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PARAMETRIC STUDY OF FLUIDIZED-BED GRANULATION OF A LOW DENSITY MICRONIZED POWDER

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ABSTRACT

A pharmaceutical active principle, Amphotericin B, requires, before capsule-filling, a granulation in order to improve its handling, rheological and density properties. In a changing-process situation, a parametric study is undertaken about a fluidized-bed granulation. For yield and densification improvment, it is suggested to premix the raw materials and to add the binder, that is PVP, in external phase. When it is added in internal phase, growths tends to take place in layers, resulting in granules which are more spherical, larger and less friable. In the same time desintegration time is reduced. This study also points out the influence of some process parameters for such a microfine active principle and underlines how to enhance the quality of the granulated material inside the specific limits of equipment and formula.

INTRODUCTION

This study is part of a feasibility study of fluidized bed granulation of a micronized active constituent. The general advantages which suggested this study were as follows :

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- it is possible to successively mix the dry powders, granulate, dry and, if required, lubricate within a single facility;
- the constitutional homogeneity of the granules ensures the quality of the final product,
- handling of the raw materials is reduced and this makes it a very suitable method for compounds with irritant or toxic properties which call for special precautions during handling,
- the number of steps in the manufacturing process is reduced, thus shortening the manufacturing time and giving yields which are often high and these are major financial advantages of fluidized bed granulation.

However, in the context of the rational definition of a technological strategy, it is important to define the substances requiring such a process and simultaneously consider the raw material and technological performance required to obtain the most appropriate active constituent, formulation and process.

Numerous studies have proposed trial methods intended to identify powders which are good candidates for fluidization (1-10).

The active constituent investigated in this study belongs to Geldart's group C, i.e., is a cohesive powder which is difficult to fluidize. A preliminary study (11) has shown that optimization of the usual parameters, identified in the literature as those with the greatest impact (12-16): input air temperature, spray pressure and spray flow rate of the binding liquid, are not sufficient to guarantee a good result.

The present study is intended to improve granulatability by changing parameters linked not only to the operating conditions of the apparatus, but also the preliminary qualitative and quantitative processing of the material to be granulated. The aim is to cut down the wide dispersal of the raw material, which compromises both the feasibility and yield of the operation, and to use an industrially viable protocol to produce a granulate with high enough density (> 0.42 g/cm^3) to allow filling into capsules.

MATERIALS AND EXPERIMENTAL PROTOCOL

1.1. Raw Materials

1.1.1. Active constituent

The active constituent for granulation was amphotericin B, an antifungal used to treat digestive candidiasis (buccal or intestinal), which is used prophylactically in high risk subjects: immunodepressed individuals and patients receiving antineoplastic chemotherapy.

The aim was to achieve a concentration of 65 to 70% of the active constituent in the final formulation, depending on the active constituent content of the batch of raw material used.

The physical, chemical and mechanical characteristics of the raw material determine the hydrodynamic properties of the system and the parameters of the process.

Granularity:
the granularity of the active constituent (Table 1) results in a risk of uneven fluidization taking the form of fingering, preferential passages or "ball up" (16).

Density:
the very low apparent density (0.16 g/cm^3 determined using an Engelsmann packing volumenometer) and its Hausner index of 1.27 are characteristic of a type C powder and constitute further obstacles to fluidization which optimization of the process must attempt to solve.

Stability:
amphotericin is not photostable, but can withstand temperatures of up to 90°C for several hours without suffering degradation, which leaves considerable latitude in fixing the temperature conditions of the process.

Solubility:
the antifungal activity of the substance is linked to its insolubility in the digestive tract, where it is not resorbed. It coats the intestinal mucus and acts on *Candida* by direct contact (fungistatic and fungicide). This insolubility, combined with water repellance due to the size of the particles, makes it difficult to wet the substance and impairs the adhesiveness of the binder.

1.1.2. Binder

The binder used was a polyvinylpyrrolidone (PVP) marketed under the trade name of Kollidon K30[1] (17). This is a water-soluble PVP; the 10% (w/v) aqueous solution with a viscosity of 7 mPa.s at 20°C. Figure 1 shows the change in viscosity with concentration and temperature. The specifications for the apparent specific gravity and the particle size distribution are shown in Table 2.

1.1.3. Other excipients

- magnesium stearate was added at the end of the process to improve capsule filling.

