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STUDY OF THE INFLUENCE OF SPHERONIZATION AND DRYING CONDITIONS ON THE PHYSICO-MECHANICAL PROPERTIES OF NEUTRAL SPHEROIDS CONTAINING AVICEL PH 101 AND LACTOSE

B. BATAILLE[1], K. LIGARSKI[1], M. JACOB[1]
C. THOMAS[2], C. DURU[1]

SUMMARY

Beginning with binary Avicel-lactose (20/80) mixtures, the present study focuses on the influence of the spheronization speed

1 - Laboratoire de Pharmacie Galénique,
Pharmacotechnie et Biopharmacie
Faculté de Pharmacie
Avenue Charles Flahault
F - 34060 MONTPELLIER Cédex 01

2 - Laboratoire de Pharmacie Galénique et
Pharmacotechnie
Faculté de Pharmacie
Boulevard Jeanne d'Arc
F - 21033 DIJON Cédex

and the drying process on the porousness, surface condition and the pressure resistance of neutral spheroids prepared by extrusion/ spheronization. Any increase in the spheronization speed provokes a decrease in the porousness and the average diameter of the pores, and gives a greater hardness and a smoother surface condition. In the final production phase, oven drying gives less porous and harder minigranules and a more homogenous surface than those dried by microwaves. In the experiment conditions, a negative correlation between porousness and hardness was established.

INTRODUCTION

The production of spherical minigranules for pharmaceutical usage through extrusion-spheronization (1, 2, 3, 4, 5, 6, 7, 8) calls for two specific operations (extrusion and spheronization) preceded and followed by an ensemble of annex steps. This process, derived from the traditional technique of granulation through humidity, necessitates a former preparation of the formulation before extrusion (wetting the mass) and a drying of the spheroids after spheronization. The follow-up work led us to study the influence of the parameters found before and during the spheronization (9, 10, 11, 12).

In the present report, we propose to study for a given formula the effect of the spheronization speed and the drying process of the spheroids on the characteristics of the obtained grains including: the porous structure (total porousness, average diameter of the pores and the porosimetric profile), the surface condition and hardness. Four spheronization speeds are intended: 475, 620, 900 and 1,320 rpm^{-1}, and two drying processes will be used:

- in a ventilated oven

- through hyperfrequency waves, a desiccation method already studied for granulated and compressed forms (13, 14, 15, 16, 17, 18).

MATERIAL AND METHODS

Material:

The primary matter used is made of microcristalline cellulose Ph. Eur. (Avicel PH 101, FMC Corporation represented in France by SEPPIC, Paris), a fine lactose powder Ph. Eur. (HMS, represented in France by S.A. Sucre de Lait, Sains-du-Nord) and distilled water.

For the production of spheroids, we have used a Kenwood Major type planetary mixer with a 5 liter capacity (to prepare the humid mass), a Pharmex 35 T (WYSS-TEC A.G., Péry, Switzerland) monoscrew axial extruder, equipped with a 1.5 mm screen, a Sphaeromat SPH 250 M.A. (WYSS-TEC A.G.) spheronizer with a cylinder measuring 30 cm in diameter, a ventilated oven (Prolabo, Paris) and a microwave oven (Moulinex, Paris).

The characteristics of spheroids have been evaluated with a Micromeretics (Micromeretics, Creil, France) semiautomatic 9300 porosimeter, a Jéol (Jéol, Paris) type J.S.M. 25 electronic scanning microscope. The hardness of the minigranules was determined with a Erweka (Machines Euraf, Paris) type TBH 28 apparatus.

Methods:

. Obtaining the spheroids:

On the basis of binary mixtures of Avicel and lactose at a 20/80 (m/m) ratio. The granulation liquid was incorporated at 34 percent (m/m), a quantity which is compatible with the extrusion of the mixtures.

The preparation of the humid mass was completed in the planetary mixer under the following conditions:

rotation speed: 50 rpm^{-1}
dry mixing of the powders: 5 minutes
wetting time: 10 minutes
mixing time: 3 minutes.

The extrusion was completed at a screw speed constant and equal to 80 rpm^{-1}. The extrudents were immediately spheronized. For each of the speeds tested (475, 620, 900, and 1,320 rpm^{-1}), the spheronization time was held constant and equal to 10 minutes.

