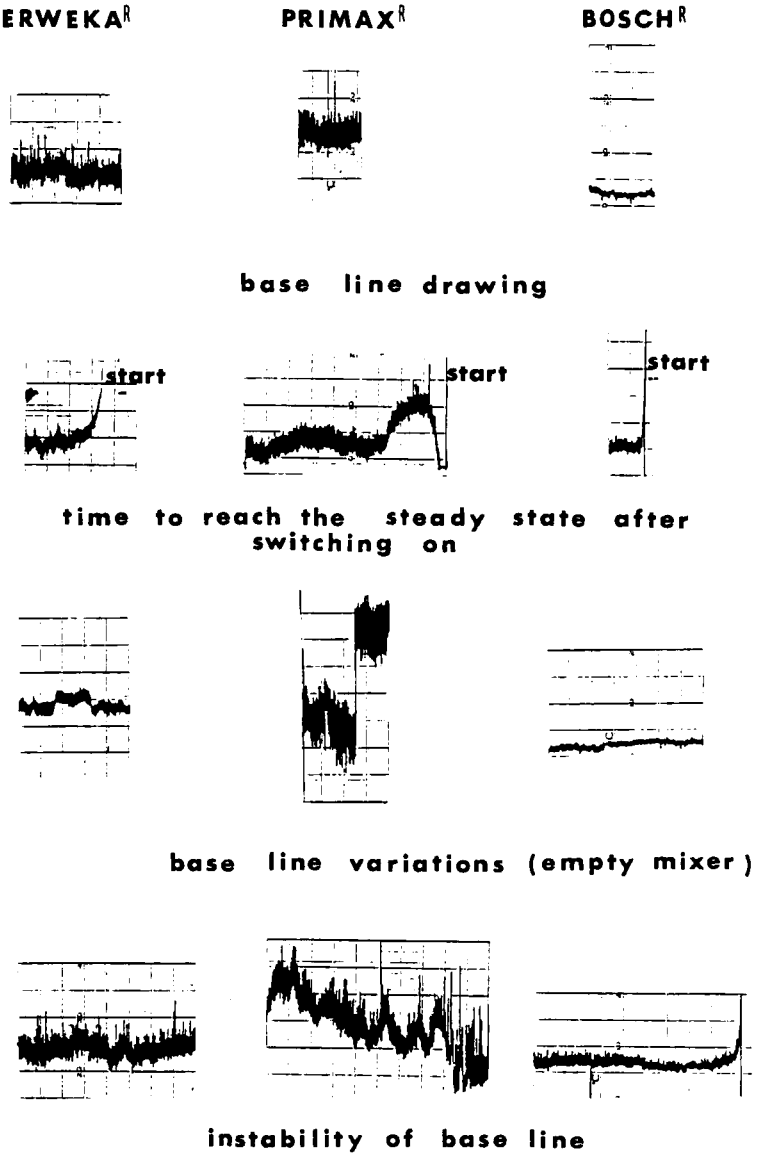


FIG : 6 - POWER CONSUMPTION RECORDS

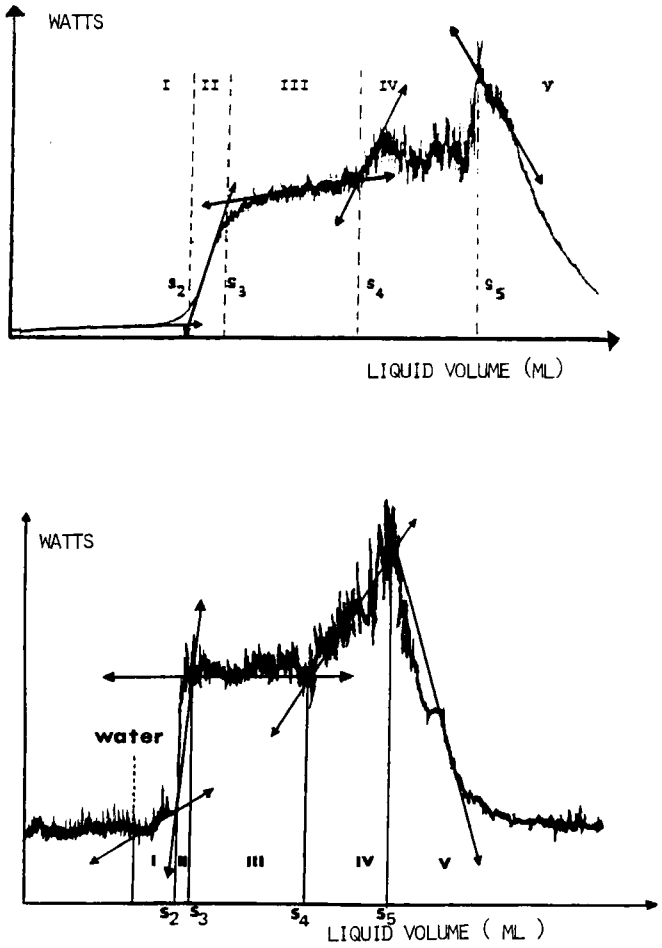


FIG : 7 - POWER CONSUMPTION RECORDS OBTAINED BY LEUENBERGER ET AL. (1) (TOP)AND OUR DEVICE (BOTTOM)

We found :

- 44 ml for the first power variation
- 60 ml for the first peak S_2
- 80 ml for the beginning of the plateau S_3
- 190 ml for the beginning of the second peak S_4

So $Sm = \frac{80 + 190}{2} = 135$ ml

After drying of the different granules, a particle size analysis has been made. Figure 8 gives the percent of particles of a given size as a function of the added liquid volume. These curves have a gaussian shape. They are more precise than it could be expected from the number of experimental points plotted on the figure : in fact, for each point, the sum of the four curves is equal to 100 %, so, even between two experimental points the curves can be drawed with a certain accuracy by calculation of the coordinates of additional points.

The curves show that 86 % of particles having a size between 500 and 1000 µm can be obtained with a granulation liquid amount of 135 ml. It could seem surprizing that with a granulator screen of 630 µm such an amount of particles having a size between 500 and 1000 µm could be obtained. In fact not only the diameter of granules but also their length must be considered in a screen particle size analysis.

The optimum liquid volume resulting from the granule size analysis (135 ml) is the same as this calculated by the theory of LEUENBERGER and al.

To confirm these first data an other batch of granules (batch 2) was produced, without consumption recording, by adding slowly an exact amount of 135 ml of water to the lactose. The granules were dried and the particle size distribution analysed by sieving.

Table 2 shows that this quantity of liquid gives the expected results, showing a good reproducibility of the method.

