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# EVALUATION OF A NEW FINE PARTICULATE CELLULOSE AS A DIRECT COMPRESSION TABLET AID

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## ABSTRACT

A new grade of α-cellulose, composed of a mixture of amorphous and crystalline cellulose was evaluated in this preliminary study for its potential as an inert direct compression tablet vehicle. Though not a microcrystalline cellulose, this product, identified as EGC, possesses the tabletting characteristics of microcrystalline cellulose. It is prepared by a physicochemical procedure that does not require severe heat or acid treatment but yields a product which is white, fine granular, free-flowing and highly compressible.

## INTRODUCTION

One of the ingredients that has been extensively used in solid dosage forms, especially in the manufacture of tablets by the direct compression process, is microcrystalline cellulose (MCC). The tabletting properties of microcrystalline cellulose have been very thoroughly studied since its introduction in 1961. Shangraw, et al., had reported that extremely





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hard tablets could be made with microcrystalline cellulose with ease and without applying much pressure. These researchers summed up their findings "..... no other single substance has proved to be an effective filler, binder, disintegrating agent and lubricant" (1).

The extremely high direct compressibility of microcrystalline cellulose is shown to be due to its specialized manufacturing process. In this patented process, purified wood cellulose is subjected to severe acid hydrolysis which removes the amorphous portion and frees the microcrystals from their fibrous packed structure. They are then re-hydrogen bonded together by spray-drying to give the porous random structure. This yields a product that contains a high proportion of alpha-crystalline cellulose (2),(3).

In recent years, other forms of purified wood cellulose have been introduced but none has matched the tabletting characteristics of microcrystalline cellulose. Combinations of these products with microcrystalline cellulose have shown properties which are somewhat similar to those of microcrystalline cellulose but are still restricted in their application on a universal basis (4).

A new, unique grade of α-cellulose has been developed and produced by a physico-chemical process. In this patented process, finely divided and purified cellulose floc is intimately mixed with an agglomerating agent. This causes packing of the fibers. Further treatment, washing and drying causes the resulting product to granulate, thus imparting to it the fine particulate and free-flowing characteristics and very high compressibility.

The object of this preliminary work is to evaluate and compare the physical properties, including

tabletting characteristics, of EGC with some of the most commonly used α-cellulose products.

## EXPERIMENTAL

Two grades of microcrystalline cellulose - powdered, MCC-1[1] and fine granular, MCC-2[2] - and a microfine cellulose[3] were evaluated along with EGC for the following:

### Particle Size Distribution

Particle size distribution was determined by using a 25 gram sample on Rotap sieve shaker[4]. This instrument operates at 285 revolutions and 150 taps per minute. Each sample was run for 20 minutes.

### Bulk Density

Bulk density was determined by filling a 50 ml graduated cylinder to volume. The cylinder was tapped on a hard surface until no more settling of the material occurred.

### Loss on Drying

O'Haus moisture determination balance[5] was used. The settings were adjusted so as to calibrate to a temperature of approximately 95°C.

### Flow

A recording powder flowmeter (5) consisting of an analog balance connected to a strip chart recorder was utilized to determine the flow of a 100 gram sample that was allowed to fall through a funnel stem of 14 mm ID. The rate of flow was calculated.

### Preparation of Tablets

Five hundred gram batches of the formulations containing the cellulose and active ingredient[6] were blended in a Twin-shell blender[7] for 15 minutes. Lubricant[8] was then added and blending continued for another 5 minutes. These formulations are listed in Tables 2 and 3. Microfine cellulose failed to produce

TABLE 1

Comparison of Physical Characteristics

| Sieve Analysis: | EGC | Microfine Cellulose | MCC-1 | MCC-2 |
|---|---|---|---|---|
| Percent > 800 um | 0 | 0 | 0 | 0 |
| " " 246 " | 30.52 | 15.20 | 0 | 0.92 |
| " " 147 " | 23.80 | 80.00 | 2.16 | 21.68 |
| " " 74 " | 26.00 | 3.08 | 24.12 | 36.64 |
| " " 44 " | 13.52 | 0.96 | 33.04 | 21.20 |
| Percent < 44 " | 6.14 | 1.12 | 40.68 | 19.56 |
| Bulk Density(g/ml) | | | | |
| Loose | 0.28 | 0.35 | 0.31 | 0.32 |
| Packed | 0.36 | 0.47 | 0.45 | 0.44 |
| Loss on Drying(%) | 2.3 | 4.5 | 5.0 | 3.3 |
| Flow(g/sec) | 19.0 | 16.0 | - | - |
| pH[5] | 5.0 | 5.3 | 6.2 | 6.3 |

tablets of acceptable hardness at these concentrations of active ingredients and was therefore excluded from the tables.