Each batch of spheroids was divided into two sub-batches:

. one dried in a ventilated oven at 40° ± 1°C,

. the other in a microwave oven (2450 megahertz frequency, wavelength 12.24 cm, magnetron output per sequence of 30 seconds with a 10 second stop).

All the minigranules were dried until the weight was constant (12 hours in the oven, 30 minutes in the microwave oven).

. Spheroid control:

This control measures three characteristics: the porous structure (total porousness, average diameter of the pores, and the porosimetric profile), the morphology of the grains and their hardness. Only the spheroids with a granulometry between 1.00 and 1.25 mm, which lead to the most satisfying yield for the 4 spheronization speeds studied, were analyzed.

TABLE 1
Porosimetric characteristics depending on the spheronization speed

Spheronization of speed (rpm^{-1})	Porousness (%)	Average diameter the pores (μm)
475	15.5	0.7328
620	11.75	0.5073
900	8.99	0.2487
1320	7.91	0.2634

- study of the porous structure:

This was achieved through the method of mercury intrusion (19, 20, 21, 22, 23). We undertook two measures on each sub-batch tested under the following operating conditions:

- a test sample of about 800 mg (+- 10%),
- a special 5 cc cell for borosilicate glass powder equipped with a 1.1 cc capillary,
- a mercury contact angle measuring 130° and a superficial tension measuring 484 dynes per cm (values taken into consideration for the calculation of the total porousness and the average diameter of the pores).

In these conditions, we evaluated the sensitivity of the method at 1% on the porous volume. We found no significant difference between the results of the two tests done on the same sub-batch.

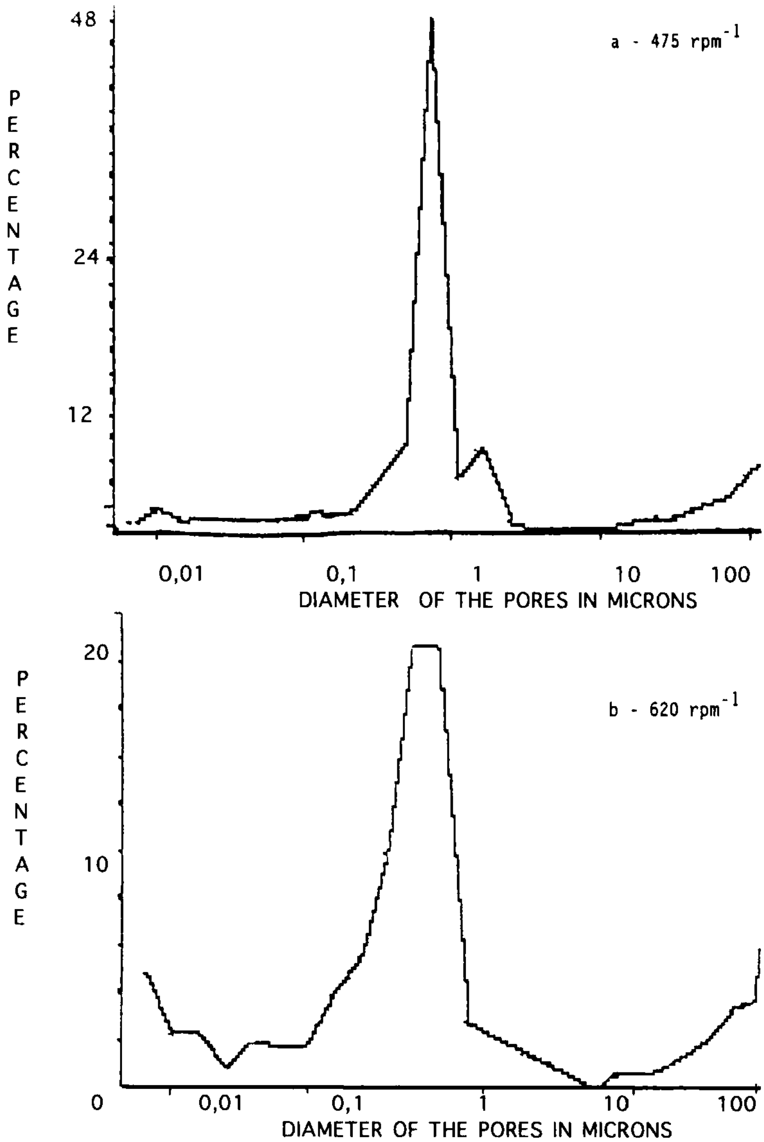


Figure 1 - Evolution of the porosimetric distribution depending on the spheronization speed.

