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PREFORMULATION OF FIVE COMMERCIAL CELLULOSES IN DRUG DEVELOPMENT : RHEOLOGICAL AND MECHANICAL BEHAVIOUR

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ABSTRACT

The physical quality of pharmaceutical powders is one of the main element in quality assurance.

A particular attention must be paid to physical and physico-mechanical properties of materials in order to avoid difficulties due to the variability of physical properties, batch to batch, in industry.

Physical characterization, packing characteristics and tableting behaviour applied to five celluloses are studied.

The Authors insist on the importance of packing properties and on his influence on compacting behaviour.

INTRODUCTION

Today, to obtain international manufacture and product registration, a manufacturer must ensure that the materials meet the requirements and specifications of Pharmacopeias, but is it sufficient ?

Recently excipients have been highlighted in Pharmacopeias and drug regulatory agencies, as a class for which international harmonization of standards is essential, and the International Pharmaceutical Excipients Council (I.P.E.C.) is born to facilitate cooperation between USA - Japon - Europe (1).

Actually, a problematic situation is developing due to variabilily in the physical properties of particulate materials. The behaviour and capacity of solid particles : homogeneity, flowability, compressibility, cohesion are the results of synergistic and antagonist effects between various physical and chemical properties at the interfaces.

The purpose of this work is to compare physical properties of five commercial types of cellulose by an approach with molecular, particulate and bulk level to an understanding of the behaviour in all states of production of tablets (2).

According to Shangraw (3), the fundamental properties of solids, such as density, particle size, surface area, moisture (type and content) as well as applied properties, such as fluidity and compactibility, are essential for characterizing not only the excipient but its functionality.

In study we retain :

• *Among the tests and specifications proposed*

For basic properties

- particle shape and surface quality
- particle size and particle size distribution
- particle cristallinity (qualitatively only)
- sorption isotherms.

For applied properties

- Packing
- Fluidity
- Compactibility

• *as a material raw : celluloses. Why ?*

Cellulose powders are very important products used in pharmaceutic, food, cosmetic and others industries (4).
In tableting, cellulose is an excipient with various functions like : filling, binding, desintegrating and colubricating. That explains their description in pharmacopeias and numerous works about them (5-10).

Cellulose is a polymer chain composed of repeating cellobiose units (in brackets). In the cellobiose, when the hydroxyle groups are in equatorial position, they associate together by hydrogen bonds giving a dish and rigid ribbon. Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account, almost exclusively, for the strength and cohesiveness cellulose fibers. Cellulose fiber is composed of microfibrils in which we can differentiate two regions :

• a paracrystalline region with amorphous and flexible mass of cellulose chains

• and a crystalline region with tight bundles of cellulose chains in a rigid linear arrangement.

Two types of cellulose are recognized in French and Europa pharmacopeias.

• cellulose powder and

• cellulose microcrystalline.

MATERIAL and METHODS

1. Starting materials were :

ELCEMA P 100	Lot 901 102	DEGUSSA FRANCFORT WEST GERMANY (DEGUSSA FRANCE)
AVICEL PH 101 AVICEL PH 102	Lot 6027 Lot 7015	FMC CORPORATION USA PHILADELPHIA (SEPPIC FRANCE)
MICROCEL PH 101 MICROCEL PH 102	Lot 840/90 Lot 1205/90	BLANVER PHARMACOQUINICA COTIA BRESIL (SAPA FRANCE)

Why this choice ?

- Elcema P 100 is referred as a powdered cellulose.
- Avicels stand, to day, as the single most important tablet excipient developed in modern times. They are recognized as microcrystalline cellulose.
- Microcels are introduced, more recently, into the marketplace to compete with Avicels.

For this, we wish to compare them to the Avicels and Ecelma P 100.

2. Equipments

- Diffraction system INEL, equipped with localization curve counter (anticathode Cu)
- Counter Coulter (in isopropanol)
- Scanning electron microscope. Cambridge Stereoscan 250 MK 2 - super rollex equipped.

- Volumenometer Engelsman
- Tableting machine EKO instrumented - punch d= 12 mm
  - depth of the die = 10 mm
- Schleuniger (for radial tensile strength)

RESULTS AND DISCUSSION

1• Basic properties

Complete investigation of particles requires numerous tests, because different techniques used, don't see the particles in the same way.