Tablets were compressed on a rotary tablet machine[9] that had been instrumented with Piezo transducers to give a graphic illustration of the compression and ejection forces. Tablets were compressed at 3-5 different compression forces using 7/16" standard concave tooling, and at a rate of 150 tablets per minute. The target weight of tablets with active ingredients was set at 480 mg and those of the celluloses per se at 270 mg. Tablets were stored in tightly closed plastic containers and tested the same day for the following:

TABLE 2

Formulations Containing Acetaminophen

| Ingredient | % W/W | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| EGC | 39.25 | 29.25 | 34.25 | - | - | - | - | - |
| MCC-1 | - | - | - | 39.25 | 29.25 | 34.25 | - | - |
| MCC-2 | - | - | - | - | - | - | 39.25 | 29.25 |
| Acetaminophen, USP granular | 60 | 70 | 65 | 60 | 70 | 65 | 60 | 70 |
| Magnesium Stearate | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |

TABLE 3

Formulations Containing Ascorbic Acid

| Ingredient | % W/W | | | | | |
|---|---|---|---|---|---|---|
| EGC | 39.25 | 29.25 | - | - | - | - |
| MCC-1 | - | - | 39.25 | 29.25 | - | - |
| MCC-2 | - | - | - | - | 39.25 | 29.25 |
| Ascorbic Acid, fine granular | 60 | 70 | 60 | 70 | 60 | 70 |
| Magnesium Stearate | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |



Hardness

Tablets were tested for hardness on a Schleuniger hardness tester.[10] Average of 10 tablet values are reported.

Friability

Roche friabilator[11] was used. Twenty tablets were tested for four minutes at 25 rpm and percent friability was calculated.

Thickness

A hand held micrometer[12] was used to check the thickness of 10 tablets. Average values in inches are reported.

## RESULTS AND DISCUSSION

Physical Characteristics

A comparison of physical characteristics from Table 1 shows a significant difference in particle size distribution between the four products tested. A direct advantage of the coarser particles of EGC is manifested in a high rate of flow which is almost comparable to that of microfine cellulose and considerably superior to MCC-1 and MCC-2. The lower bulk density of EGC offers the potential benefit of