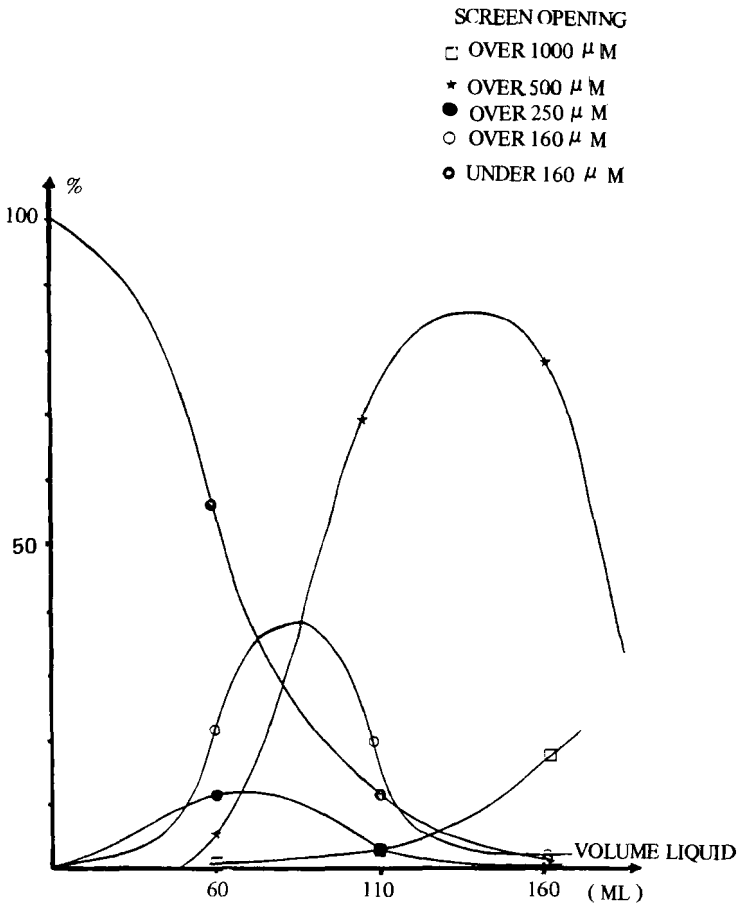


FIG : 8 - PARTICLE SIZE DISTRIBUTION AS A FUNCTION OF THE LIQUID VOLUME ADDED

3.2.1.3. Influence of the powder quantity

Very recently LEUENBERGER (6) has shown that the power consumption method allows a good monitoring of granulation scale up ; this author demonstrated a good linearity of the measurement in charges ranged from 3.75 kg up to 60 kg. We tried to see if the method is also sufficient to study very small charges (less than 1 kg).

Table 2 : Particle size analysis of batch 1 and 2.

Screen opening (µm)	Batch 1	Batch 2
1000 µm	2.1 %	3.0 %
500 µm	86.1 %	85.6 %
250 µm	3.2 %	2.4 %
160 µm	1.0 %	1.0 %
0 µm	7.6 %	7.0 %

In the mixer quantities of 250, 500, 750 and 1000 g were granulated with a quantity of liquid equal to 135 ml for 1000 g (optimal quantity according to our previous results). The particle size analysis (Table 3) shows that the differences between batches of different sizes are not very great : the biggest particle class is between 500 and 1000 µm. It seems however that the proportion of particles larger than 500 µm is increased when the batch size is increased. This is represented in figure 9. The difference of particle size could be related to a difference of wetting, or a difference in the screen massing : in fact it seems that with very small quantities of powder, the powder is well wetted by the liquid, but the granulator crushes the granules, because of the small layer on the massing screen. This phenomenon explains the proportion of "fine particles" in the granulate.

3.2.1.4. Influence of the mixer speed

The mixing of the powder mass during wetting has been performed at two different speeds (170 r.p.m. and 220 r.p.m.).

Table 3 : Granule size analysis of the different batches.

BATCH SIZE / SCREEN	250 g	500 g	750 g	1000 g
1000 µm	1.79 %	1.88 %	3.34 %	2.96 %
500 µm	59.17 %	73.58 %	83.37 %	85.59 %
250 µm	19.94 %	9.65 %	3.68 %	2.44 %
160 µm	2.64 %	2.15 %	0.73 %	0.99 %
0 µm	16.42 %	12.71 %	8.84 %	7.01 %

In both cases the optimal liquid requirement was approximately the same : the maximum amount of particles having a size between 500 µm and 1000 µm is obtained at the lower speed with 135 ml and at the higher speed with 140 ml. It seems that, in that range, the speed factor is not essential for the liquid volume determination. The whole particle size distribution of the granules obtained is not given here ; figure 10 only gives the particle size distribution between 500 µm and 1000 µm. It can be seen that there is only a slight difference in the optimal granulation liquid volume, but a certain difference in the shape of the curves. So the area under the curve, in the limits of 46-140 ml has been measured : it was 5068 % x ml in the case of the slower mixing speed, and 4571 % x ml in the case of the higher mixing speed. This difference can be

