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SCALING-UP OF WET GRANULATION
A STATISTICAL METHODOLOGY

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ABSTRACT

Wet granulation is studied in different granulators: conventional planetary mixers (Collette® and Ours®), high speed granulators (Moritz® TS10 and TS50) and Lödige® mixer. Apart from the type and size of apparatus, the quantity of granulating liquid and the kneading time vary according to experimental designs. A great number of variables are measured before, during and after compression of the produced granules. Results are collected and treated using the Response Surface Methodology. Comparison of the obtained response surfaces and superimposing the contourlines lead to a best knowledge of the scaling-up operation. A Multifactorial Analysis, more global but complement of the previous method, is performed in order to reveal the main differences as well as common properties between the different granulators, allowing so a general interpretation of their characteristics.

INTRODUCTION

Until recently, wet granulation was an expensive process because of labour, time, equipment, energy and space requirements. The development of new granulation technics such as high speed or high shear mixers allows to conduct nowadays the operations of mixing, wetting, kneading and drying in only one step and in a close circuit (1-3). But when a granulation equipment is to be changed, different questions must be answered. What are the main differences between conventional and new generation of granulators? Is it possible to produce the same type of granules? Is the scaling-up operation easy to perform? This work describes a methodology allowing to give some elements of response.

MATERIALS AND METHODS

Composition of the granules

The starting product is a standard powder made up of lactose 150 mesh (Tollu et Lavolle S.A. F75012 Paris, France), corn starch (Roquette, F59022 Lille, France) and polyvinylpyrrolidone (BASF, Ludwigshafen, Germany). The amount of each component is kept constant and corresponds respectively to 75, 20 and 5 percent of the whole formula. The wetting liquid is an hydro-alcoholic solution in order to hasten the drying phase.

Equipment

Different types and sizes of granulator are tested:

- conventional planetary mixers Collette® MP600 and Ours® of a capacity of respectively 60 and 12 litters (MACHINES COLLETTE N.V., Keerbaan 70, B2220 Wommelgen BELGIUM)
- high-shear mixers, such named because they are equipped with a main impeller rotating at a moderately high speed and a chopper working at a very high speed. A 50 litters Lödige® mixer fitted out with ploughshare shape mixing tools is studied (Gebrüder Lödige Maschinenbau-Gmbh, Elsener Str.7/9 - Postfach 2050 - D4790 Paderborn1, Germany). "Turbosphères" Moritz® TS10 and TS50 with 10 and 50 litters capacities are also tested. They are equipped with a three shaped impeller, a twin-shell blender with a heated jacket and a vacuum air-pump (Société Moritz 7, avenue des Pommerots - 78400 Chatou, France).

Operating conditions

Apart from the type and size of granulator, two main parameters vary during this study: quantity of granulating liquid and kneading time. All other parameters are kept constant. After a dry-blending phase of 10 minutes, the granulating liquid is added with a flow rate of 60 ml/min.Kg. Wet granulates are then dried an calibrated through the 0.71 mm screen of an oscillating granulator.

Response variables

In order to collect the maximum of information about wet granulation in the different granulators, a great number of response variables are registered before, during and after compression.

Flowing ability is assessed by measuring the flow time of 100g of granules through a standardized funnel set upon a test-tube.

Height of granules in the test-tube indicates the bulk volume.

The graduated test-glass is then submitted to vertical taps. Differences between volumes after 10 and 500 taps are measured (4).

A set of sieves permits to calculate the mean diameter and the uniformity of size distribution.

Friability is evaluated by shaking granules with little balls.

Each batch of granules is mixed with 0.5% of magnesium stearate as a lubricant and then compressed with a single punch press instrumented with strain gauges and displacement transducers on both upper and lower punches.

This equipment allows controlling the force applied and measuring energy displayed by the upper punch, force transmission index, residual and ejection forces and expansion energy of the tablet in the die wall (5).

The obtained tablets are characterized by their weight, thickness, hardness, friability and disintegration time.

PRELIMINARY STUDY AND STATISTICAL METHODOLOGY

During formulation and process investigations, in order to understand precisely the relationships between variables, proceeding by trial and error is no more efficient, a rational statistical approach must be applied. The chosen one combines the Response Surface Methodology and a Multifactorial Analysis (6).