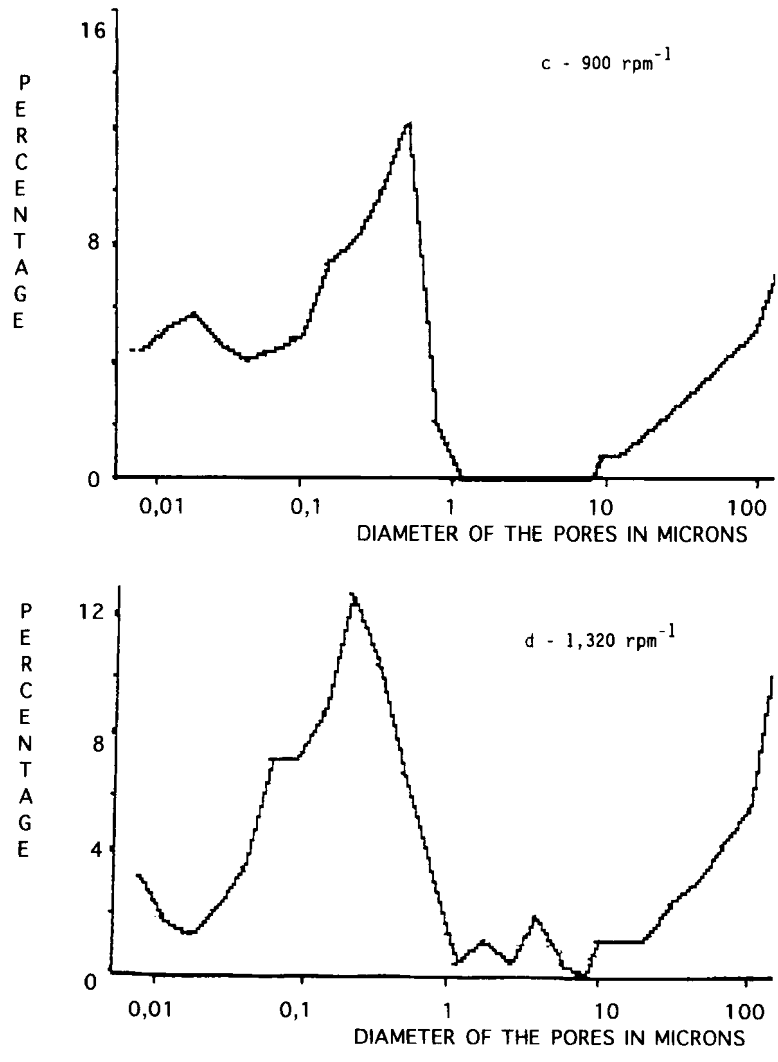


Figure 1 Continued

- study of the surface condition:

The photographs taken with the electronic sweeping microscope were enlarged at 1.200%.

- hardness evaluation:

This was determined on a sample representing 20 elements, after adapting the apparatus to measure the reduced sized grains (24).

RESULTS AND DISCUSSION

The analyses we approached bear on the effect of the pharmaco-technical parameters, spheronization speed and drying method, on the characteristics of the spheroids.

Influence of the spheronization speed on the porosimetric characteristics

The results point out that any increase in the spheronization speed provokes a decrease in the porousness and the average diameter of the pores (Table 1).

Through the study of the porograms (fig. 1), we observe that for lower speeds (475 and 620 rpm^{-1}) the porosimetric distribution is situated in the zone of diameters between 0.1 and 10.00 µm (fig. 1a and B) with a maximum of around 1.00 µm. Increasing the spheronization speed will provoke a change in the porosimetric division (0.01 - 1.00 µm) with a maximum of around 0.10 µm (fig. 1c and d).

