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PHYSICAL CHARACTERIZATION OF TWO TYPES OF MICROCRYSTALLINE CELLULOSE AND FEASIBILITY OF MICROSPHERES BY EXTRUSION/SPHERONIZATION

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ABSTRACT

The influence of the physical properties of two types of commercial microcrystalline cellulose (Avicel[R] PH 101 and Microcel[R] MC 101) on the feasibility of minigranules production using an extrusion/spheronization process has been studied. Both raw materials were compared using IR spectrometry (*molecular level*), X-Ray Diffraction, DSC, TGA, morphology, texture and particle size distribution (*particle level*), and specific surface-area and density (*bulk level*). The differences observed during the step of mass moistening and on the spheroids obtained (particle size distribution, hardness) demonstrate that the variations in the physical characteristics of the excipients have an impact on the technology of manufacture of spherical granules, as well as on their specifications.

INTRODUCTION

The control involved in the industrial transformation of raw materials into elaborate substances is crucial during the development of any pharmaceutical formulation (1, 2). Thus, the production of pharmaceutical spheroids using an extrusion-spheronization process involves the use of raw materials, generally polymeric substances, as their 'building blocks'. Once associated with a fluid, usually water, these substances should produce a plastic, pressure-deformable compound, ultimately to provide spheres of given galenic properties which meet both technological (flowability, compression...) and biogalenic requirements. For this reason, the understanding of the physico-chemical structure of these polymers has direct implications for the formulation conditions, the technical means involved and the active compound lyoavailability.

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In the present study, we have examined the possible relationship between the physico-chemical properties of such polymers and the extrusion-spheronization process. Three levels of study (3, 4, 5) have therefore been tackled:

- the molecular level, using techniques such as infra-red spectroscopy and nuclear magnetic resonance;

- the particle level, using methods such as X-ray diffraction, thermal analysis, and texture, visual and particle size determinations;

- the bulk level, where the density, porosity and specific surface-area characteristics are examined.

In the field of pelletization, the extrusion-spheronization process is the preferred technology for industrial production of spherical minigranules (6, 7, 8, 9). Microcrystalline cellulose (MCC) seems to be a particularly efficient polymer (10, 11, 12, 13, 14) in the granulation step which follows the obtainment of a hydrous technological balance (HTB) with a liquid (water) necessary for extrusion, as well as, for the manufacture of spherical entities (spheronization). The industrial production of MCC involves the chemical treatment of woodpulp. The cellulosed structure of a high alpha-cellulose percentage is subjected to hydrolysis with a strong mineral acid; this results in the destruction of the amorphous part, and in the isolation of the crystalline parts. Following filtration, rinsing with water, and pH adjustment, the MCC suspension is then spray-dried (15).

Production steps may vary from one manufacturer to another, and it seems essential to study the structural characteristics of these polymers using physical techniques, to establish a predictable behaviour during their transformation into spheroids by extrusion-spheronization. In this study, we have exposed two commercial types of MCC to an identical protocol.

MATERIALS AND METHODS

Materials

Avicel^{R} PH 101, batch 6027 (FMC Corporation, Philadelphia, PA, USA).
Microcel^{R} MC 101, batch 232/92 (Blanver Farmacoquimica Ltda, Cotia, SP, Brazil).

Methods

Studies on Raw Materials

- Infra-red spectroscopy (Perkin Elmer 983). Measurements taken between 200 and 4000 cm^{-1} following compression by KBr disc method.
- X-ray diffraction diagrams using a horizontal goniometer CGR with copper anticathode ($K\alpha$= 1.5404°A); measurements made between 2.3°θ and 20°θ (Philips generator, 40 KV, 20 mA).
- Differential scanning calorimetry (Perkin Elmer DSC - 4/TADS System). The measurements were made at 20°C min^{-1} under nitrogen current using indium as a thermometric reference.
- Thermogravimetry (thermobalance Setaram B60 , sensitivity 0.01 mg) with a heating gradient of 2°C min^{-1}.
- Microphotography (scanning electron microscope Hitachi S-4000) following platinum metallization of the samples.
- Specific surface-area (Micromeretics 2100-E): measurement of specific surface-area using gas adsorption at low temperature (System B.E.T.).
- Particle size distribution (Malvern laser granulometer, Mastersizer X Version 1.2.B2 Serial 6208).
- Bulk density (Stampsvolumenometer STAV 2003) using the method described in the French Pharmacopoea (16) with 50 g samples.
- Particulate density (air comparison pycnometer Beckman 930) using 10 g samples.