11 • Particle shape and surface quality

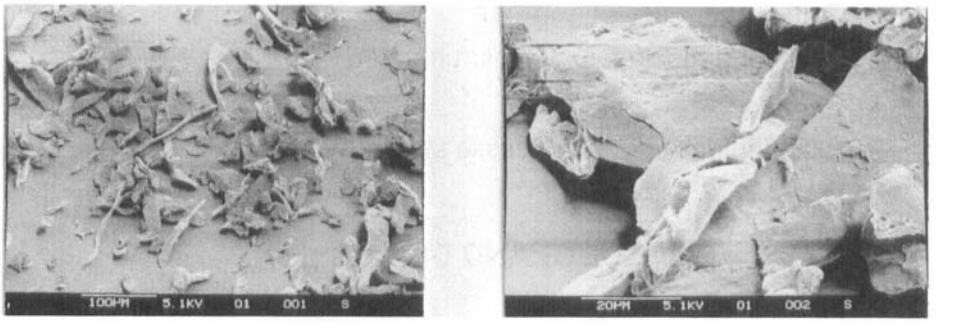
Particle shape and surface quality's observation is performed using scanning electron microscope which allows visual examination **(figure 1).**

• Elcema P100 presents lengthening and lamellar particles. Surface is smooth and flat.

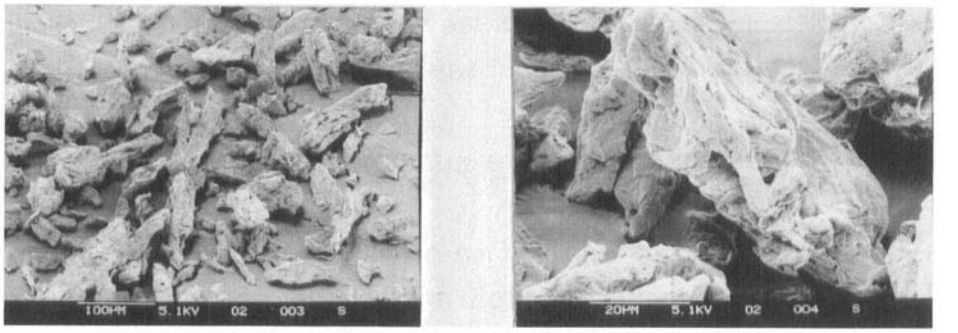
• Avicel 101 presents large particles irregular and elongated with some truncated fibers. Surface is rough and porous wich gives properties in terms of crushing strength and desintegration.

• Avicel 102 is spray dried and presents large particles in form of spherical aggregates with elongated large particles.

• Microcel 101 and Microcel 102 have a morphology intermediate with lamellar and truncated fibers. Surface is less porous and rough than Avicels but more than Elcema P 100.



a) Elcema P 100

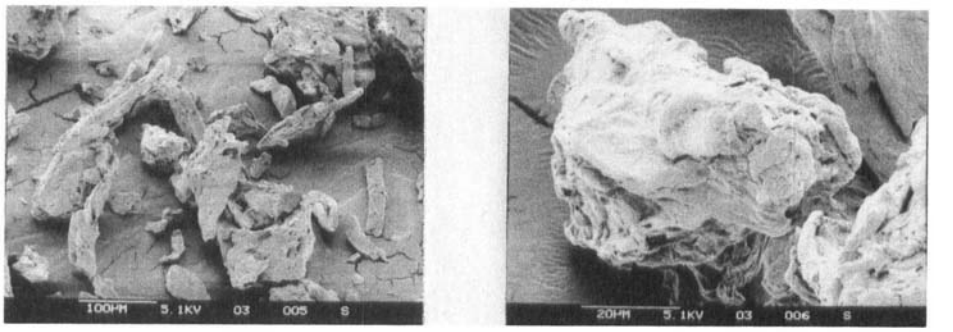


b) Avicel 101

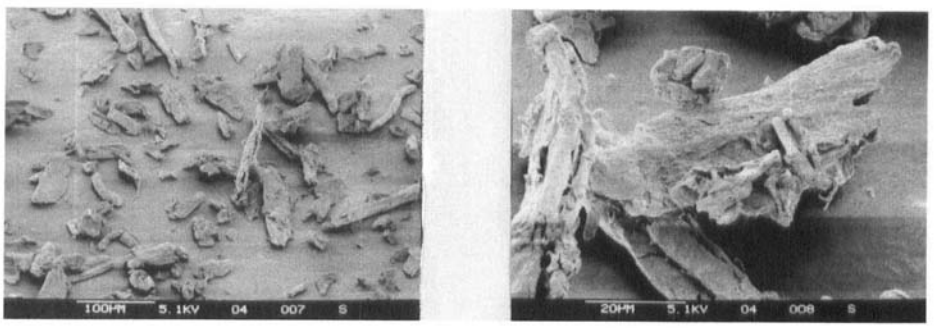
Figure 1 - Scanning electron photomicrographs of :
a) Elcema P 100, b) Avicel 101.