TABLE 2

Porosimetric characteristics depending on the drying method

Spheronization speed (rpm^{-1})	Porousness (%)		Pore diameter (μm)	
	Oven	Microwaves	Oven	Microwaves
475	15.50	22.20	0.7328	1.6551
620	11.75	18.23	0.5073	1.0526

Influence of the drying method on the porosimetric characteristics

For the two spheronization speeds studied (475 and 620 rpm^{-1}), the porousness of the minigranules dried by microwaves is higher than that of grains dried in an oven (about 50%) and the average diameter of the pores is almost double (Table 2).

In the experiment conditions (475 to 620 rpm^{-1}), the comparative analysis of the porograms (fig. 2 and 3) highlight a notable move in the pore division towards higher diameters for microwave drying.

Surface condition:

We studied the influence of the spheronization speed and the drying method on spheroids dried in an oven and having been spheronized at 475 and 1,320 rpm^{-1}. The photographs (fig. 4 and 5) clearly show us that:

. any increase in the spheronization speed gives spheroids with a smoother surface condition (fig. 4a and b),

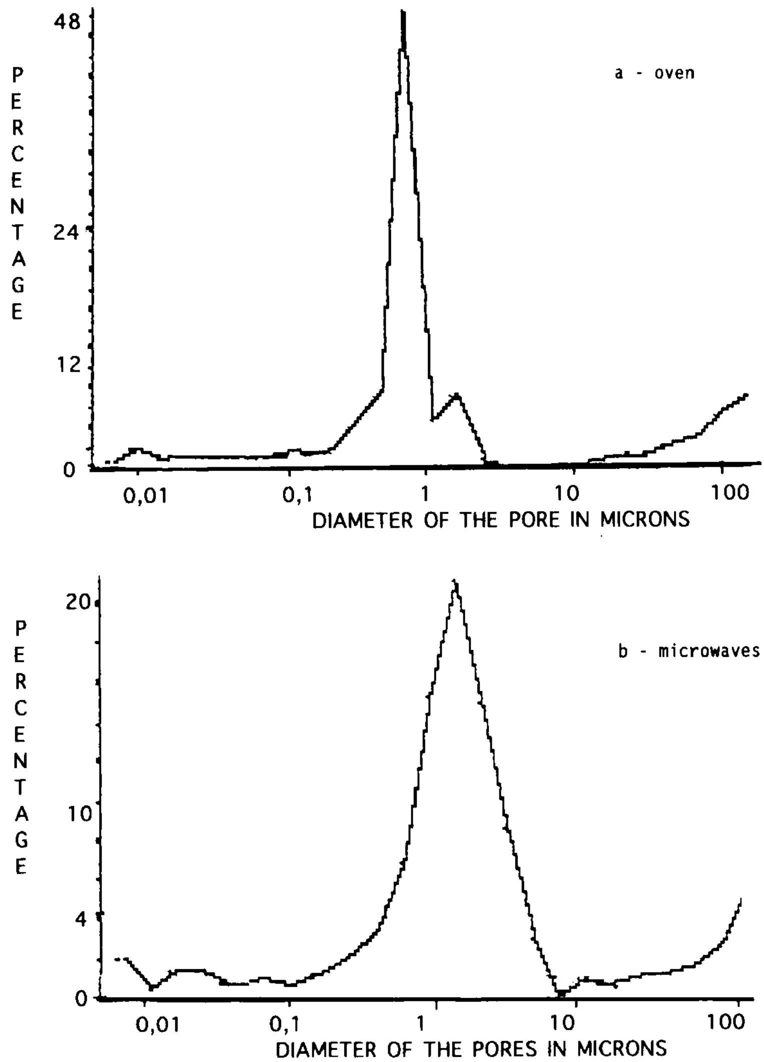


Figure 2 - Evolution of the porosimetric distribution depending on the drying method (speed = 475 rpm^{-1})