Spheroid Production

For each of the two raw materials studied, five batches were produced using 500 g of microcrystalline cellulose. After defining the volumes of moisturising fluid (purified water) required for granulation, the wet mass was prepared in a planetary paddle mixer Kenwood Major (speed of the paddle 50 rpm, solid-liquid contact 10 min, mixing time 2 min). Extrusion followed immediately using a single-screw axial extruder Gabler Machinenbau Pharmex 35 T equipped with a 1.0 mm diameter screen, and functioning at a speed of 50 rpm. The extrudate was spheronized for 2 minutes at 1000 rpm using a spheronizer Gabler Machinenbau Sphaeromat SPH 250 MA equipped with a 30 cm diameter plate.

The spheroids were dried in an oven (Prolabo E.U.) at 50 ± 1°C until moisture content was ≤3% (determined with a moisture analyzer Sartorius MA 30). To determine the feasibility of spheroid production, we used the following parameters:

- Particle size distribution, evaluated by a standard sieving method (Sea Langrade Granulotest 150) on 100 g of spheroids.
- Bulk density and particulate density, using the methods described above for raw materials.
- Hardness, using a durometer (Erweka TBH 28) on a 60 grain sample, the particle sizes of which were between 0.800 and 1.000 mm (in order to minimize the effect of size on the measurement of hardness).
- Morphology, using scanning electron microscope photography (Hitachi S-4000).

RESULTS AND DISCUSSION

Raw Materials Physical Characterization

Infra-red spectroscopy. For both types of microcrystalline cellulose, infra-red spectra measured between 200 and 4000 cm^{-1} showed vibrational groups at the same frequency, indicating the presence of the identical chemical entity (Fig. 1).

X-ray diffraction. The diffraction diagrams shown in Fig. 2 indicate that the diffraction profiles of Avicel (line a) and Microcel (line b) were similar, as previously demonstrated by Nikai et al (17) and Thomas & Pourcelot (2). In the same conditions, the main peak is however more intense for Avicel (Fig. 2, line c), but is not necessarily indicative that the crystallinity of this material is higher.

Thermal analysis. The results of differential scanning calorimetry (DSC) are shown in Fig. 3. Two observations can be made: for each MCC, an initial endothermic reaction occurs at approximately 100°C, which corresponds to the temperature of water evaporation (18); for both products, a second endothermic reaction occurs above 280°C. According to Gerst (18), this reaction corresponds to a depolymerisation of the substances, followed by degradation. The energy consumed during this phenomenon is three times less for Microcel than for Avicel, indicating a structural or behavioral difference. This difference can be attributed either to a variation in crystallinity or to different bulk level properties (19). These observations are in agreement with the thermogravimetry results (Fig. 4), where two characteristic zones were defined. The first corresponded to the weight loss due the dissipation of water, the second being due to the weight loss associated with the decomposition of the products, which starts at 230°C and 243°C for Microcel and for Avicel, respectively.

Morphology and particle size distribution. Fig. 5 shows the micrographs obtained with the two raw materials. In both cases, a similarity in morphology was observed, with long particles of laminated and fibrous type (depending on the cellulosed origin of the compounds). However, some