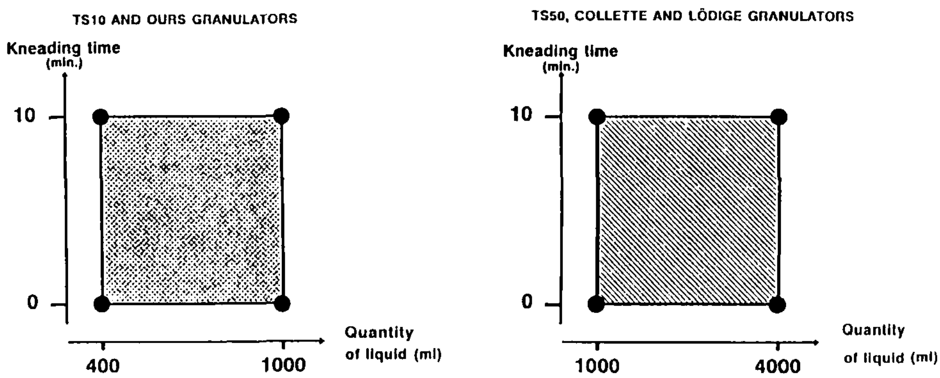


Figure 1. - Experimental Fields.

Response Surface Methodology (7-11) using experimental designs is an economical method leading to collect a maximum of information with a minimum of experiments allowing calculation of mathematical models. Factorial Analysis (12-16), complement of the previous method, is helpful to perform some general comparisons without proceeding by modelization.

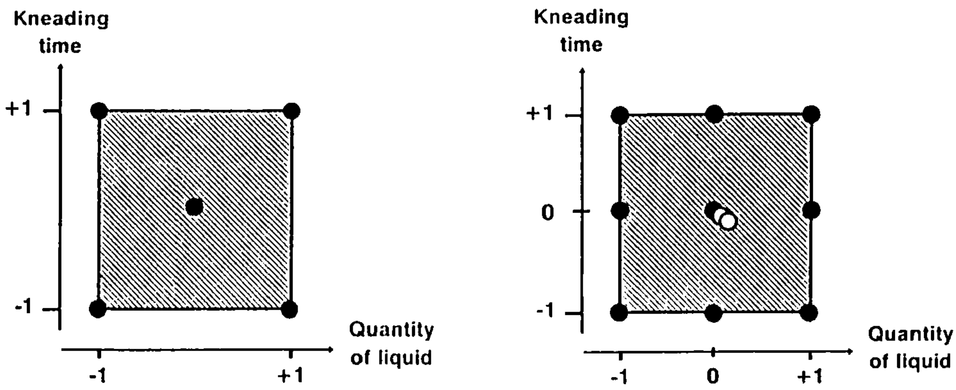
Preliminary study

Before building an experimental design, it is very important to define precisely the experimental field. This experimental field must not be too large, leading to non realistic experiments and not too small, far from an optimal region. Lower limits correspond to the minimum of granulating liquid quantity and to the minimum kneading time which can produce granules although not very different from the starting product but flowing through the standardized funnel. Quantity of liquid and kneading time leading to an overwetted mass but not pasty and able to be compressed set the upper limits.

For granulators of highest capacity, quantity limits are 1000 and 4000 ml. They are fixed to 400 and 1000 for the smallest ones. For all mixers, kneading time limits are 0 and 10 minutes. The experimental fields are represented on figure 1.

Statistical methodology

The vertices of the experimental field do constitute a typical 2^2 experimental design allowing calculation of a linear model:



Figures 2 and 3. - Experimental designs: $2^2 + 1$ and $3^2 + 2$.

$$Y = a + b.Q + c.T + d.Q.T$$

Y : response variable,
Q : quantity of liquid,
T : kneading time,
a : constant,
b,c,d : regression coefficients.

The linear model is verified by performing an additional experiment in the centre of the experimental field (figure 2). Difference between the experimental response in this point and the evaluated value according to the linear model must be zero, if not, an other model must be tested. A 3^2 experimental design (figure 3) can be build by adding only four experiments to the previous one so that a quadratic model can be calculated:

$$Y = a + b.Q + c.T + d.Q.T + e.Q^2 + f.T^2$$

Such a model is able to describe the response surface curvature.