12 • Particle Size and particle size distribution

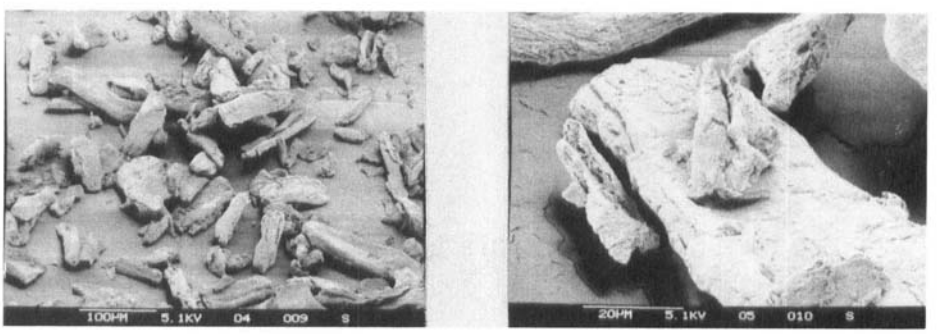
It is a very important parameter but complex (11).
The "diameter" as the only caracterization can be very misleading.
More over, particle size determination concernes a three dimensional problem.
For this, particle size distribution is observed using coulter counter (so volume diameter) **(Figure 2).**



c) Avicel 102

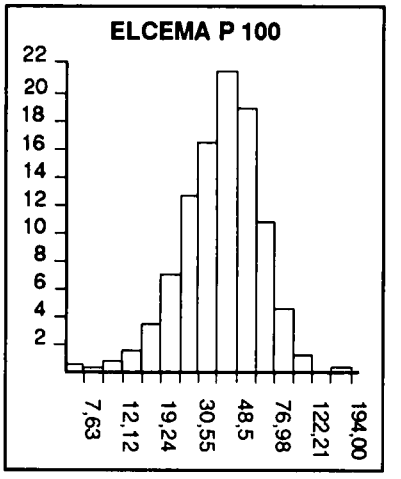


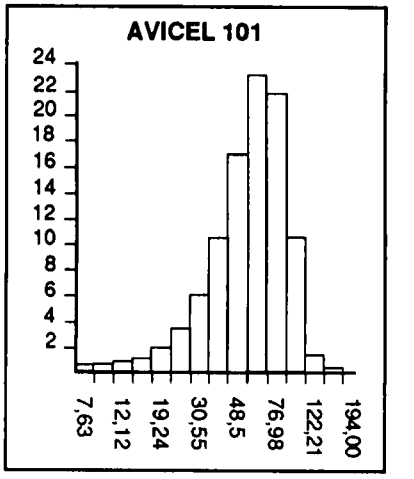
d) Microcel 101



e) Microcel 102

Figure 1 - (CONTINUED) **Scanning electron photomicrographs of :** c) Avicel 102, d) Microcel 101, e) Microcel 102.





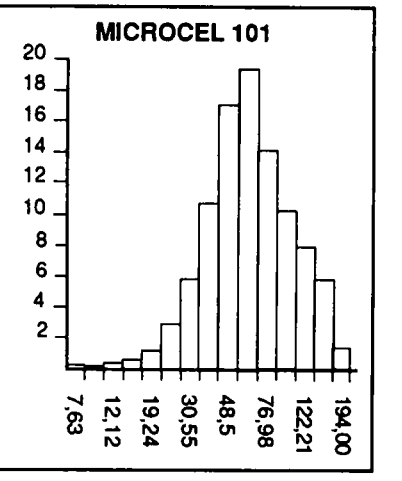


Figure 2.

Particle Size and Particle Size Distribution

We see that celluloses investigated are polysize powders.
In order to discriminate together, we retain simultaniously three parameters.