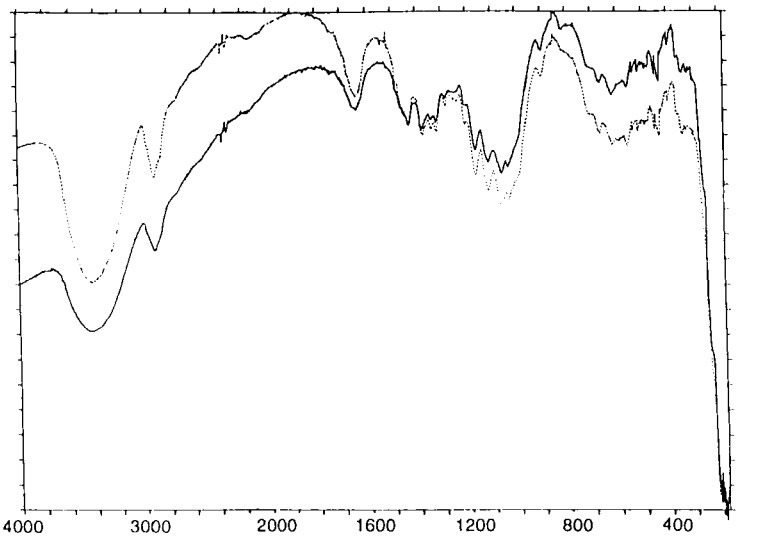

FIGURE 1
Infra-red spectrums: Microcel (—), Avicel (-----).

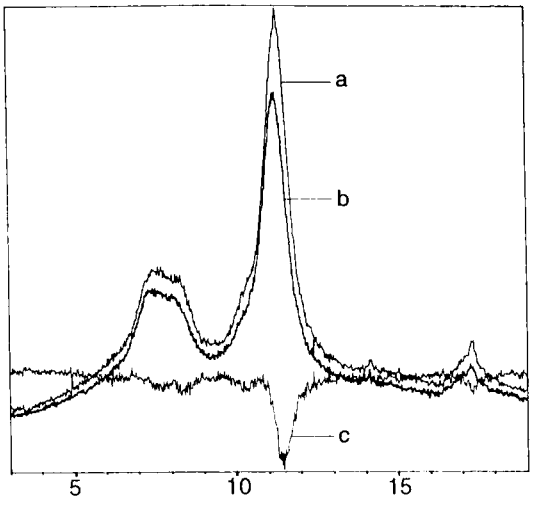

FIGURE 2
X-ray diffraction patterns Avicel (a), Microcel (b) and soustraction (c).