To quantify the experimental error, two additional central experiments are realized. The complete model is statistically validated by analysis of variance, calculation of the multiple correlation coefficient and estimation of lack of fit.

This methodology using sequential experimental designs is efficient to define precisely the influence of the controlled variables on each individual response variable. To obtain a more global and general view of all the data and of all the relations between the variables, it is possible to complete this interesting but reducing approach by the use of the so called Factorial Analysis. Factorial Analysis is helpful to treat great tables of data crossing individual experiments and variables measured on these experiments. They are efficient to point out general relations between these variables. When the experiments can be regrouped in different homogeneous populations, for instance populations corresponding to the different granules produced in the 5 studied granulators like in this work, Factorial Discriminant Analysis is particularly efficient. Using this method, simple graphs can be obtained. By projection, each experiment of a population is as close as possible to the mean of this population and the mean of each population as far as possible from one group to an other. The main consequence is that variables able to separate the populations at best can be brought to light pointing out differences as well as common properties between the granulators. Classification of an additional unidentified experiment is a second interest of this factorial method.

RESULTS AND DISCUSSION

Optimization for each granulator - Example of TS10 mixer.

Because linear models are found unsuccessful to describe the majority of the response variables, the first experimental design is completed in order to calculate quadratic models. The only perfectly validated ones are reported in table I. The rapid analysis of the regression coefficients shows that granulating liquid by the linear or quadratic terms has a great influence on each variable. If kneading time is present for the majority of the models, it is mostly less influent than the quantity of granulating liquid. An interesting result is that kneading time has no significant effect on the friability of granules, uniformity of size distribution, hardness and friability of tablets.

To visualize the influence of the controlled variables response, surfaces and contourplots can be drawn. Examples are given on figure 4.

Table II shows response variables displaying characteristic optima like for the granules mean diameter. Controlled variables leading to these optima correspond to quite similar levels varying from 680 ml to 760 ml, for a kneading time of 10 minutes. In this range of variation all the different response variables do not vary significantly (Table III).

Table I : Validated models.

RESPONSE VARIABLES	REGRESSION COEFFICIENTS OF THE VALIDATED MODELS					
	CONST.	Q	T	Q^2	T^2	Q.T
Flowability	4.24	-0.03	-0.22	0.56	*	*
Bulk volume	155.60	-4.00	-3.67	9.73	*	3.50
Mean diameter	147.00	6.83	8.00	-17.83	*	*
Size distribution	2.80	0.28	*	-0.25	*	*
Granules friability	27.00	-7.08	*	5.75	*	*
Tablets weight	0.724	0.010	0.013	-0.027	*	-0.013
Tablets hardness	13.40	1.17	*	0.57	*	*
Tablets friability	1.10	-0.14	*	0.07	*	*
Disintegration time	7.55	0.72	0.38	*	-0.61	-1.04

* : non significant term, α>0.05.