- median fifty percent diameter
- range
- cumulated percentage over size diameter of :
  - . twenty four micrometers
  - . sixty one
  - . ninety seven and
  - . one hundred and ninety four micrometers

Table 1. Particle Size and Particle Size distribution

	ELCEMA P 100	AVICEL 101	MICROCEL 101	AVICEL 102	MICROCEL 102
Median 50 % Diameter (um)	41,86	52,53	54,74	89,38	85,73
Range (um)	6,06 - 153,98	6,06 - 153,98	6,06 - 194	6,06 - 244,42	15,28 - 307,96
% cum. > . 194	0	0	0	2,71	13,16
Diameter . 97	1,50	1,99	15,52	43,59	43,43
(um) . 61	16,82	34,19	40,14	74,05	70,43
. 24	85,89	91,11	93,69	96,39	96,94
	ELCEMA P 100	AVICEL 101 - MICROCEL 101		AVICEL 102 - MICROCEL 102	

Results are collected in **table 1**.

- **Concerning median diameter**

For all the powders, median diameter is lower than one hundred micrometers. We can distinguish two groupes :
The first with Elcema P100, Avicel 101 and Microcel 101,
the second with Avicel 102 and Microcel 102.

- We can do practically the same classification for the range.
- Concerning cumulated percentage over size, its examination is very important to explain some applied properties.

We see that Elcema P100, Avicel 101 and Microcel 101 have no particles above diameter of one hundred and ninety four um. Avicel 102 shows a percentage of three per cent and Microcel 102,

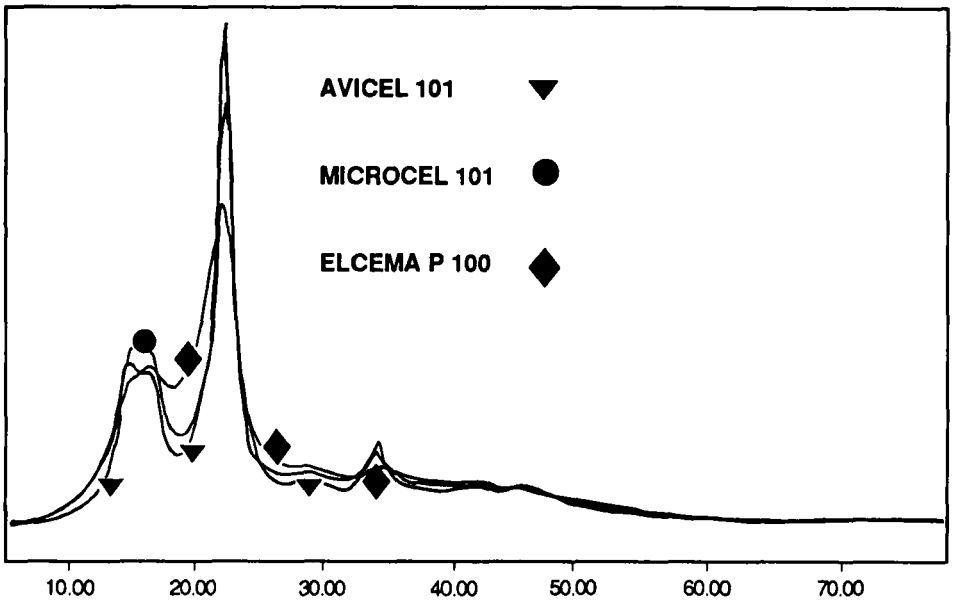


Figure 3 . Particle Crystallinity (Qualitatively)

thirteen per cent. The other percentages are practically the same for Avicel 102 and Microcel 102.
Elcema P 100 presents the lower percentages at all cumulated percentages over size.

Difference between Avicel 101 and Microcel 101 is seen essentially for the diameter of ninety seven micrometers.
We can list together in order :

- Elcema alone
- Avicel 101 with Microcel 101
- Avicel 102 with Microcel 102

13 • Particle crystallinity

Different value found in the litterature concerning a same cellulose material prove the difficulty of this analysis and we have made a