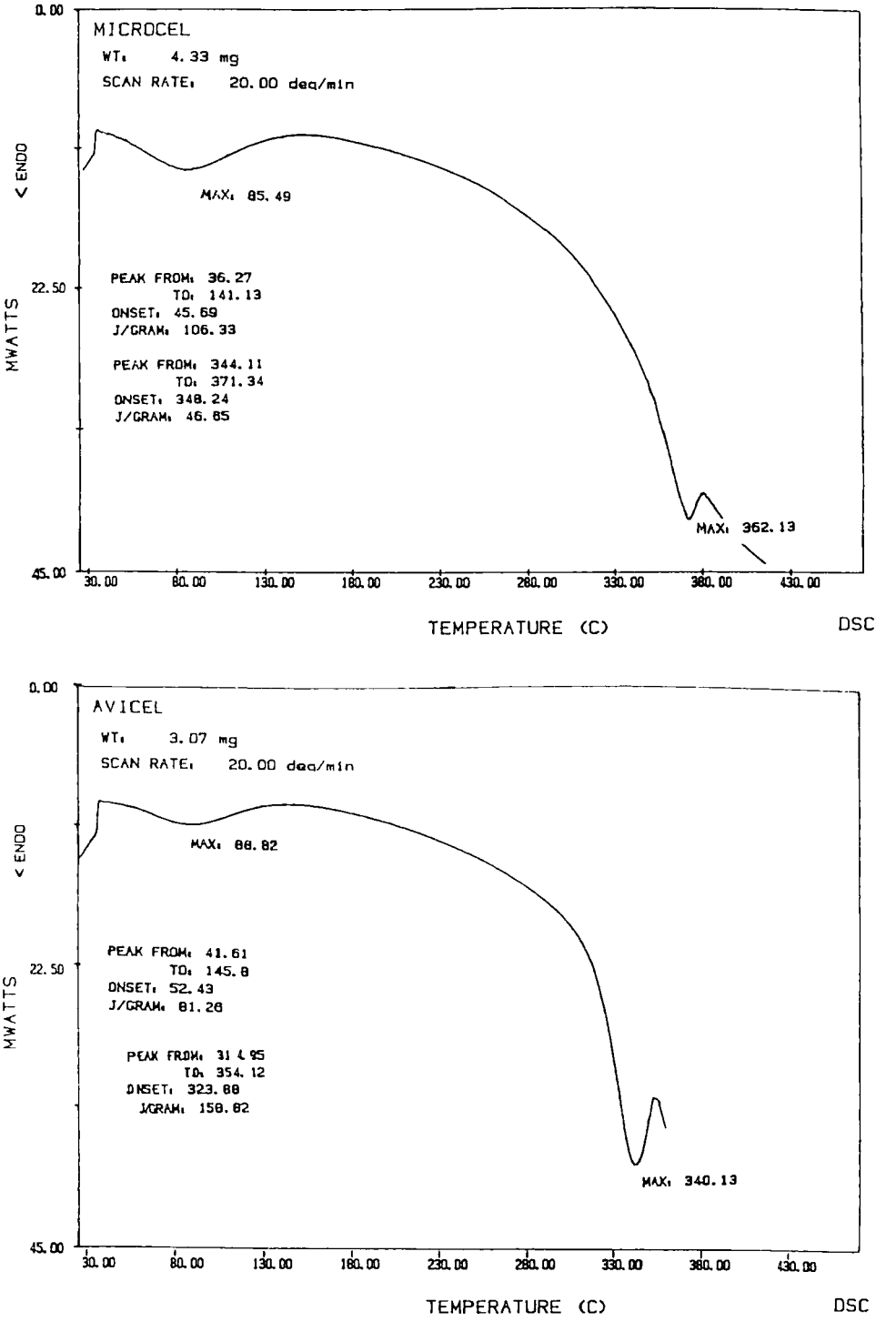

FIGURE 3
Differential scanning calorimetry thermograms obtained for the two MCC.