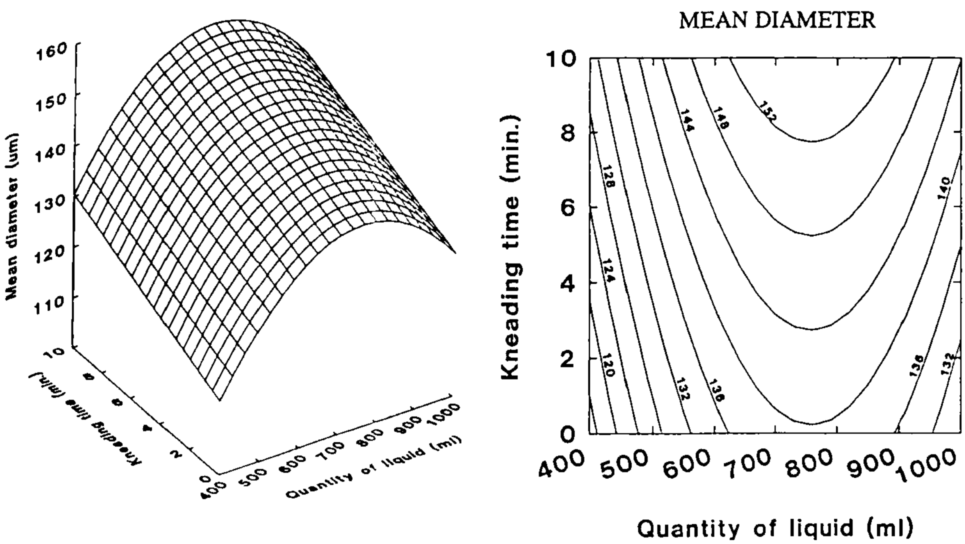


Figure 4 : Granules mean diameter - Response Surface and Contourplot.

Table II : Characteristic points.

RESPONSE VARIABLES	OPTIMUM	QUANTITY (ml)	TIME (min.)	RESPONSE VALUE
Flowability	minimum	740	10	4 s.
Bulk volume	minimum	710	10	152 ml
Mean diameter	maximum	760	10	155 µm
Tablet weight	maximum	680	10	735 mg

Table III : Response variations between 680 and 760 ml, (kneading time: 10 min.).

Flowability	4.02 - 4.04 s
Bulk volume	152.20 - 152.22 ml
Mean diameter	154.5 - 155.7 µm
Size distribution	2.78 - 2.85
Granules friability	27.5 - 25.8 %
Weight of tablet	735 - 731 mg
Hardness of tablet	13.2 - 13.6 kg
Tablets friability	1.10 - 1.07 %
Disintegration time	7.3 - 7.5 min.

So it is possible using experimental designs not only to optimize the process of wet granulation in a high shear mixer but also to validate it, leading to the best properties for the produced granules and tablets. This approach is applied to each apparatus and completed by a comparison of them, two by two.

Comparison of the granulators two by two - Example of high-shear mixers Moritz® TS10 and TS50.

Since mathematical models are calculated and validated for all the different granulators, it is possible to make some comparisons studying the mixers two by two. For example, response variables which have been accurately modelized for both granulators Moritz® TS10 and TS50 are reported in table IV.

Table IV : Comparison of the validated models.

RESPONSE VARIABLES	REGRESSION COEFFICIENTS OF THE VALIDATED MODELS					
	CONST.	Q	T	Q^2	T^2	Q.T
Bulk volume, TS10	155.60	-4.00	-3.67	9.73	*	3.50
Bulk volume, TS50	146.4	-4.0	-7.7	17.27	*	*
Granules friability, TS10	27.00	-7.08	*	5.75	*	*
Granules friability, TS50	16.10	-13.25	-4.50	20.82	*	*
Disintegration time, TS10	7.55	0.72	0.38	•	-0.61	-1.04
Disintegration time, TS50	8.25	1.18	0.52	•	•	•

* : non significant term, $\alpha > 0.05$.

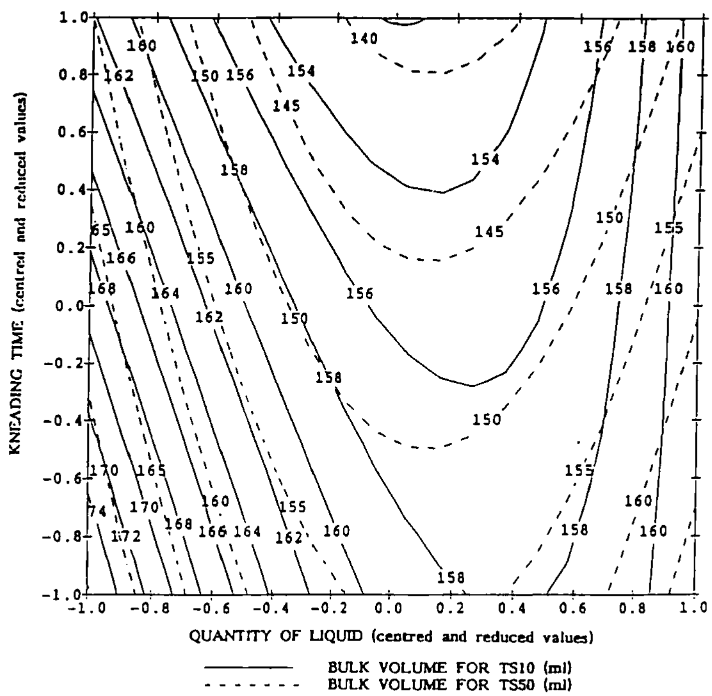


Figure 5 : Superimposed contourlines (bulk volume, TS10 and TS50 mixers).