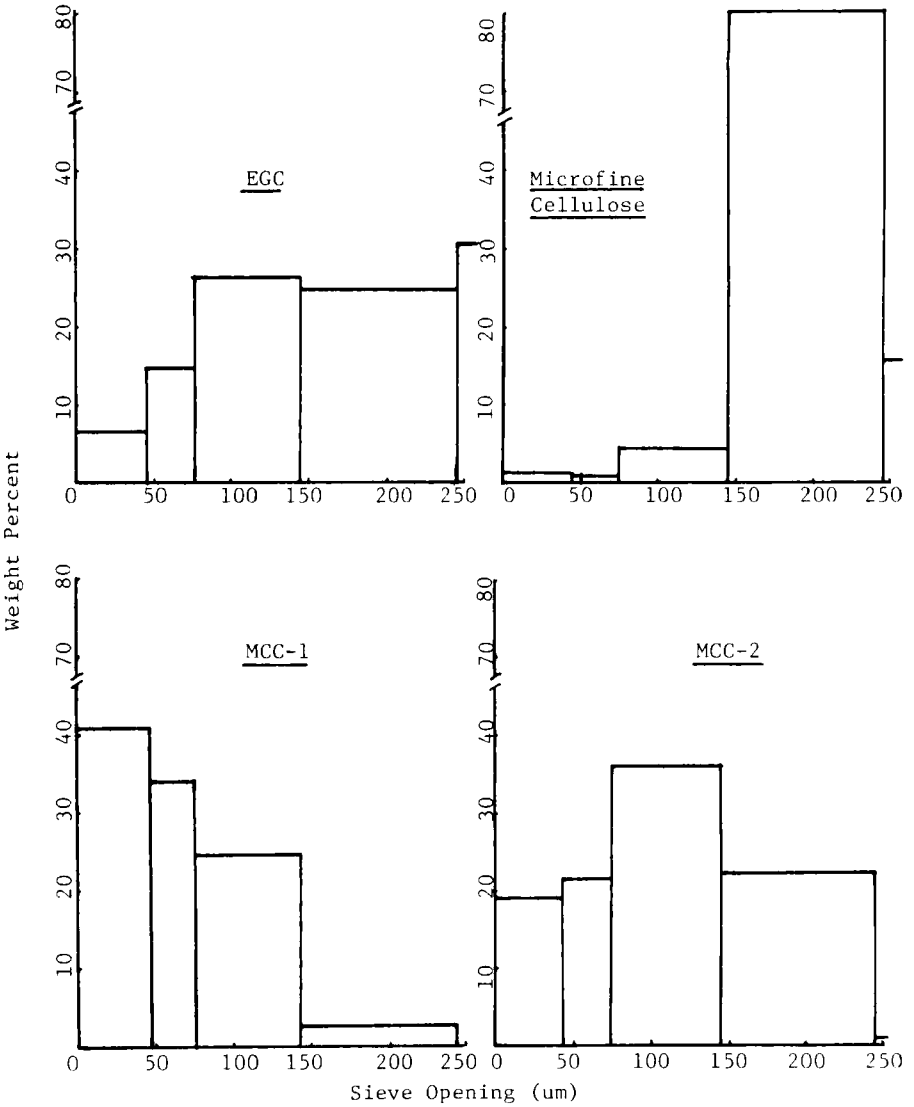


FIGURE 1

Particle Size Distribution

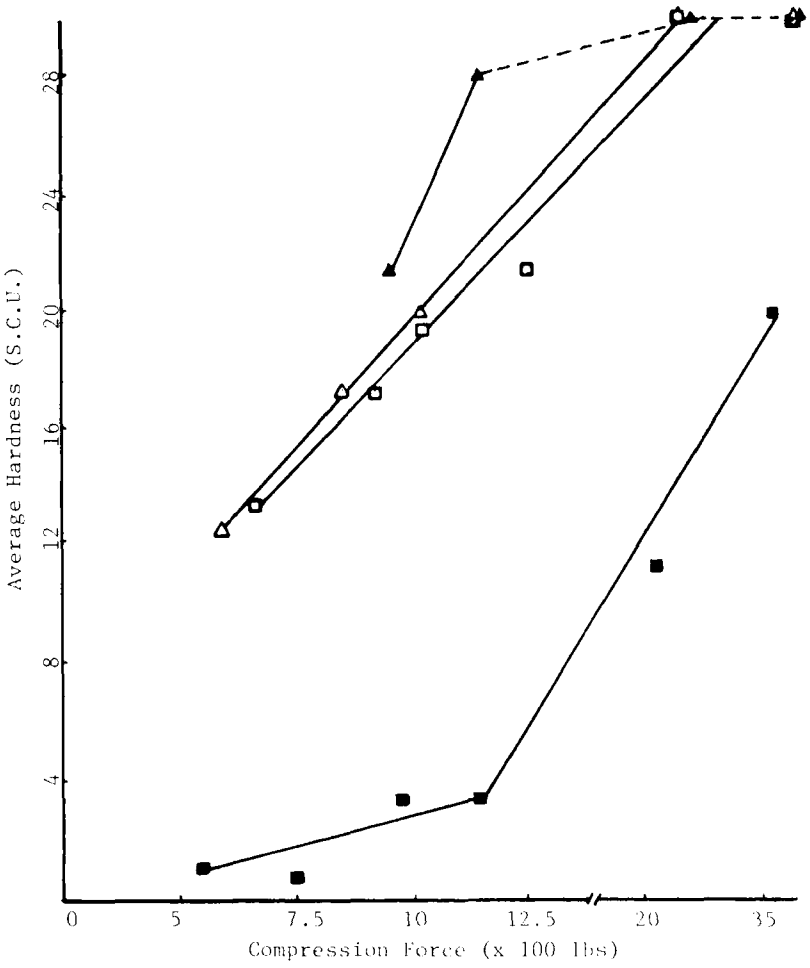


FIGURE 2

Effect of Compression Force on the Hardness of Tablets Compressed to the Same Weight (0.269-0.272g). Key: ▲ = EGC; △ = MCC-1; □ = MCC-2; ■ = Microfine Cellulose.

requiring lesser amounts than other celluloses to attain similar tablet dimensions. Loss on drying evaluation shows EGC to contain half the moisture content of MCC-1 and microfine cellulose and about 33% less than that of MCC-2.

Compressibility

Figure 2 shows the high compressibility of EGC when all four cellulose products are compressed to