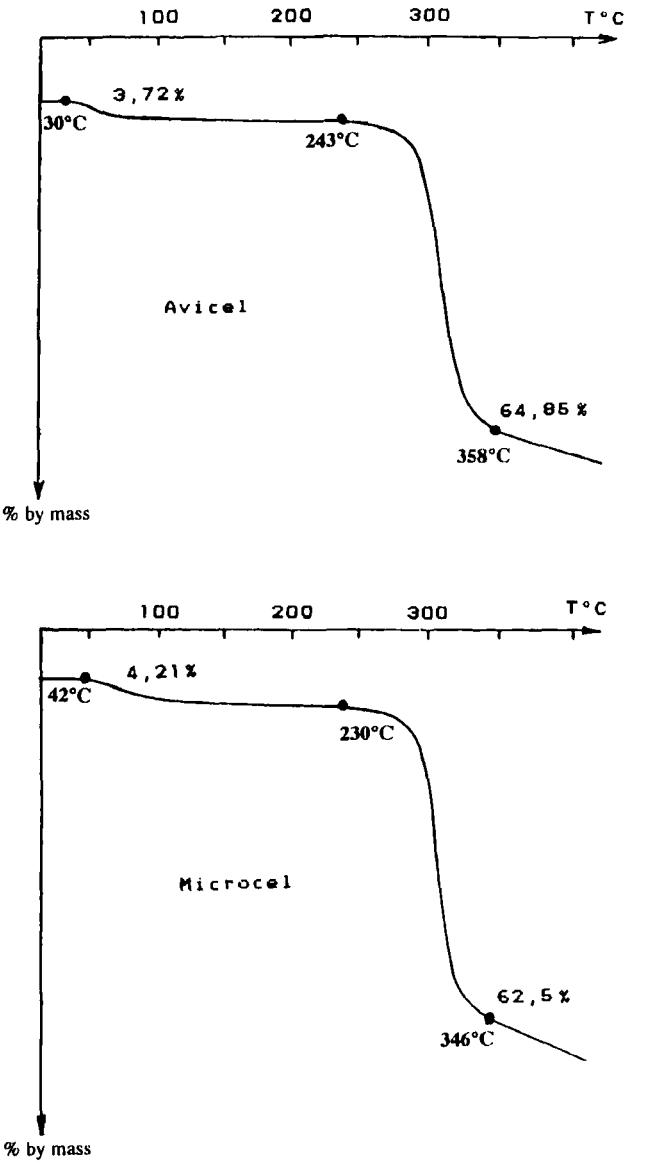

FIGURE 4
TGA curves of the raw materials.

differences were noted, Microcel generally forming particles of a larger size than Avicel. These observations are confirmed by particle size distribution laser analysis following suspension of the particles in air (Fig. 6). Examination of the histograms shows that size distribution was similar for both products, although the mean size was 75.32 μm for Avicel and 101.47 μm for Microcel.

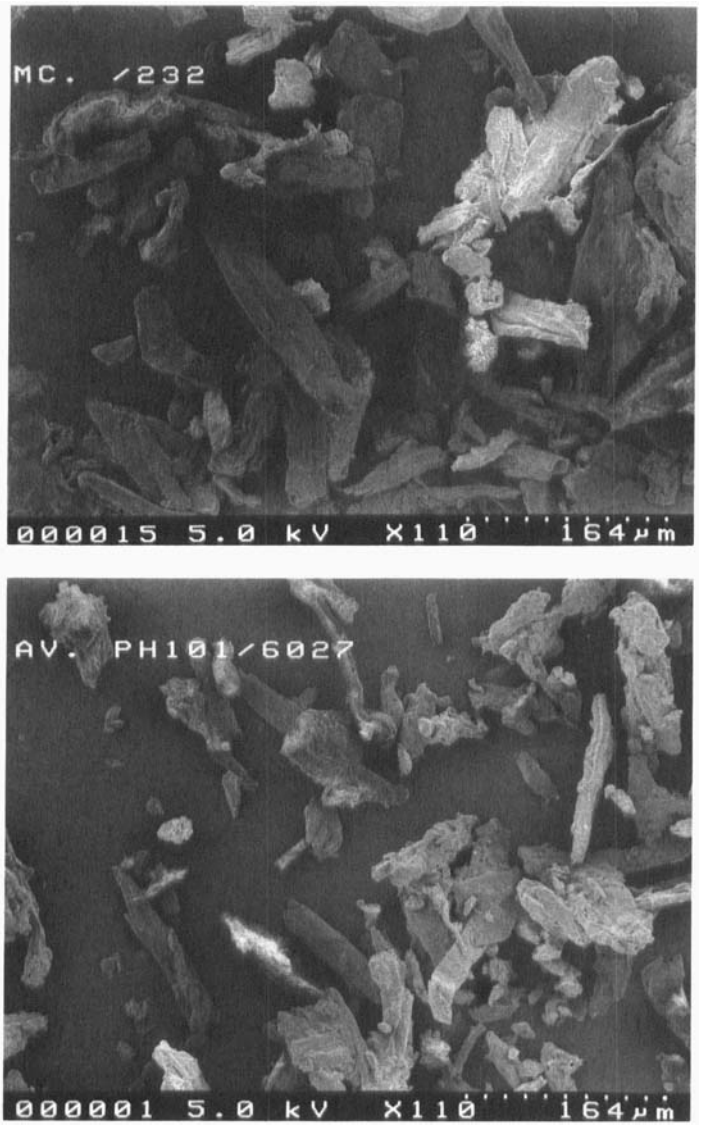

FIGURE 5
Scanning electron microscope photos of Microcel (MC) and Avicel (AV).

Specific surface-area and density. The results, which are shown in Table 1, are the mean of 5 determinations. There was no significant difference between the two MCC in terms of density or specific surface-area. The behavioral variation observed during packing tests is related to the difference in particle arrangement between Avicel and Microcel, as shown previously by particle size distribution.