- the capsule filling process was based on the compression-dosing principle[2]. Packing of the powder makes it necessary to use a disintegrator: corn starch, to ensure acceptable disintegration times.

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[1]BASF

[2]Macophar MT5 capsulator

TABLE 1
Particle Size Distribution of Amphotericin B
determined using a Coulter counter

Percentage of particles	measuring no more than
1.6	1.93 μm
30	2.43 μm
100	3.07 μm

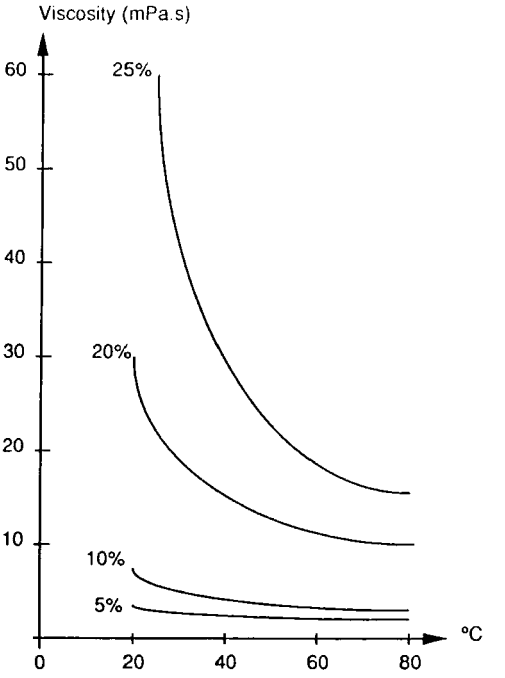

FIGURE 1
Viscosity of 5, 10, 20 and 25% Solutions of Kollidon K30
in Water at Various Temperatures (17)

TABLE 2
Specifications of Kollidon K 25/30
BASF data (17)

Particle size distribution (Alpine screen)	
Screen	cumulated percentage stopped
50	1
100	5
200	50
250	90
Apparent specific gravity : 400 - 600 g/l	

- lactose was used as a diluent, with a mean $d_{0.50}$ diameter of about 60 µm. Lactose and the active constituent were the main constituents. The d_{max}/d_{min} ratio (highest mean diameter over the smallest mean diameter) was 20, a value considered acceptable by Bergougnou (16).

1.2. Apparatus

The granulator used is a Glatt GPCG1 apparatus (Figure 2).

The stainless steel tank has a capacity of 5 liters, and is fitted with a longitudinal inspection window, through which the interior of the tank can be viewed. The bottom of the tank is fitted with a screen. The nozzle, a binary 970/4S, has a single head and can be set to two different heights.

The air input temperature can be set at values up to 120°C.

The air flow rate can range from 0 to 100% (percentage opening of the outlet, which can be converted into a pressure value of 0.2 to 1 bar).

Spraying by the peristaltic pump can be adjusted to flow rates of 0 to 100 ml per minute. The spray pressure ranges from 0 to 10 bars.

The apparatus is fitted with nylon filters which form a set of four sleeves. Shaking is carried out manually or automatically with variable cycle lengths. Shaking can be done with concomitant or suspended spraying and fluidization. A digital display shows the temperatures of the product, the air inlet and outlet.

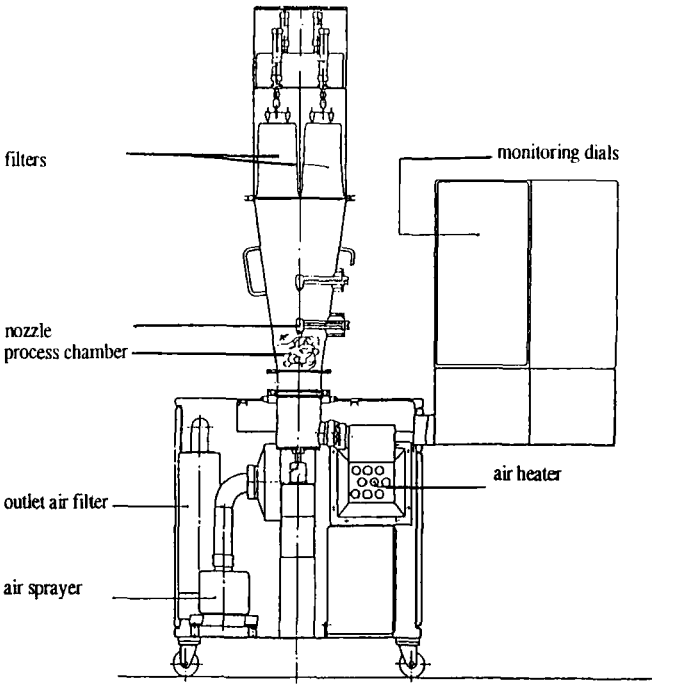

FIGURE 2
GPCG1 fluidized bed granulator

Two dials display the pressures measured at the screen at the bottom of the tank, in order to detect clogging, and in the exit filter in order to detect any spillage of the product.