Table V : Characteristic optima.

RESPONSE VARIABLES	OPTIMUM	RESPONSE VALUE	TIME (min.)	QUANTITY (ml)	Ratio TS50/TS10,V/V
Bulk volume, TS10	minimum	152 ml	10	710	2670/710
Bulk volume, TS50	minimum	139 ml	10	2670	3.76
Granules friability, TS10	minimum	25.0 %	/	885	2980/885
Granules friability, TS50	minimum	9.5 %	10	2980	3.37

Kneading time and quantity of granulating liquid have an almost the same effect on bulk volume for both Moritz® TS10 and TS50 as it appears also on the superimposed contourlines (figure 5).

On the contrary, the model for the granules friability is quite different. Kneading time especially, is not influent for mixer TS10®. When compared with mixer TS50®, a greater quadratic effect of the quantity of liquid can be observed for mixer TS10®.

Table V displays the operating conditions corresponding to characteristic optima.

In proportion to its size, TS10® mixer requires a greater amount of granulating liquid than TS50® granulator. The ratio between the optimal quantities of liquid for these two granulators is 3.76 or 3.37, different to the expected one which is 5, corresponding to the ratio between the granulators sizes.

General comparison of the 5 granulators using the Discriminant Analysis

The 1760 results obtained for all the 55 different granules produced with the 5 studied granulators are statistically treated by Discriminant Analysis. Table VI shows that axes 1 and 2 explain 85.6 % of the whole discriminant power. So, the 32 response variables can be analysed on this two axes.

The first discriminant axis is mainly due to the bulk volume (BUV), but also to the friability of the granules and tablets (FRG, FRC), the fractions of granules higher than 160 micrometers. This group of variables is in opposition with: harness of tablets (HRD), residual and ejection forces (RES, EJE) and fractions of granules smaller than 160 micrometers. The second axis is explained by the flowability (FLO) and, with a smaller contribution, by the uniformity of size distribution (SID).

Table VI : Discriminant Power of the Axes.

AXIS	EIGEN VALUES	INERTIA	CUMULATIVE %
#1	36.74	57.6%	57.6
#2	18.02	28.3%	85.9
#3	5.84	9.1%	95.0
#4	3.16	5.0%	100.0

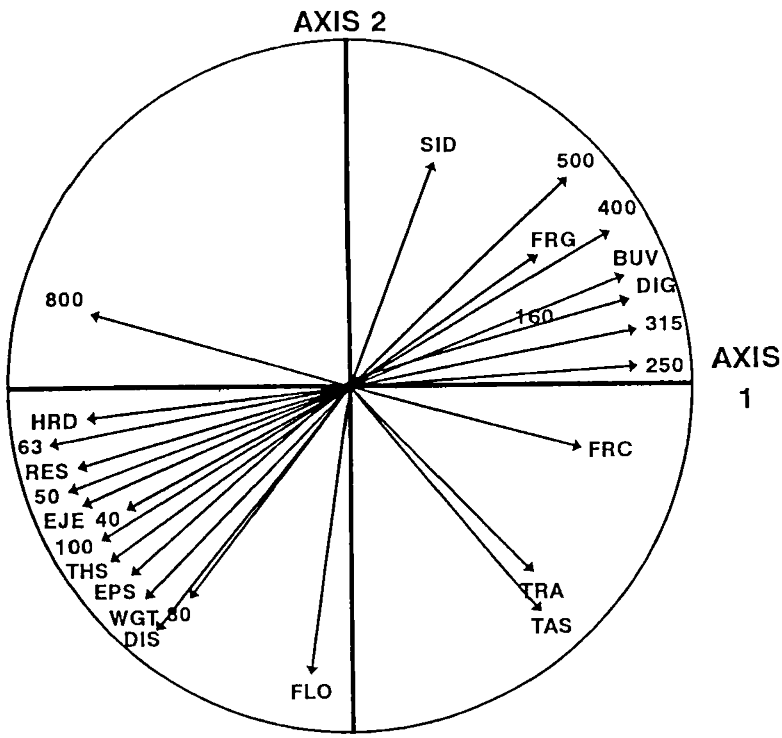


Figure 6 : Discriminant axes.