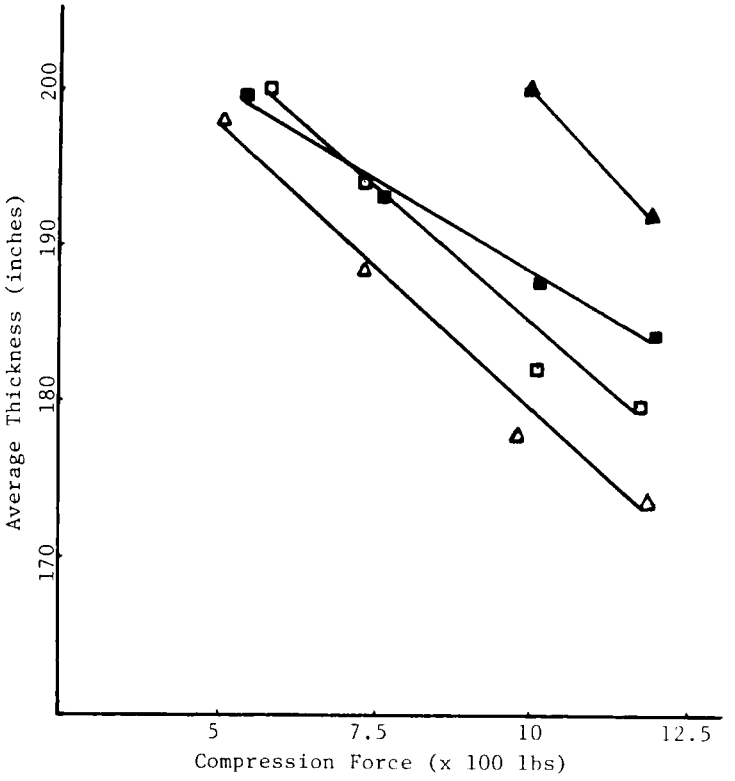


FIGURE 3

Tablet Thickness as a Function of Compression Force for Tablets of Same Weight (0.269-0.272g). Key: ▲ = EGC; △ = MCC-1; ◘ = MCC-2; ■ = Microfine Cellulose.

the same weight. On first glance and comparison with Figure 3, it appears that this high compressibility could be attributed to greater thickness of the tablets, but this factor could be advantageous in that the thickness of tablets can be reduced close to that of MCC-1 and MCC-2 and still obtain similar tablet hardness values for the three products as illustrated in Figure 4. This figure also indicates that same tablet dimensions can be obtained by using less EGC than MCC-1 or MCC-2.

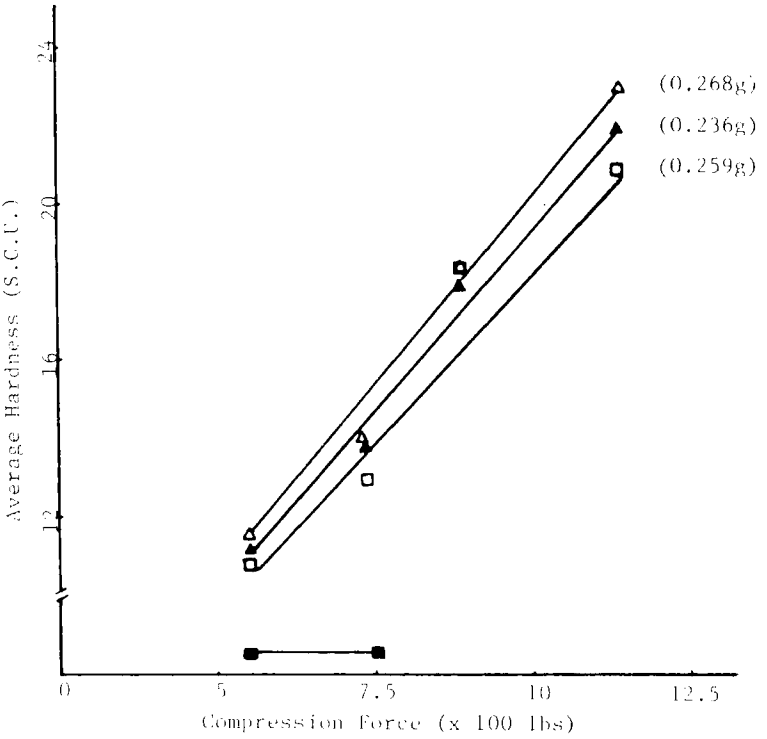


FIGURE 4

Effect of Compression Force on the Hardness of Tablets Compressed to the Same Thickness. Key: ▲ = EGC; △ = MCC-1; □ = MCC-2; ■ = Microfine Cellulose. (Figures in parentheses indicate average tablet weight).

As demonstrated by Figure 5, while EGC has half the water content of MCC-1 and microfine cellulose and 33% less than that of MCC-2, this water is not released on storage at 50°C. All other celluloses lose their water content and equilibrate at levels equal or close to that of EGC. Whereas this loss of water causes a reduction in compressibility of from 30 to more than 50 percent in MCC-1, MCC-2 and microfine cellulose, Figure 6 shows negligible change in the compressibility of EGC. While loss