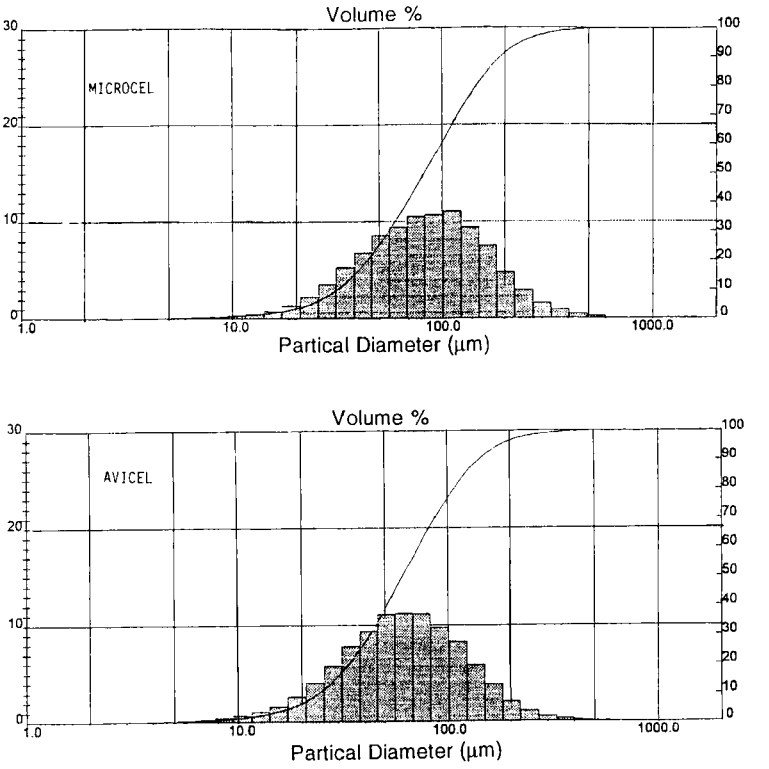

FIGURE 6
Particle size distribution of Microcel and Avicel powders.

TABLE 1
Specific Surface-area, Densities and Packing of the Two Raw Materials

Product	Specific Surface area (m^2/g)	Density (g/ml) unpacked	packed	particulate	Packing (ml) V10 - V500
AVICEL	1.5 (±0,11)	0.33 (±0,01)	0.40 (±0,01)	1.68 (±0,01)	25 (±0,58)
MICROCEL	1.4 (±0,15)	0.34 (±0,01)	0.39 (±0,01)	1.68 (±0,02)	18 (±1,05)