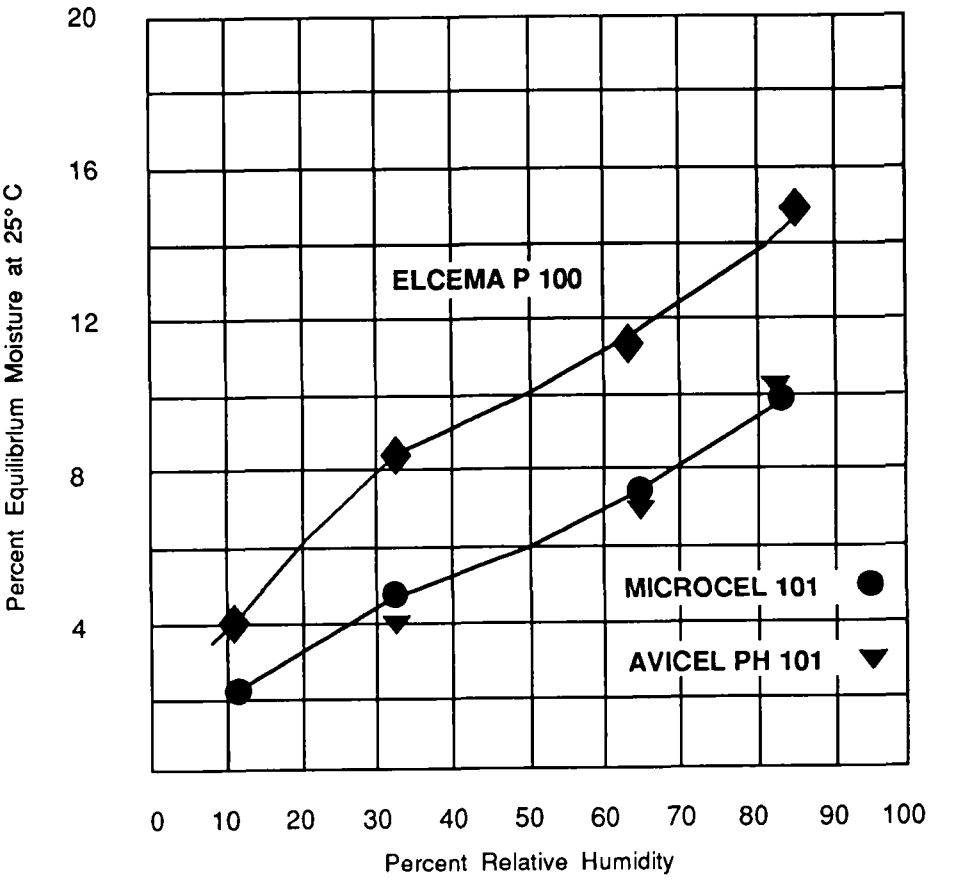


Figure 4. Sorption Isotherms

qualitative appreciation only. Results are visualized **figure 3**. In the same conditions cellulose X ray diffractogram indicate that Avicel 101 presents the higher intensity peak above the background. Elcema P 100 having the smaller intensity peak and Microcel 101 intermediate.

Quantitative determinations with amourphous standard and crystalline standard are in study.

14 • Sorption Isotherms

The effects of moisture on solids are developed for handling - storage and compaction. A number of important bulk properties are affected by moisture content and water solid interactions considered total amount of water, but also adsorption and absorption, specific surface area, effects of temperature and relative humidity to various factors.

Sorption Isotherms were assessed by measuring water sorption as a function of relative humidity by the use of saturated salt solutions in a closen system and at constant temperature (25° C) and occuring independently of time.

Figure 4 shows that Elcema P 100, amorphous cellulose powder, presents an isotherm greatly above of Avicels and Microcels that are practically confounded.

Its explains differences between powdered and microcrystalline quality, and amorphous accessible regions. The location of the water molecule and its physical state are very important and much works remain to be done in this way.

2 • Applied properties

21 • Packing and Rheological tests (11).

They are considered in terms of predicting mechanical and processing properties for tableting.

They depend on particle size, shape and surface conditions (12).

Packing density of polysize powder is potentially higher than that of a monosize powder since, small particles could fit into the voids left between the largest ones.

To compare the five celluloses together we have selected :

Table 2 . Packing and Rheological tests

HR : 55 %	BULK DENSITY		Hausner RATIO Tap density / Loose Density	Compressibility Index (Tap-Loose x 100) / Tap	V10 - V500 (weight 53 g)	V10 - V500 (Volume 250 ml)
	Loose	Tap				
Elcema P 100	0,21	0,34	1,64	39	78	78
Microcel 101	0,28	0,42	1,52	34	46	57
Avicel 101	0,30	0,42	1,40	29	34	51
Microcel 102	0,30	0,44	1,46	32	33	55
Avicel 102	0,32	0,44	1,35	26	23	38

• Bulk density

Loose and tap in relation with the true density and morphology.

• Hausner ratio

Which refers to the interparticulate frictions between powder particles.

It depends on the friction coefficient of the material, on the particule size and shape, as well as the surface conditions.

• Compressibility

Which is useful indirect method of measuring powder flow.

It is a direct measure of the potential powder arch or bridge strength and stabilily.