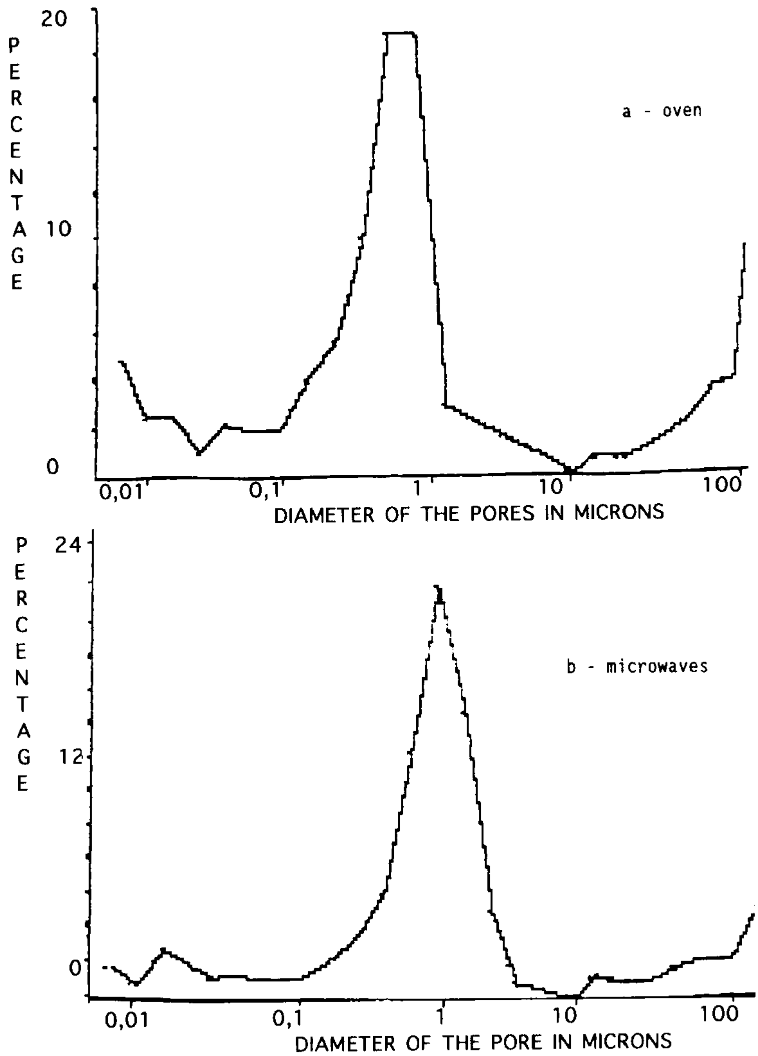


Figure 3 - Evolution of the porosimetric distribution depending on the drying method (speed = 620 rpm^{-1})