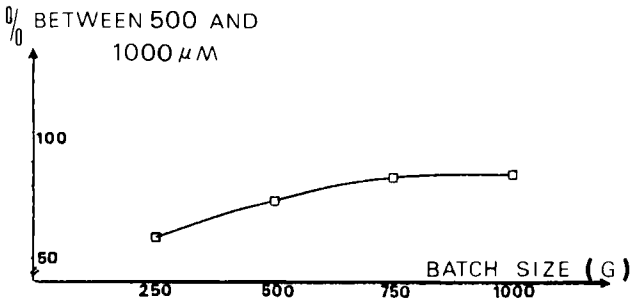


FIG : 9 - PARTICLE SIZE BETWEEN 500 AND 1000 μM AS A FUNCTION OF BATCH SIZE

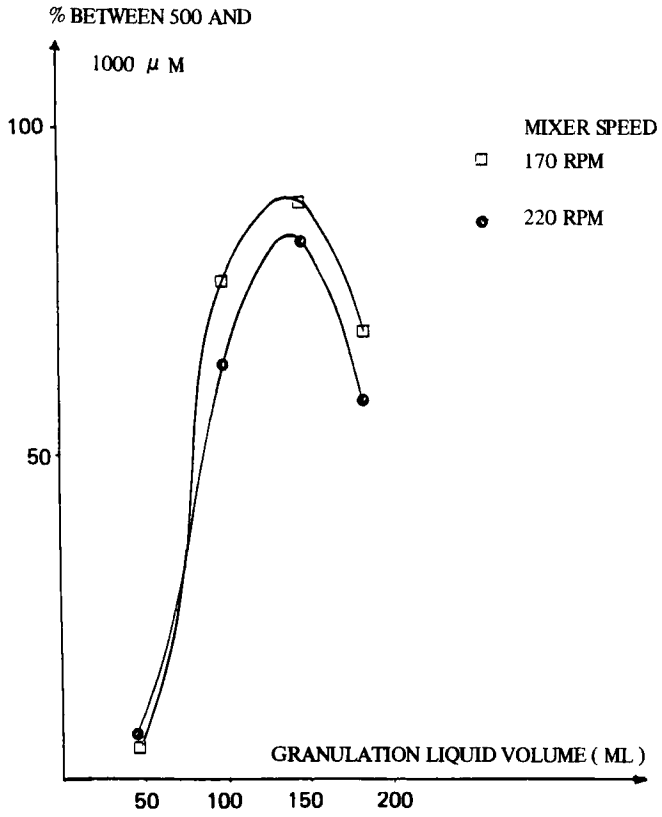


FIG : 10 - INFLUENCE OF THE MIXERS' SPEED ON THE PARTICLE SIZE DISTRIBUTION

related to the suspension of particles in the mixer under high speed : a more uniform contact between liquid and solid is realised during wetting, so that any local over-wetting is avoided.

3.2.2. Factors related to other devices

Factors which are independent of the kind of mixer used may also have an influence on the resulting granulates. Among them, the liquid addition speed, the massing screen opening, and the mixing time after the wetting is achieved were studied.

3.2.2.1. Liquid supply

Granules were prepared with a liquid flow rate of 5, 10 and 20 ml/min. After mixing at low speed, granulation and drying of the granules, the particle size has been analysed.

It could be seen from the power consumption recording and the particle size distribution curves that the liquid flow rate does not have any influence on the optimal liquid quantity requirement, but, as it was seen previously (cf. 3.2.1.4.) the area under curve, taken between 40 and 140 ml, seems to be different (fig. 11) : 4583 % x ml at 5 ml/min ; 5068 % x ml at 10 ml/min and 5394 % x ml at 20 ml/min. It seems however that a kind of equilibriumwould be reached with higher liquid flow rates (fig. 12). This area under curve increase could be related to a local over wetting during the first steps of granulation mixing.

3.2.2.2. Screen size

To study the influence of screen size opening, the wet mass was granulated through three kind of screens : 630 µm, 1000 µm