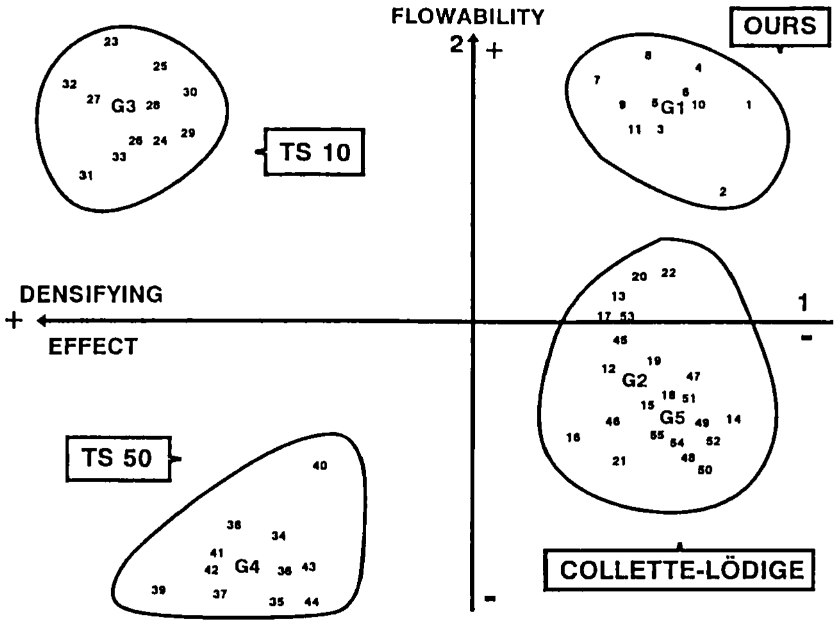


Figure 7 : Representation of the Granules on the Discriminant Axes.

The characteristics of the produced granules are reported in figure 5. The granules numbered from 1 to 11 are realised with Ours® mixer, the ones numbered from 12 to 22 with Collette® mixer, the ones from 23 to 33 with Moritz® TS10, the ones from 34 to 44 with Moritz® TS50 and the ones numbered from 45 to 55 are realised with Lödige® mixer.

It clearly appears (figure 7) that Ours®, Moritz® TS10 and TS50 granules are represented in homogeneous and very well separated groups showing this way that they display their own characteristics for their corresponding granules. Nevertheless, small granulators (Ours® and TS10®), whatever the type, are characterised by granules having the best rheological properties when compared with the apparatuses of highest size. The new generation of granulators (Moritz® TS10, TS50), whatever the size, mainly differs from the conventional ones by producing granules: smaller, more cohesive and less friable. During compression residual and ejection forces are higher and the resulting tablets are harder and less friable.