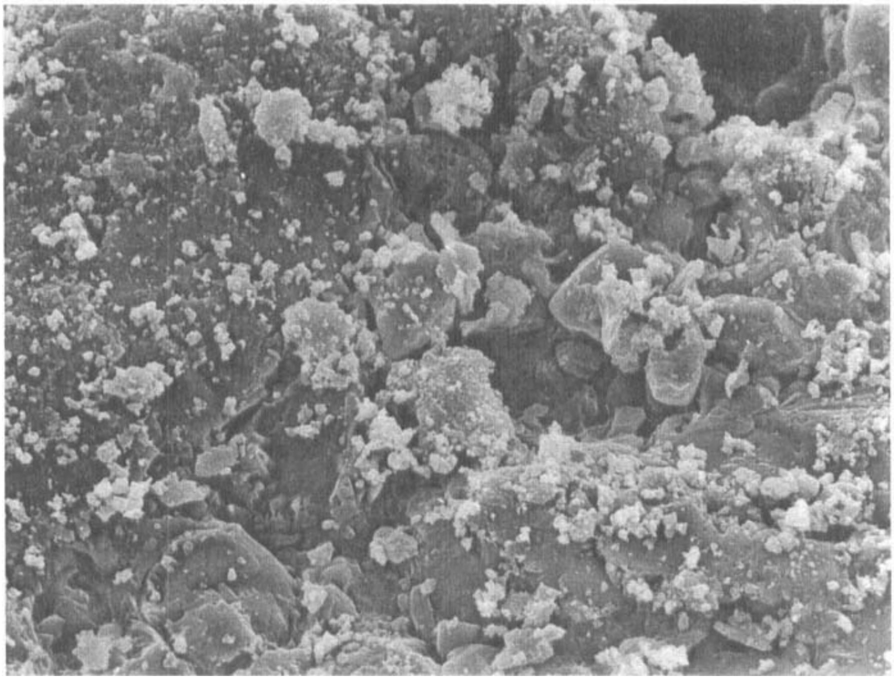


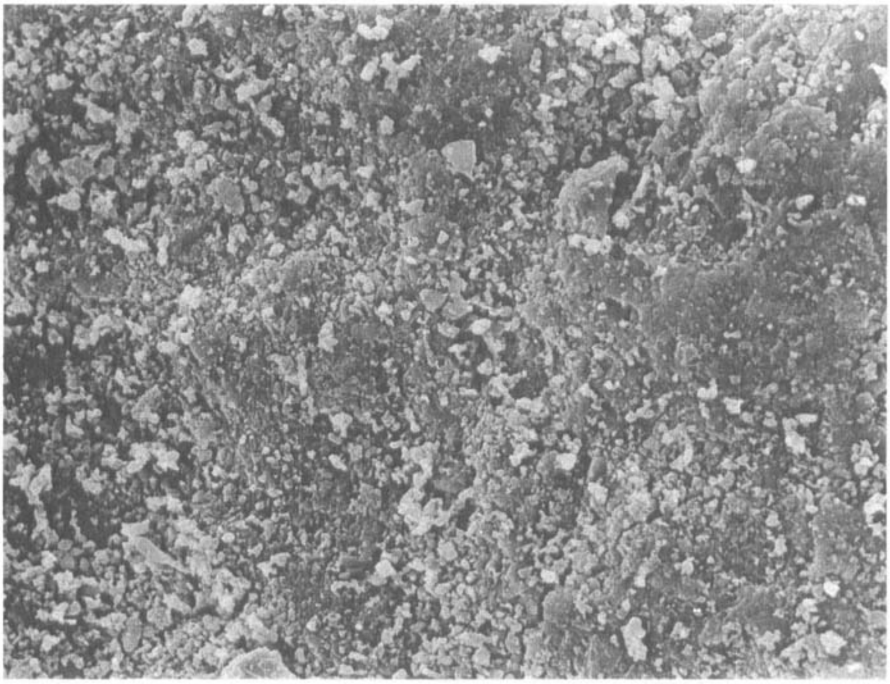
Figure 4 - Surface condition of the spheroids depending on the spheronization speed (oven dried)

. grains dried with microwaves have a more heterogeneous surface condition, with large crevice-cavities compared to those dried in an oven (fig. 5a and b).

This analysis also confirms the preceding observations on the modification of porosimetric characteristics.

Hardness:

The hardness of the spheroids was determined on a sample representing 20 elements. The results (fig. 6) confirm that the two factors used for the study (speed, drying) do, indeed, have an influence on the hardness:



(b) b - 1,320 rpm⁻¹

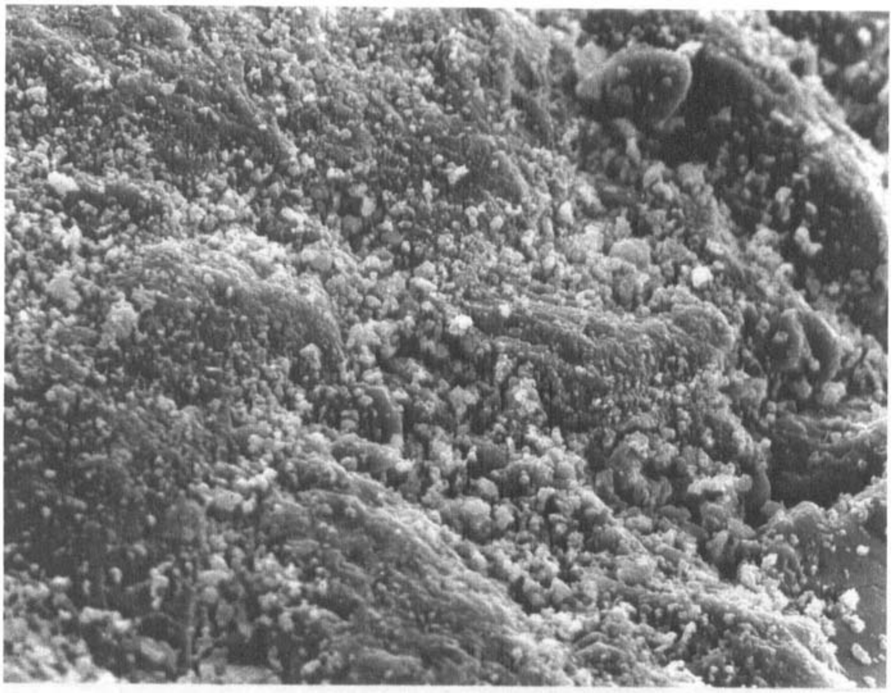
Figure 4 Continued

. an increase in the spheronization speed leads to an increase in this property, no matter which drying method is used,

. for a given speed, the minigranules dried by microwaves are not as hard as those dried in an oven (by about half).