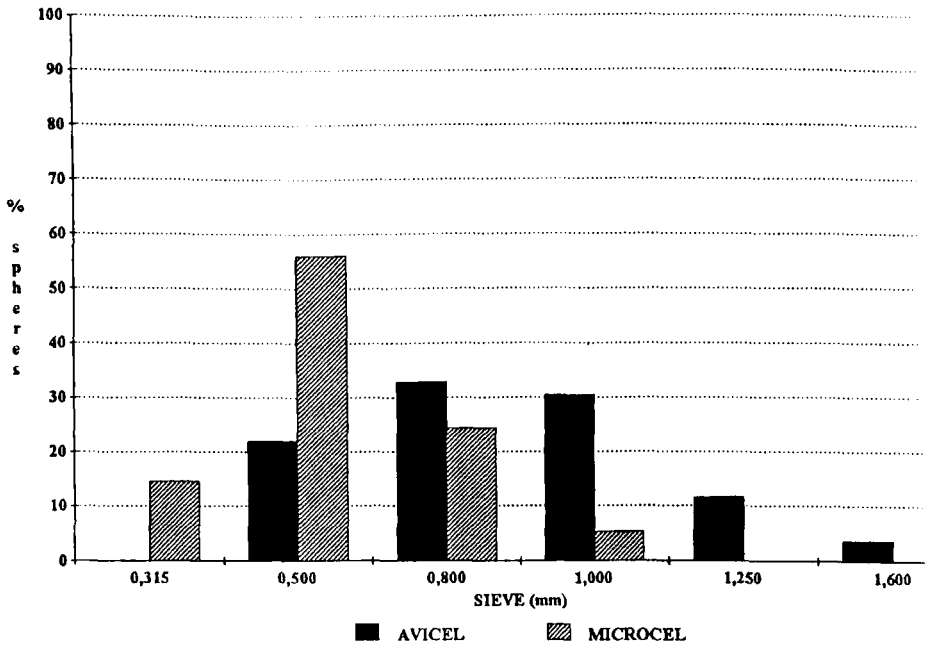

FIGURE 7
Particle size distribution of the spheroids.

Extrusion/Spheronization

Preliminary tests. In previous studies which used defined operational conditions (10, 20), Avicel was shown to present a technological extrusion ratio at 120 ml of water for 100 g of dry raw material (54.54% of added water). Despite the product extrudability, however, these tests demonstrated the impossibility of obtaining spheroids with a satisfactory yield when using Microcel. Indeed, after drying the finished product, the percentage of powder was approximately 50%, indicating that bulk moistening of Microcel is insufficient. A minimum quantity of 140 ml (58.33% of added water) was needed to achieve production of minigranules. Therefore, it seems that the differences previously noted in the particle properties of raw materials, notably in mean particle size, can induce perturbations in technology. According to Parker & Rowe (21), particle size distribution interferes with compaction during the moistening step; the smaller the size of particles, the higher their compaction. The quantity of liquid necessary for granulation is therefore decreased. When comparing the two products used in the present study, the mean particle size is higher for Microcel than for Avicel. The quantity of liquid required for the moistening step can therefore be expected to be higher.

Spheroid characterization. The results of spheronization tests using Microcel (HTB = 58.33%) and Avicel (HTB = 54.54%) showed in both cases the feasibility of spherical minigranules production. However, the analysis of particle size distribution histograms (Fig. 7) indicates that the

TABLE 2
Densities and Hardness of the Spheroids

Product	Density (g/ml) unpacked	packed	particulate	Hardness (N)
AVICEL	0.83 (±0,02)	0.86 (±0,07)	1.43 (±0,02)	23.90 (±0,91)
MICROCEL	0.81 (±0,02)	0.84 (±0,03)	1.45 (±0,02)	20.10 (±0,67)

final products obtained have different characteristics. For each MCC, the production of minigranules of identical mean size and reduced variability must therefore be achieved by optimization of operational parameters. This relates primarily to the conditions for obtaining a hydrous technological balance of the mass, and to the requirements of spheronization, the length and speed of this step indicating the force of centrifugation necessary to obtain spheroids. Similarly, the results obtained for density and hardness of the spheroids showed some variation (Table 2) related either to particle size differences of the finished products (bulk density) or to differences in the amount of fluid used for achieving HTB (hardness).

CONCLUSION

In terms of understanding and control of the raw materials which have a pharmaceutical use, this study has shown variations in the physical behaviour of the same cellulosed polymer (MCC) supplied by two different manufacturers. The tests performed, notably at the particle level, have shown differences which can have an impact on the subsequent use of these raw materials.

Thus, although it is feasible to use both of the tested MCC to produce spheroids by extrusion/spheronization, the differences noted during the physical characterization studies can influence:

-the conditions of transformation of the raw materials into spherical materials, notably those required to obtain a hydrous technological balance;

-the final properties of the spheroids obtained (particle size distribution, hardness), which are linked to the physical structure of these materials in relation to the lyoavailability of an active marker during the production of pharmaceutical spheroids.

Thus, during the development of a pharmaceutical formulation, it will be necessary to perform these analyses systematically in order to define the limits of utilization of the ingredients of a formula, and to adjust manufacturing conditions prior to optimization of a given formulation. Additional tests should also be developed to control the extrusion-spheronization process and the formulations which use this method, in terms of the mechanisms controlling the obtainment of a hydrous technological balance on one hand, and in terms of the physical requirements involved to obtain highly homogeneous spheroids on the other hand.

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