1.3. Experimental Protocol

Amphotericin was granulated in the GPCG1 granulator with the diluent, lactose, and the binder, PVP.

The granulate was then calibrated on an oscillating granulator[3] with a 0.8 mm grid and then the lubricant and disintegrating agent were added to the external phase[4] for 45 seconds.

3oscillating Erweka granulator

4planetary mixing

After the granulate had been subjected to the pharmacotechnical control tests described in 2-4, it is filled into n°0 capsules containing 520 mg (amphotericin titrated to have 250 µg activity per mg). The disintegration time and mass uniformity of the capsules were then determined.

METHODS

The study was organized as a series of experiments. A study strategy was devised which involved setting up a battery of carefully selected tests from which a mathematical model was obtained of the influence of the parameters investigated and their interactions with the selected responses.

2.1. The Fixed Parameters

These parameters were fixed on the basis of technical or bibliographical data or the findings of previous studies.

- equipment

the *nozzle* is set to the high position;
the *filter shaking* cycle consists of shaking for 4 seconds every 30 seconds,

- process

the *input air flow* is set to its lowest value to avoid dispersing the fine particles or scattering the amphotericin in the upper part of the tank. It is important to keep the flow rate as steady as possible, as this parameter is responsible for the water supply/evaporation equilibrium. The air input also creates the hydrodynamic conditions responsible for suspending the particles. The growth of the particles which occurs during granulation may make it necessary to increase the flow rate: in this case, the same sequence is used for all experiments.

air supply humidity: the GPCG1 unit has no air conditioning system. The humidity could not be fixed, but its value was recorded. The changes found during the experiments were considered to be of no significance;

the *air supply temperature* was 40°C;

the *wetting fluid* was water, at a *temperature* of 22°C;

the *spray pressure* was 1 bar, and the *spray rate* corresponded to the 30 g/min sequence initially, and then 20 g/min to avoid excess wetting and to obtain control granule growth;

the *drying air temperature* was 60°C;

the *drying time* was generated by the final temperature of the product, i.e., 43°C.

- formulation

the *amphotericin content* was 914 µg/mg;
the *percentage of PVP in the final formulation* was 3% (m/m).

2.2. The Variable Parameters

In order to determine the best binding effect and the maximum yield, it was decided to investigate the influence of the three following characteristics:

- method of adding the PVP

this was carried out either in an external phase (15% solution of PVP K30 in water) or in an internal phase (PVP added by dry mixing and wetting with water)

- batch size

batches of 600 g (18) and 800 g were granulated in order to observe particularly the impact of batch size on yield

- densification of the active constituent

in the various experiments, granulation was either carried out from the outset on the active constituent placed in the granulator bowl or else the amphotericin was subjected to preliminary densification. The low specific gravity of the active constituent and its electrical charges can be blamed for the losses due to sticking to the walls of the bowl and the filters. The premixing of the powder excipients with amphotericin could reduce these difficulties. This step was carried out in a planetary mixer for 15 minutes.

2.3. The Design of the Experiments

The design is that of a complete factorial design on two levels with interactions. It consists of eight tests constituting the experiment grid shown in Table 3.

2.4. The Responses

The measurements taken make it possible to assess the granulation process and to express the final properties of the granulate which allow capsule filling. The following solutions were adopted:

2.4.1. Granulation yield

This involved determining the quantity of granulated product actually available, thus excluding losses due to sticking to the sides of the bowl (related to static electricity) and the fine particles clogging the filters. The mass of the granules obtained at the end of the operation was related to the theoretical quantity.

2.4.2. Apparent specific gravity

This is an essential aspect of capsule filling, and the packed and unpacked specific gravities provide a good indication of the quality of the batches produced. The V_{10} and V_{500} volumes obtained after 10 and 50 jolts respectively from 40 g of calibrated granules in a volumenometer (Engelsmann) were used to calculate the apparent specific gravities d_{10} and d_{500}.