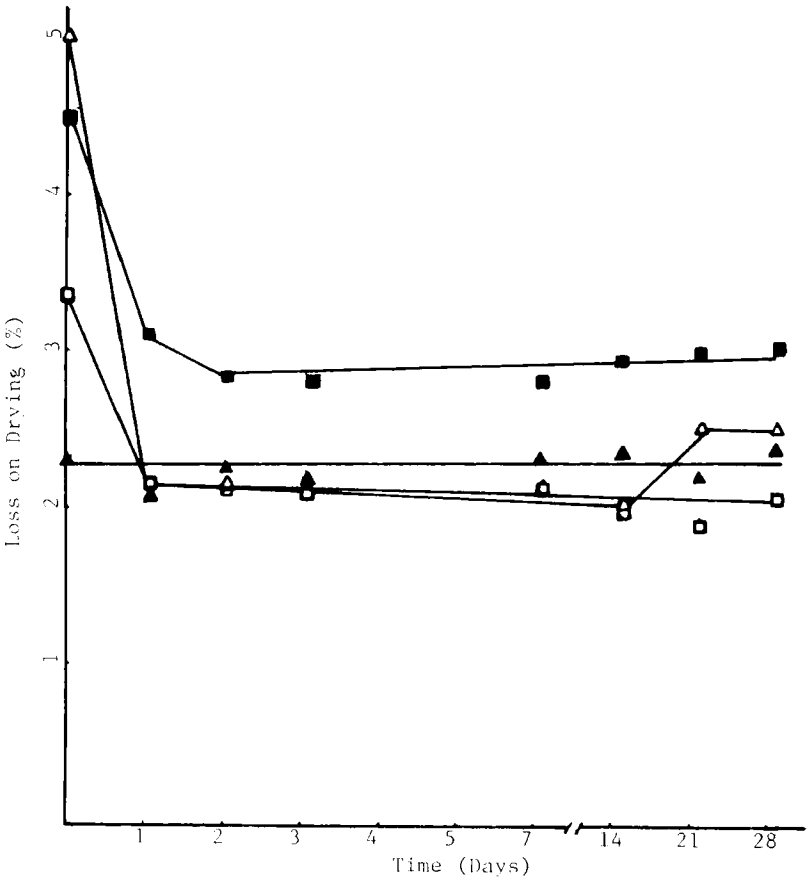


FIGURE 5

Loss on Drying as a function of High Temperature (50°C) Storage.
Key: ▲ = EGC; △ = MCC-1; □ = MCC-2; ● = Microfine Cellulose.

of water had caused a reduction in compressibility of MCC-1 and MCC-2, both celluloses demonstrated a vast increase in ejection force as seen in Figures 7 and 7A. A proportional decrease in the ejection force was exhibited by EGC.

The above data exhibit that the compressibility of EGC per se is equal to or superior than that of MCC-1, MCC-2 and microfine cellulose. Figures 8, 9, 10 and 11 demonstrate that like MCC-1 and MCC-2,