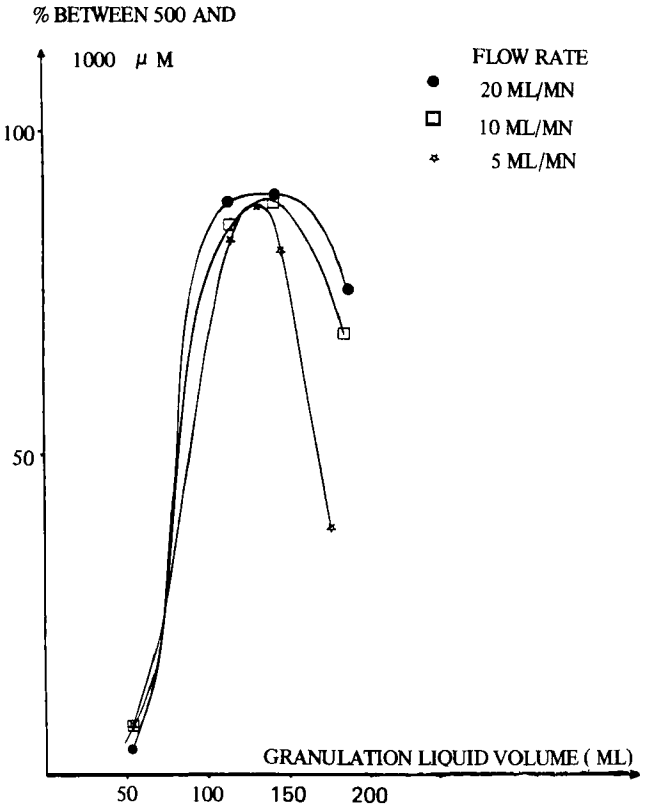


FIG : 11- INFLUENCE OF THE LIQUID FLOW RATE ON THE PARTICLE SIZE DISTRIBUTION

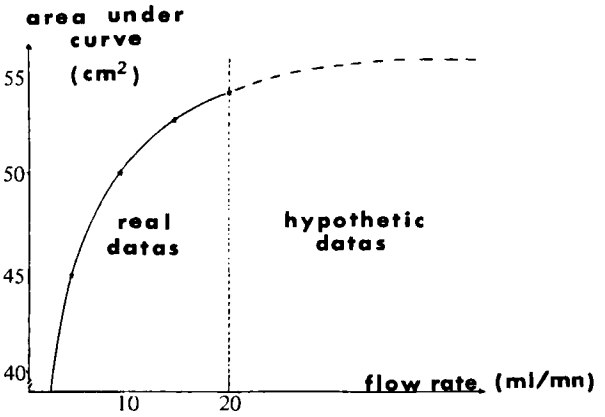


FIG : 12 - INFLUENCE OF THE LIQUID FLOW RATE ON THE AERA UNDER PARTICLE SIZE CURVE

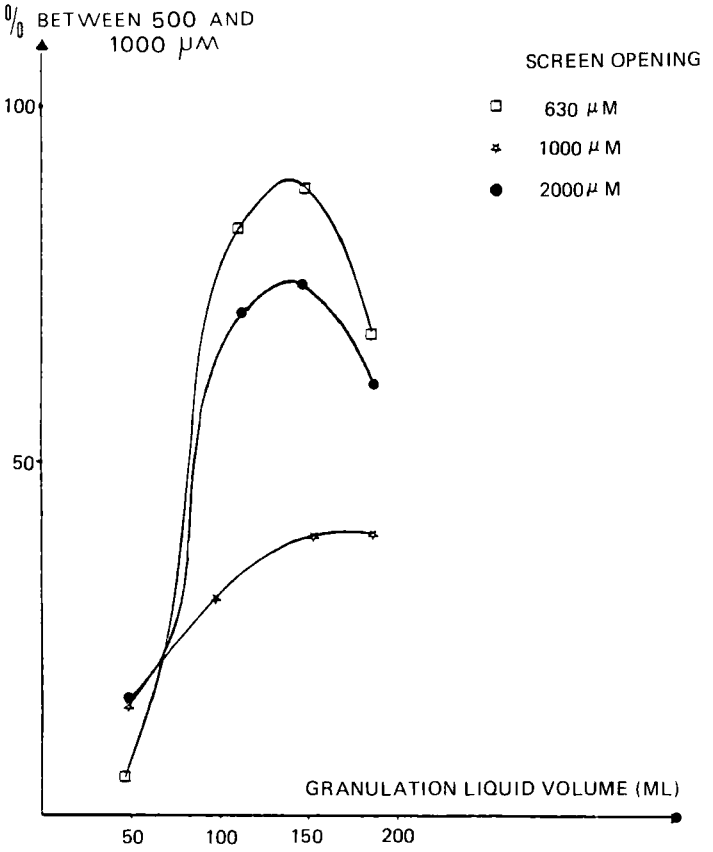


FIG : 13 - INFLUENCE OF THE SCREEN OPENING ON THE PARTICLE SIZE DISTRIBUTION

and 2000 µm. The optimal quantity of liquid required and the particle size distribution was fairly different : for example figure 13 gives the percentage of particle between 500 µm and 1000 µm as a function of liquid volume used. It can be seen that the most interesting granule size distribution, for these particles, is reached with the 630 µm screen. The main results of these experiments are summarized in table 4 :

Table 4 : Results of the granulations on various screen sizes.