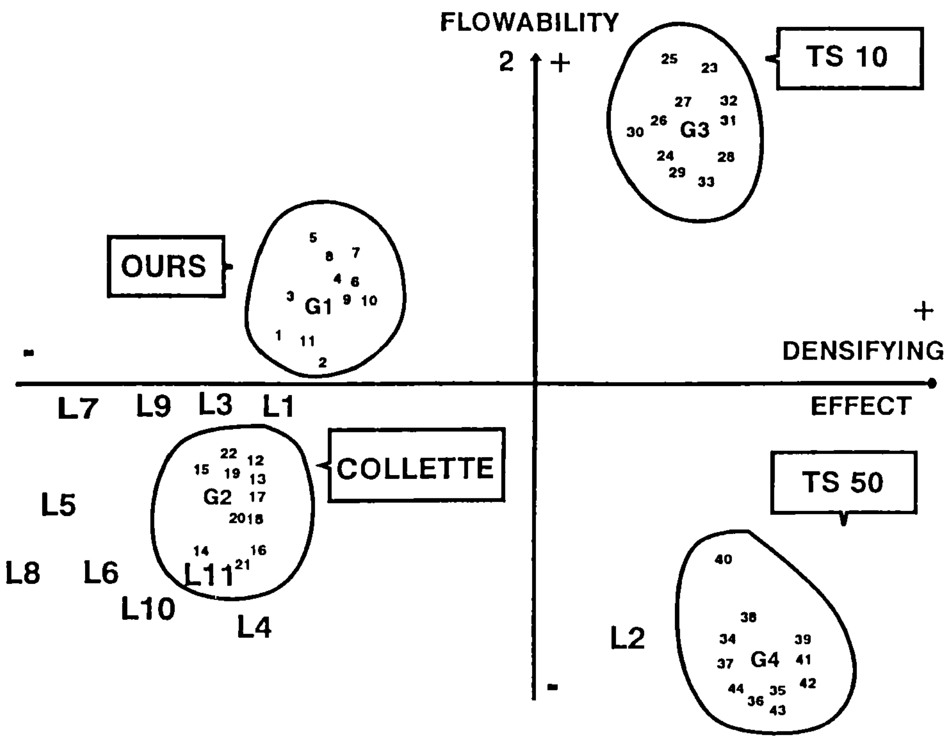


Figure 8 : Representation of Lödige® granules as outliers (L)

It is very interesting to see that granules produced in the Collette® conventional mixer and the Lödige® granulator are plotted in the same group suggesting that these granules have quite similar characteristics.

In order to verify this point, a second analysis is performed, Lödige® granules taken as outliers (L). Discriminant axes are recalculated and all the different granules except Lödige® granules are represented again on the first discriminant plan. Outliers are then introduced in the analysis so that it is possible to see graphically which group they belong to.

As figure 8 shows it, all outliers (L), except one, are assigned to the group corresponding to Collette® mixer.

This is confirmed by the Mahalanobis distances calculated between each outlier and the centre of gravity of the different groups (Table VII).

Same results are obtained when Collette® granules are considered as outliers. The majority of them is also allocated to the Lödige® group

Table VII : Distances between "Lödige® granules" and the centres of gravity of the different groups.

	- —— INCREASING DISTANCES ——► +			
L1	0.883(G2)	1.845(G1)	2.447(G3)	2.671(G4)
L2	1.548(G4)	1.936(G1)	3.258(G3)	3.277(G2)
L3	0.596(G2)	2.189(G1)	2.506(G3)	2.794(G4)
L4	0.876(G2)	2.274(G4)	2.406(G1)	3.087(G3)
L5	3.132(G2)	5.054(G3)	5.603(G1)	5.666(G4)
L6	1.543(G2)	3.883(G1)	4.123(G3)	4.222(G4)
L7	2.047(G2)	4.139(G3)	4.305(G1)	4.779(G4)
L8	3.202(G2)	5.450(G3)	5.606(G1)	5.812(G4)
L9	0.750(G2)	2.718(G3)	2.978(G1)	3.344(G4)
L10	0.811(G2)	3.365(G4)	3.435(G1)	3.475(G3)
L11	0.349(G2)	2.775(G4)	2.903(G1)	3.065(G3)

L_ : "Lödige individual trials",
G1 : centre of gravity of OURS group,
G2 : centre of gravity of COLLETTE group,
G3 : centre of gravity of TS50 group,
G4 : centre of gravity of TS10 group.

highlighting definitly that Collette® and Lödige® mixer produce the same kind of granules. Transposition of wet granulation is obviously easier for these granulators.

CONCLUSION

Influence of the quantity of granulating liquid and effect of kneading time on granules characteristics are studied for different types and sizes of mixers. A mathematical strategy combining multiple regression and factorial analysis is applied. The first approach using experimental designs allows to optimize and to validate the process of wet granulation in each apparatus. By comparison of the response surfaces and by superimposing the contourlines it is possible to describe and to quantify the scaling-up operation. Discriminant analysis, complement of the first method, leads to a general interpretation of the granules characteristics pointing out differences as well as common properties between the 5 studied granulators.

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