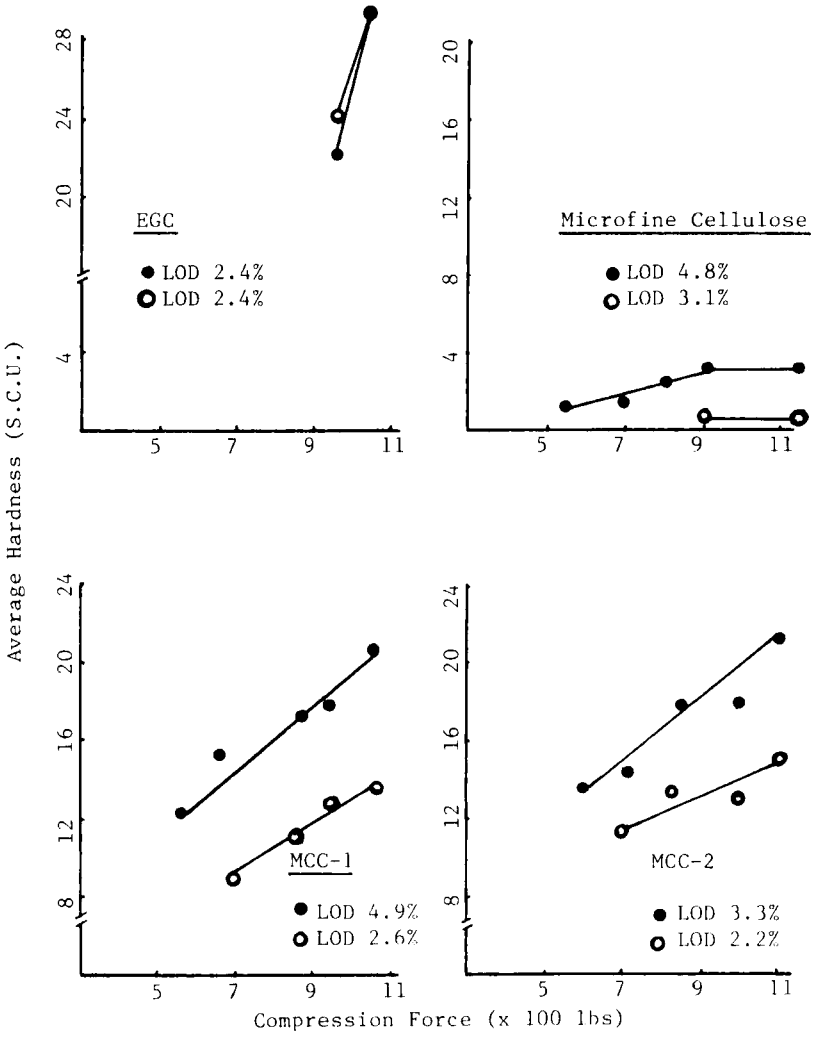


FIGURE 6

Effect of High Temperature (50°C) Storage and Compression Force on the Hardness of Tablets Compressed to the Same Weight (0.269-0.272g). Key: ● = initial; ○ = after four weeks storage.

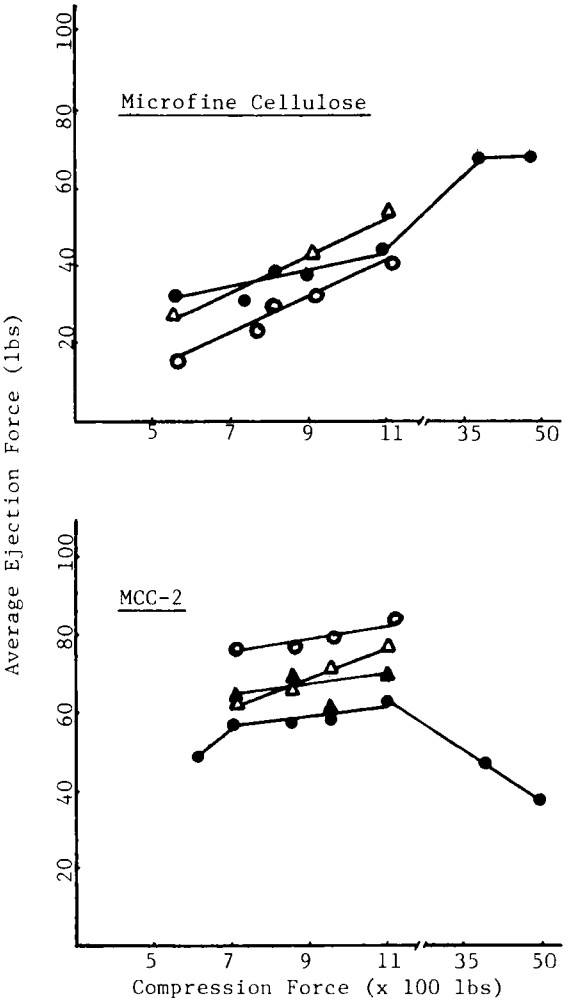


FIGURE 7A

Effect of Age and Compression Force on the Ejection of Tablets Compressed to the Same Weight (0.269-0.272g). Key: ● = initial; ○ = 50°C for 4 weeks; ▲ = 12 weeks at RT; △ = 26 weeks at RT; □ = 52 weeks at RT.

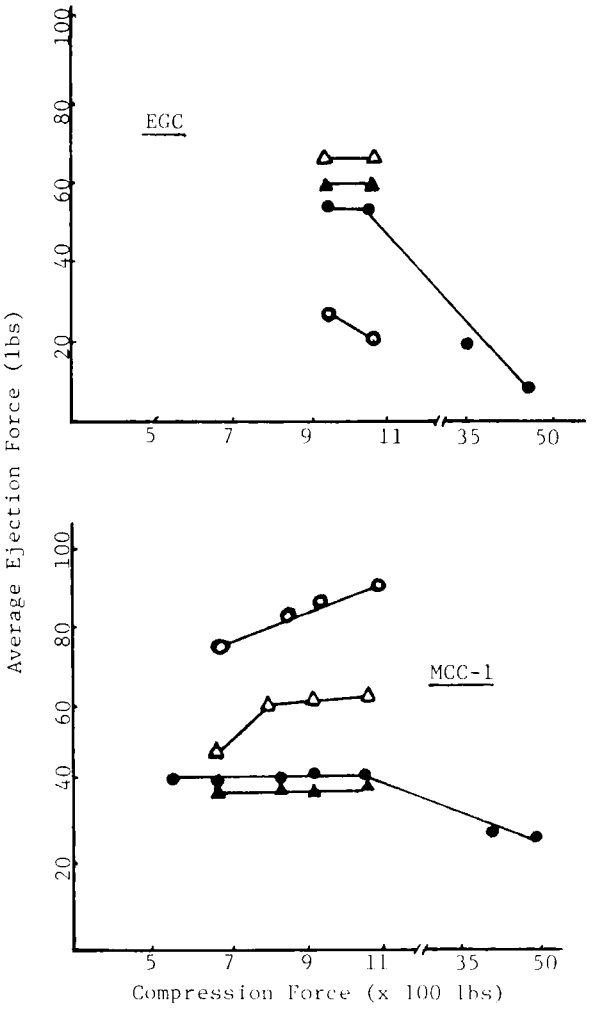


FIGURE 7

Effect of Age and Compression Force on the Ejection of Tablets Compressed to the Same Weight (0.269-0.272g). Key: ● = initial; ○ = 50°C for 4 weeks; ▲ = 12 weeks at RT; △ = 26 weeks at RT; ◘ = 52 weeks at RT.