Screen opening	Optimal liquid quantity	Percentage of particle between 500 and 1000 µm	Area under curve (46-140 ml)
630 µm	135 ml	89,5 %	5068 % x ml
1000 µm	140 ml	75,0 %	4532 % x ml
2000 µm	165 ml	30,5 %	2593 % x ml

The optimal liquid quantity was 140 ml in the case of a screen of 1000 µm, and 165 ml (+ 22 %) in the case of a screen of 2000 µm. The percentage of particles between 500 µm and 1000 µm, and the area under the curves showed also some differences ; these differences are well related to the screen opening (fig. 14). The bad results in particles between 500 and 1000 µm with the 2000 µm screen could be related to the granulator pressure decrease during wet screening

3.2.2.3. Mixing time after the end of liquid addition

Once the whole quantity of liquid required is added to the powder mixture, this mixture can either be granulated immediately, or granulated after an additional mixing time.

The influence of this additional mixing time has been investigated by recording the power consumption during 15 minutes after the granulation liquid addition was ended. This study was

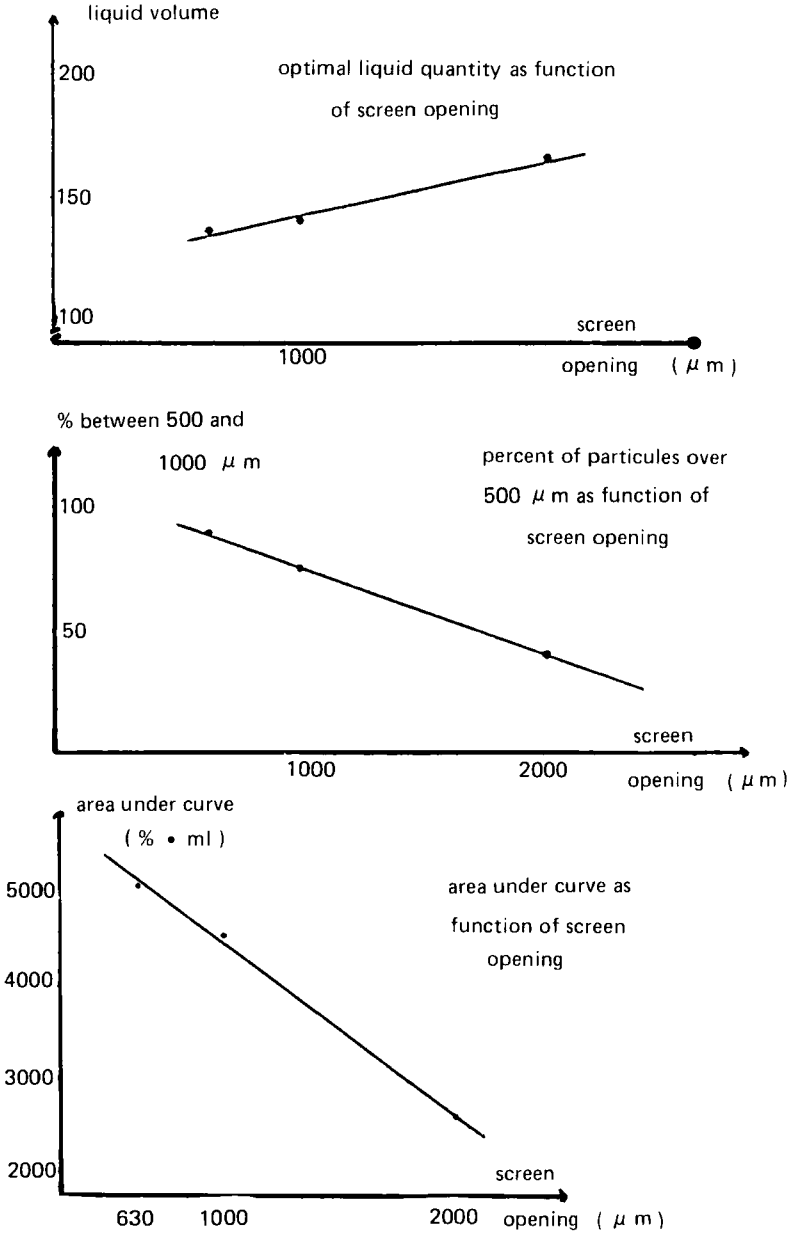


FIG : 14 - INFLUENCE OF SCREEN OPENING ON VARIOUS FACTORS

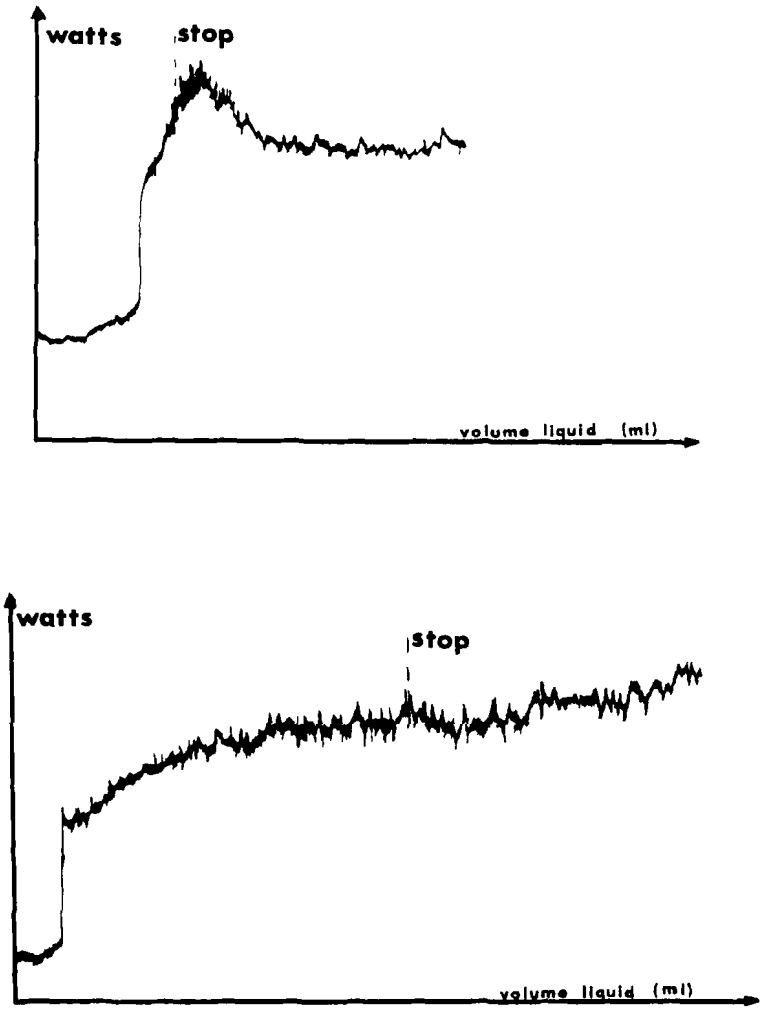


FIG : 15 - STUDY OF POWER CONSUMPTION AFTER THE END OF LIQUID ADDITION

made with the different liquid flow rates, and the different mixer rotation speeds used previously. The liquid addition was stopped at different stages of wetting. It could be seen (fig. 15) that if the liquid addition is stopped at a quantity under 120 ml/kg, the power consumption of the mixer increases after the liquid addition has ceased. This indicates that with less than 120 ml