TABLE 3
Level of the Parameters and Experiment Grid

- Method of adding the binder, X_1
  level +1: external phase
  level -1: internal phase
- Batch size, X_2
  level +1: 800 g
  level -1: 600 g
- Prédensification of the active constituent, X_3
  level +1: with premixing
  level -1: without premixing

Experiment no.	X_1	X_2	X_3
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+

2.4.3. Granularity

The granularity was evaluated for the granules before and after calibration; the first determination gives information about the influence of the process parameters and formulation on granule quality and the second determination describes the granulate actually filled into the capsules. It takes into account the attrition due to calibration, and makes it possible to investigate the relationship between particle size and specific gravity, for instance. The measurement is carried out using a column with a battery of sieves (Tamisor). The test sample was 100 g and the screen mesh sizes 650, 500, 400, 315, 250, 160 and 125 µm. The time taken for the test was 15 minutes and the vibration amplitude was 70.

2.4.4. Friability

A test sample of 10 g of granules from fractions stopped at the 315 and 400 screens obtained after calibration and screening was subjected to the impact of 36 g

of glass spheres with a diameter of 5 mm in an Erweka friabilator for 5 minutes at a speed of 5 rpm. The quantity of powder remaining on the 315 screen at the end of the operation was weighed, w. The friability index is given by the expression FI = (10 - w) 100/10.

2.4.5. Residual moisture

The measurement was made using an IR Mettler LP16 scale with a test sample of 10 g heated to 80°C for 15 minutes.

2.4.6. Height of the compression/dosing die

The setting of the compression/dosing die of the Macrophar MT5 capsulator depends on the tendency of the granulate to rearrange itself. The die height, adjusted by depressing the doser, consequently increases when the aptitude of the granulate diminishes for volumetric assay.

2.4.7. Disintegration time of the capsules

The disintegration time was measured using the method described in the Pharmacopée Française. One of the objectives of this study is to reduce the disintegration time.

RESULTS AND DISCUSSION

The values of the responses in the eight experiments in the factorial design are shown in Table 4. In order to describe the responses, a linear model with interactions has been postulated on the basis of the variables coded X_i associated with physical parameters:

$$Y = b_0 + b_iX_i + b_{ij}X_iX_j + b_{ijk}X_iX_jX_k$$

This general model has been fine-tuned for each response by discriminating using a Student's test, taking the intervention of a parameter or an interaction between parameters to be significant only when the non-zero probability of the associated coefficient exceeds 95%. The resulting equations are shown in Table 5 when the response models were found to be pertinent.

In these models, the amplitude of the impact of a parameter or an interaction is proportional to the absolute value of the corresponding coefficient; its sign obviously indicates whether this action results in an increase or a reduction in the response. Thus a first-degree model, such as that used in this study, is able to determine which are the key parameters and whether each of the study parameters has to be increased or reduced to obtain the intended objective (an increase or reduction in the response as appropriate).

3.1. Granulation Yield

The yield is improved if X_3 is at its highest setting and therefore if the active constituent is premixed with the excipients. This additional operation makes

TABLE 4
Results of the Experiment Design : Experimental Responses

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8
Yield (%)	87.7	84.9	84.6	87	89.8	89.3	87.4	93.2
D_{10} (g/ml)	0.41	0.41	0.42	0.41	0.42	0.42	0.42	0.44
D_{500} (g/ml)	0.47	0.47	0.47	0.49	0.48	0.50	0.48	0.50
Granularity (%) before calibration								
650	57.4	70.1	46.1	54.2	66.3	52.2	45.7	56.0
500	8.0	6.2	8.7	7.3	7.7	6.5	6.9	5.8
400	7.8	5.8	10.4	7.1	6.7	7.5	8.3	7.3
315	6.2	3.5	9.0	5.8	5.1	6.4	7.9	5.8
250	5.2	3.0	7.4	5.5	4.0	7.0	7.6	5.3
160	4.3	2.7	7.4	6.5	2.5	8.2	7.6	5.6
125	5.0	2.6	4.1	5.9	3.0	4.8	4.8	4.0
pan	6.7	6.3	6.8	7.4	4.5	8.2	11.0	10.0
after calibration								
650	5.0	4.8	4.3	5.1	5.2	4.3	4.4	4.4
500	14.0	14.7	12.6	14.4	15.9	11.6	11.8	11.6
400	17.7	18.1	18.1	15.9	18.6	14.6	16.0	15.5
315	15.4	14.5	16.0	13.2	15.4	13.9	14.8	14.0
250	12.0	12.8	13.3	11.9	11.4	15.3	12.4	12.0
160	12.2	10.1	13.1	12.8	11.9	14.3	14.2	14.0
125	9.5	11.0	9.5	8.9	9.1	11.2	10.0	10.1
pan	13.9	14.0	13.0	17.6	12.5	15.4	16.3	17.7
Friability (%)	82	82	76	75	81	72	75	86
Resid. moist.(%)	2.6	2.6	3.1	2.9	3.2	3.2	3.0	2.8
Die Height (mm)	2.9	2.9	2.9	2.7	2.9	2.9	2.9	2.9
Disint. time (min)	16	17	18	13	17	17	12	13