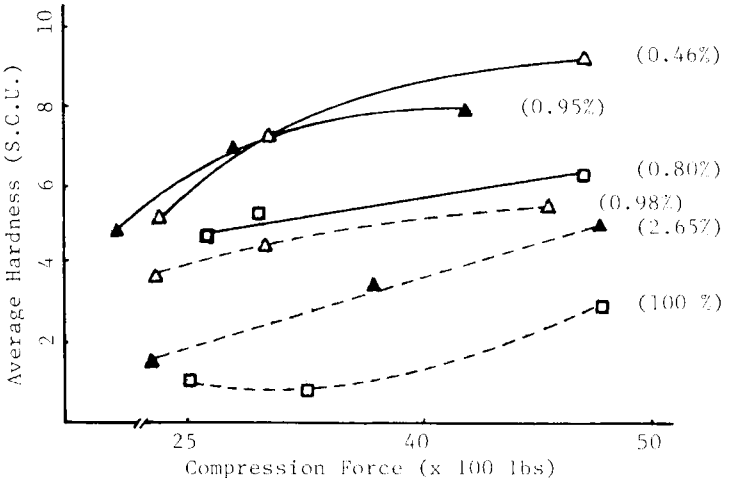


FIGURE 8

Dilution Potential with Acetaminophen (APAP) USP Granular. Key: ▲ = EGC; △ = MCC-1; ◘ = MCC-2; —— = 60% APAP; ---- = 70% APAP; (Figures in parentheses indicate friability loss).

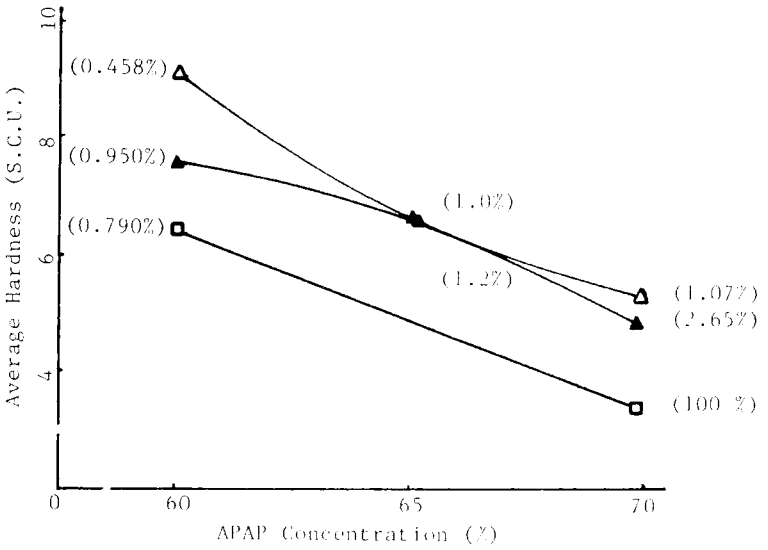


FIGURE 9

Tablet Hardness as a Function of Acetaminophen USP Granular concentration. Key: ▲ = EGC; △ = MCC-1; ◘ = MCC-2; Compaction Force = 4000-5000 lbs. (Figures in parentheses indicate friability loss).

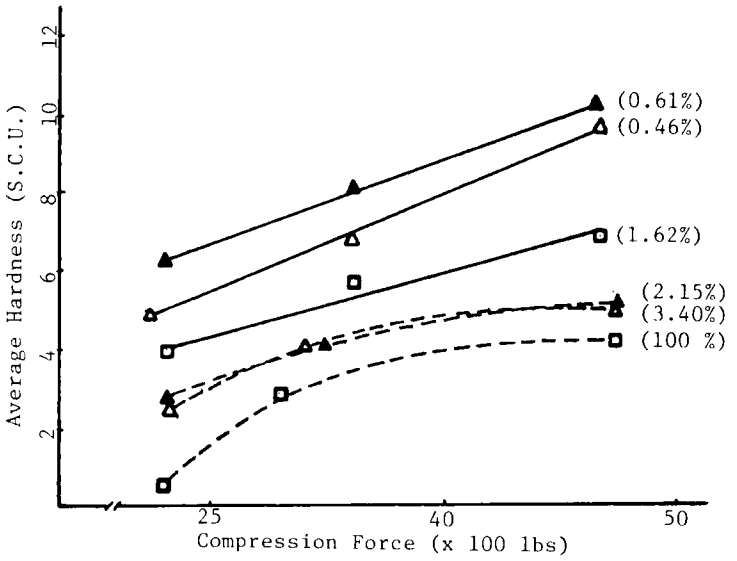


FIGURE 10

Dilution Potential with Ascorbic Acid (AA) USP Fine Granular. Key: ▲ = EGC; △ = MCC-1; □ = MCC-2; —— = 60% AA; - - - - = 70% AA. (Figures in parentheses indicate friability loss).