The results given above are explained by the mechanisms concerned in the spheronization operation and the drying operation.

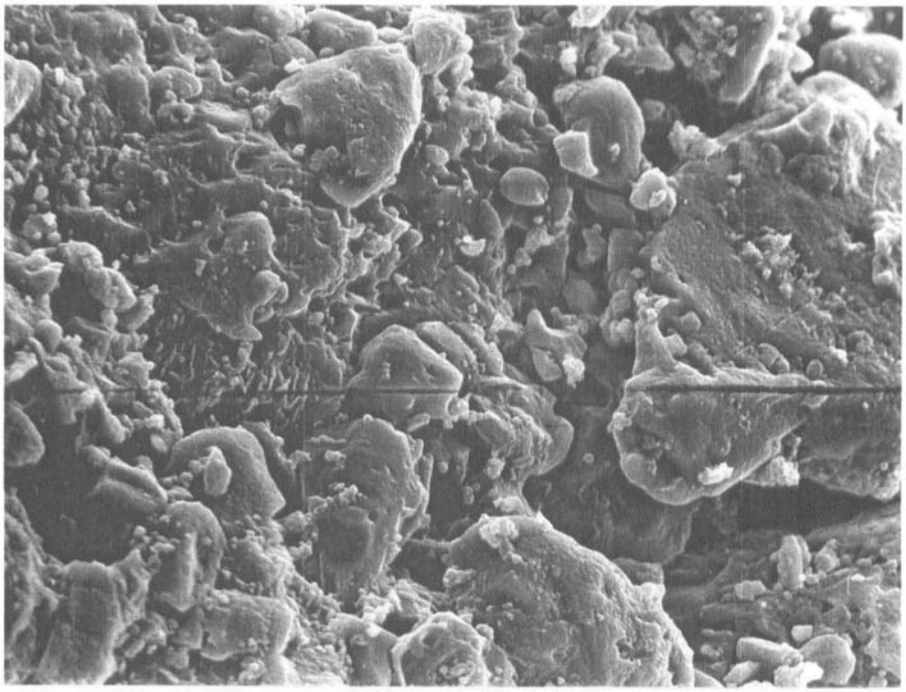
In fact, in the spheronization operation because the centrifugal force is linked to the speed (following the second law of Newton) and as we verified during the earlier works (11), it appears than an increase in this force gives greater interparticular impacts for one granule, thus a decrease in empty space. Consequently, spheroids having a more compact structure will be harder, less porous and will have a smoother surface.



(a) a - oven

Figure 5 - Surface condition of the spheroids depending on the drying method (speed = 620 rpm^{-1})

Concerning the drying influence, the oven technique produces, through thermal conduction, an evaporation of the fluid in the monomolecular layers. The migration of the water to the surface of the grains, through capillarity, will be produced through a slow and less traumatizing process. Because of the wavelength on the scale of the product to be tested, the microwaves are found to be very penetrating and lead to an instant discharge of heat inside the mass, thus giving a quasi-immediate leave to the entirety of the water molecules. The highest porousness of the spheroids dried by microwaves is, therefore, explained with the consequence of a weakening in the interparticular links translated by a decrease in the hardness of the grains.



(b) b - microwaves

Figure 5 Continued

In order to quantify the correlation that exists between the hardness **(y)** and the total porousness **(x)**, we have proceeded to the elaboration of a correlation test (25) according to the following linear model:

$$y = a + b + x$$

In the particular case of our studies, **y = 23.71 - 0.72 x**. The linear variation of the hardness depending on the porousness (fig. 7) for a correlation coefficient, **r = - 0.962**, proves the existence of a strong negative correlation **($P < 10^{-4}$)** between these two characteristics, any increase in one is therefore linked to a decrease in the other.