TABLE 5
Response Models

Response	Equation of the model
Granulation yield	$Y_{RG} = 88 + 0.6X_1 + 1.9X_3 + 1.4X_1X_2 + 0.7X_1X_3$
Specific gravity	$Y_D = 0.42 + 0.003X_2 + 0.006X_3 + 0.004X_1X_3 + 0.0015X_2X_3 + 0.003X_1X_2X_3$
Percentage of fine particles after calibration	$Y_{TF} = 15.05 + 1.12X_1 + 1.1X_2 + 0.42X_3 + 0.37X_1X_2 + 0.42X_2X_3 - 0.75X_1X_2X_3$
Disintegration time	$Y_t = 15.13 - 1.13X_2 - 0.88X_3 - 0.88X_1X_2 + 0.88X_1X_3 - 0.63X_2X_3 + 0.63X_1X_2X_3$

demands on the process and cannot be carried out in the granulator, since fluidization always counters densification of the mixture. The introduction of PVP in an external phase and an increase in batch size also have a positive effect on yield.

3.2. Specific Gravity

It appears that to increase the density of the granulate, the priority is to increase X_3, increase X_1 and increase X_2. Premixing therefore has a beneficial effect on specific gravity by improving the behavior of the powder in the container during fluidization.

3.3. Granularity

The model of the response, percentage of fine particles after calibration, demonstrates that to reduce the level of fine particles, X_1 must be reduced, i.e., PVP has to be added in an internal phase, whereas the level of X_3 and X_2 appears

to be unimportant. The effect of the way in which the binder is added confirms the findings of Wan (19). In an internal phase, growth tends to take place in layers, resulting in granules which are more spherical, larger and less friable.

3.4. Disintegration Time

The disintegration time was always acceptable. However, it was reduced when X_2 was at the +1 level, i.e., when the batch size was increased, when X_3 was at +1 level, i.e., when a premix was prepared. In order to obtain the same effect, PVP should be added in an internal phase (X_1 at the -1 level).

It is obvious from an analysis of these results that the responses were improved by simultaneously increasing the batch size (800 g in the system) and by premixing the powder constituents. Conversely, the method of adding PVP had no clear impact on the responses studied: adding it to an internal phase reduced the disintegration time and the proportion of fine particles after calibration, but the yield and specific gravity were less good.

The difficulty in modeling some responses is simply the mathematical reflection of the complexity of the granulation process in a fluidized bed. The impossibility of rigorously controlling all the parameters involved, some of which inevitable change during the operation, introduces a far from negligible random character to some responses, which means that the model is unable to provide reliable forecasts. Some situations make it necessary to adjust the air flow, temperatures, drying times, on the basis of the behavior of the mass being granulated. The hydrodynamics of the system, which are related to the size of the facility and the supply of non-conditioned air, have to be considered for a microfine powder such as amphotericin. It should be remembered that the granularity of the material chosen for this study does not make it a good candidate for fluidization granulation (10). Once the domain of feasibility has been defined, a rational approach to experiment design, such as the one described here, has made it easier to identify the avenues of research in order to enhance the quality of the product granulate, depending on to the priority given to granularity, specific gravity and yield.

CONCLUSION

This study demonstrates the need for detailed knowledge of the raw materials and a precise definition of objectives. The process becomes a technical response to a rational question. The use of multipurpose equipment or a standard process cannot be envisaged if optimal satisfaction is required. Similarly, it is easy to see that changing the process without changing raw materials cannot ensure that there is no change in the result. Combined evaluation of the equipment/process couple is essential in order to optimize the results.

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