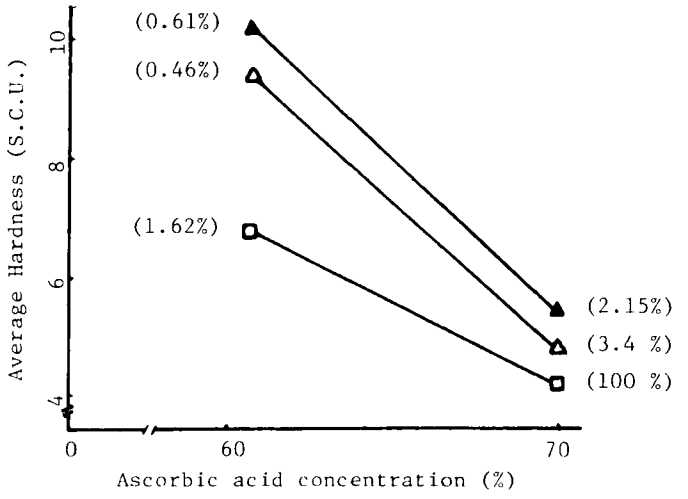


FIGURE 11

Tablet Hardness as a Function of Ascorbic Acid USP Fine Granular concentration. Key: ▲= EGC; △ = MCC-1; □ = MCC-2; Compaction Force = 4000-5000 lbs. (Figures in parentheses indicate friability loss).

EGC possesses a very high dilution potential and is a strong binder even with large amounts of non-compressible active ingredients. The two most non-compressible and common active ingredients that form a large portion of tablet formulations are acetaminophen (APAP) USP granular and ascorbic acid USP fine granular. These two products are often used in the author's laboratories to evaluate the efficiency of direct compression tablet binders.

EGC and MCC-1 produced essentially identical tablets with 60% and 65% APAP and 60% and 70% ascorbic acid respectively. The friability of tablets containing 70% APAP was better with MCC-1 than with EGC. The reverse was true with 70% ascorbic acid. In all cases, MCC-2 lacked the compressiblity of EGC and MCC-1 with lower levels of these active ingredients and failed to produce tablets of acceptable friability with higher levels. Microfine cellulose did not yield tablets of readable hardness values even with much reduced levels of active ingredients than were used with the other celluloses.

## CONCLUSION

It is generally recognized that α-cellulose consists of amorphous and crystalline celluloses and that the crystalline cellulose possesses high compressibility. Specialized and patented process to separate the crystalline cellulose has long been credited with imparting the very high compressibility to MCC-1 and MCC-2. A new grade of α-cellulose, EGC, though not solely microcrystalline in composition and not prepared by a process involving severe acid hydrolysis or heat treatment has demonstrated direct tabletting properties which are equal to, and in some cases, superior than those of microcrystalline cellulose.

## ACKNOWLEDGMENT

The authors wish to express their sincere appreciation and gratitude to the Cellulose Floc Division of James River Corp., Berlin, New Hampshire and Dr. E. E. Morse for their valuable contributions to this study.

## FOOTNOTES

1. Avicel PH101; FMC Corp., Philadelphia, Pa.
2. Avicel PH102: FMC Corp., Philadelphia, Pa.
3. Elcema G-250; DeGussa Corp., Teterboro, New Jersey
4. W. S. Tyler, Inc., Mentor, Ohio
5. O'Haus Model 6000; O'Haus Scale Corp., Union, New Jersey
6. Acetaminophen USP granular, Monsanto Chemicals, St. Louis, Missouri
   Ascorbic acid USP fine granular, Hoffman LaRoche, Nutley, New Jersey
7. Four quart capacity, Patterson-Kelly Co., East Stroudsburg, Pa.
8. Magnesium stearate USP, Mallinckrodt Chemicals, St. Louis, Missouri
9. Colton 204-31 Vector Corp., Marion, Iowa
10. Model 2E, Vector Corp., Marion, Iowa
11. Erweka Model TA3, Chemical and Pharmaceutical Industry Co., Inc., New York, New York
12. Fowler Precision Tools

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