• We present also the V10 - V500

Using volumenometer Engelsman.

From a sample in weight and from a sample in volume.

Table 3 . Tableting behaviour

	Weight (g)	Thickness (mm)			Strength (Sclheuniger - Newton)		
		MPa : 12,5	25	50	12,5	25	50
ELCEMA P 100	0,189 (3,19)	2,41 (1,32)	2,19 (2,97)	2,33 (0,86)	5,1 (31,3)	12,3 (34,7)	33,6 (20,6)
MICROCEL 101	0,293 (1,03)	3,30 (0,44)	3,40 (0,92)	2,93 (0,41)	34,2 (12,9)	72,6 (8)	162,9 (9,1)
AVICEL 101	0,323 (0,64)	3,82 (0,36)	3,24 (1,41)	2,82 (0,37)	38,9 (3,3)	86,6 (5,3)	178,7 (2,1)
MICROCEL 102	0,333 (0,50)	3,58 (0,53)	3,28 (1,49)	2,69 (0,38)	42,1 (3,6)	68,8 (9,4)	177,5 (2,6)
AVICEL 102	0,359 (0,25)	3,82 (0,70)	3,69 (0,43)	3,45 (0,37)	63,3 (3,9)	8,7 (3,1)	191,4 (2)

Depth of the die : 10 mm punch d : 12 mm ( ) : CV

Results are collected in **table 2.**

. Bulk density (loose and tap) increase from Elcema P 100 to Avicel 102.

. Avicel 101 and Microcel 102 present the same loose density but not the same tap density.

Microcel 101 and Avicel 101 present the same tap density but not the same loose density. It explains the values of their Hausner ratio and compressibility percentage. Avicel 102 presents the best Hausner ratio and Elcema the worst one. Elcema is a non flowing material.

Microcel 101 and 102 are intermediate between Elcema and Avicel 101 and 102.
If we consider the V10 - V500 we see that it is interesting to start from a volume sample which is more discriminating.

22 - Tableting behaviour (13 - 14)

Tableting behaviour is important because it is the result of three behaviours : fluidity, compressibility and cohesion (15).
The five cellulose investigated are compressed to three compression forces. 12,5 - 25 and 50 MPa in automatic processing using a constant die cavity volume and with no additives.
Examination of compacts and values in **table 3** confirm :
. The poor fluidity and strength of Elcema P100.
. The increasing of the radial tensile strength with increasing compression force used for all powders with different slopes.

. That, for a same volume of die, Avicel 102 compacts present the higher weight and strength with a lower coefficients of variation that is in agreement with Hausner ratio and compressibility percentage.
We can assume that Microcel 101 and Microcel 102 can be used as good direct compression tableting agent, but Avicel 102 stands the better.

CONCLUSION

Today excipients are becoming more and more sophisticated and important in determining the quality of final drug products, they are not inert but display chemical, physical and technological activity. IPEC (International Pharmaceutical Excipients Council) and drug regulatory agencies consider and deliberate on this question and harmonization.
Concerning cellulose powder excipients, many works are carried out but with various batchs, different methods and parameters, making comparison difficult. The influence of cristallinity, polymerization degree, factors related to the

preparation technique of celluloses and source materials are studied, but a real classification is difficult. Indeed the modification of cellulose can be a continuum between classical cellulose and microcrystalline cellulose.

The five powders considered in this study are not equivalent in functionality and after these results, the classification for flowing and tableting is done. The functionality of MCC seems not only due to its crystalline content, but also to its physical form (size, shape, aggregate and surfaces). Each functionality must be tested separately and in three directions : flowing, compressility and cohesion by a rational approach (molecular, particulate and bulk level). We completely agree with R. SHANGRAW (16), the properties of Avicel 102 are nearly optimal. *At molecular level* ; it is a special grade of purified wood cellulose, with crystalline portions of cellulose isolated from fiber chain (bundles of needle-like microcrystals), at *Particulate Level* : the nature of microcrystalline particles themselves held together by hydrogen bonds between hydrogen groups on adjacent cellulose molecules. Finally particles (with split-planes and dislocation on a microscale and deformation of spray-dry agglomerates on a macroscale) deformed plastically (clean surfaces). At *last Bulk Level*, the low bulk density and the large range of particle size made an **optimum packing density**, a high distribution potential and a low friction coefficient. This study is a first approach, but X ray diffraction, specific surface area by different methods and tableting at various pressure will be examined more precisely in a next paper.

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