(approx. 10 % under the optimal quantity) the wet mass is not perfectly homogeneous ; the homogeneity is reached after a few minutes ; then the power consumption becomes stable (a plateau, corresponding to a steady state is reached). When the liquid addition is stopped at a quantity over 120 ml, the additional mixing does not have any effect on the power consumption. This could be noticed with every liquid addition speed (5, 10, 20 ml/min) and with every mixer speed (170 and 220 r.p.m.). So it can be considered, that with a quantity of liquid lower than 90 % of the optimal quantity, the wet powder mixture to be granulated is not homogeneous, and should be mixed for an additional time before granulation. On the other side, if the quantity of added liquid is more than 90 % of the theoritical optimum, then the mixing can be stopped immediately or continued : this factor has no influence because the mass is homogeneously wetted.

4 - CONCLUSION

This work tried to show that the technique described by LEUENBERGER and al. for the study of wet granulation can be used at a very small laboratory scale.

Some factors related to the type of mixer used, as well as to the granulation technique can have an influence on the optimal quantity of liquid required : some mixers are not convenient to produce a good power consumption recording, but for a given type of mixer, the variations of mixing speed, or batch size, do not affect the optimal liquid quantity determination. Only a change

in the granulator screen size leads to a real change in the optimal quantity of liquid.

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