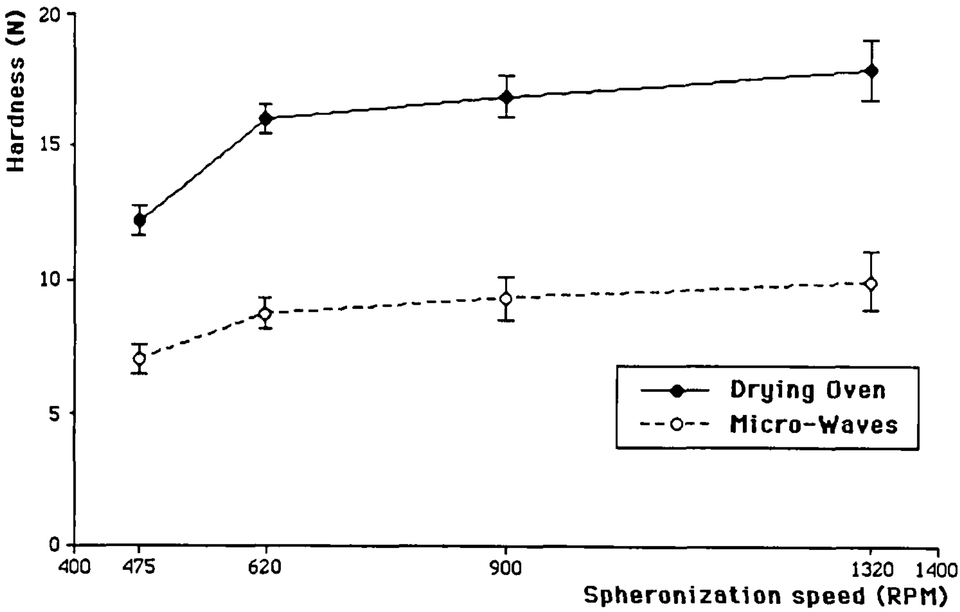


Figure 6 - Influence of the spheronization speed and the drying method on the hardness of the spheroids.

CONCLUSION

In the case of obtaining spheroids made of Avicel pH 101 and lactose, we verified that the increase in the spheronization speed and the oven-drying process, compared to microwave drying, modify the physico-mechanical characteristics of the spheroids. The structure of the latter becomes more compact. The grains are more resistant, less porous and have a smoother surface.

The mastery of the two technological parameters considered here is thus very important for insuring high quality. It may also provide an enlightened technological choice aiming for expected bio-availability.

We will continue, at a later date, experiments for complementary evaluations through physico-chemical methods, including notably the differential thermal analysis.

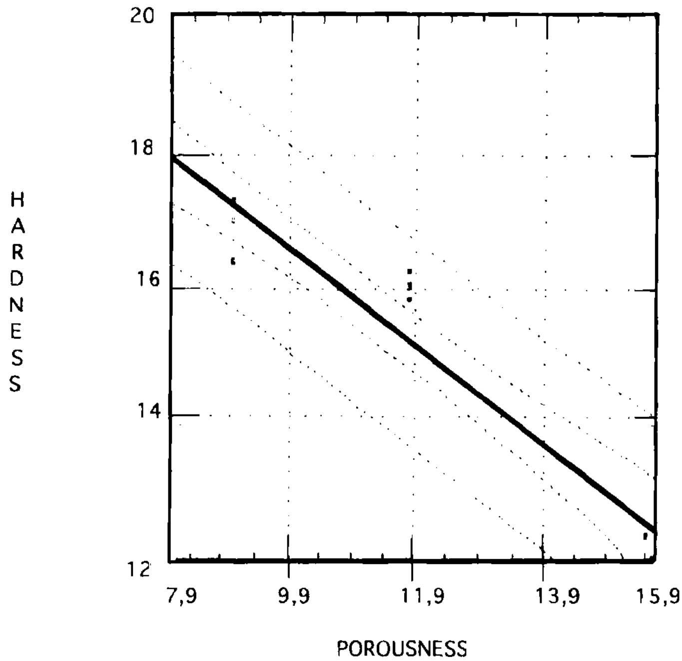


Figure 7 - Correlation between porousness and hardness of the spheroids.

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