Changes in Material Properties Accompanying the National Formulary (NF) Identity Test for Microcrystalline Cellulose

Harry G. Brittain,[1,2] Geoffrey Lewen,[1] Ann W. Newman,[1] Kenneth Fiorelli,[1] and Susan Bogdanowich[1]

Received April 7, 1992; accepted June 22, 1992

It has been found that the current NF identity test for microcrystalline cellulose is actually an assay of the response of the material to energy dissipation expended during the analysis procedure. The blending step needed to effect suspension of the material results in a disintegration of the microcrystalline particles and a concomitant increase in the viscosity of the slurry viscosity. These effects were shown not to be unique functions of either blender speed or blending time. The passage or failure of a given sample of microcrystalline cellulose under the conditions of the identity test was found to be a consequence of the test conditions used. Any given sample of microcrystalline cellulose can be made to pass the identity test if it is blended for a sufficiently long time or at a sufficiently high speed. The test is sufficient, however, to differentiate powdered cellulose from powdered cellulose.

KEY WORDS: microcrystalline cellulose; National Formulary identity test; powdered cellulose.

INTRODUCTION

In the National Formulary, microcrystalline cellulose (MCC) is described as "purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It contains not less than 97.0 percent and not more than 102.0 percent of cellulose, calculated on the dried basis" (1). The compendial tests listed for this excipient are identification, pH, loss on drying, residue on ignition, water-soluble substances, heavy metals, starch, and assay.

The identification test is designed to differentiate microcrystalline cellulose from powdered cellulose and is actually a suspendability test. This test is performed as follows: "Mix 30 g of microcrystalline cellulose with 270 mL water. Perform the mixing in a high-speed (18,000 rpm) power blender for 5 minutes. Transfer 100 mL of the dispersion to a 100 mL graduated cylinder, and allow to stand for 3 hours: a white, opaque, bubble-free dispersion, which does not form a supernatant liquid at the surface, is obtained" (1).

It has been observed recently that certain lots of microcrystalline cellulose fail the identification test in certain circumstances. Although the test does not reflect on the performance of the excipient in a formulation, failure of a material to pass the identification test does not permit its use. To gain insight into this situation, we characterized the changes in material properties that accompany performance of the identification test.

MATERIALS AND METHODS

Samples of MCC were obtained from a variety of sources, and used as received. The particular materials characterized were obtained from FMC Corporation (Avicel grade PH101, lot 35352) and Edward Mendell Company (Emcocel grade 50M, lots 9314, 9319, and 90224). For comparison purposes, some data were obtained on one lot of powdered cellulose obtained from Reed Chemicals (lot U29393C). Slurries of MCC were prepared in accordance with the NF procedure (1) and blended in a Waring Model 700 commercial blender.

Optical microscopy was used to examine the nature of all dispersions of MCC in water. An aliquot of suspension was removed from a blended mixture and dispersed into a drop of water on a microscope slide. This drop was confined to a well, formed on the slide by a thin border of vacuum grease, which was covered with a coverslip. This arrangement provides a thin optical cell with parallel sides, avoiding the lens effect of water in a standard microscope well and preventing convection currents and evaporation. Photomicrographs of the suspended particles were obtained at magnifications of 25×, 50×, and 100×.

The particle size distribution of suspended MCC particles was obtained using laser light scattering [Malvern Instruments 3600E optical bench, with the 300-mm convergent lens, and Malvern Model-Independent (M-Type) Analysis Software]. For this work, an aliquot of a MCC suspension was dispersed into a stirred sample cell filled with deionized water. Three measurements were made on each suspension, and the resultant particle size distributions were averaged.

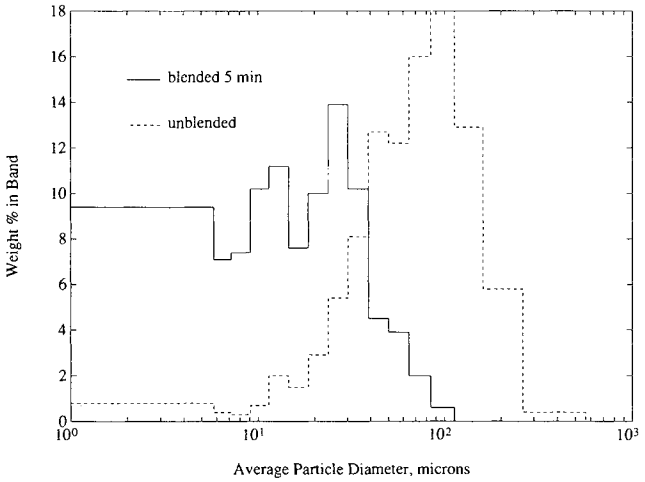

Fig. 1. The effect of blending upon the particle size distribution of a sample of microcrystalline cellulose. The slurry was blended for a period of 5 min, at a blender speed of 16.5 krpm. The distributions for unblended (dashed trace) and blended (solid trace) materials are shown.

[1] Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 191, New Brunswick, New Jersey 08903.
[2] To whom correspondence should be addressed.

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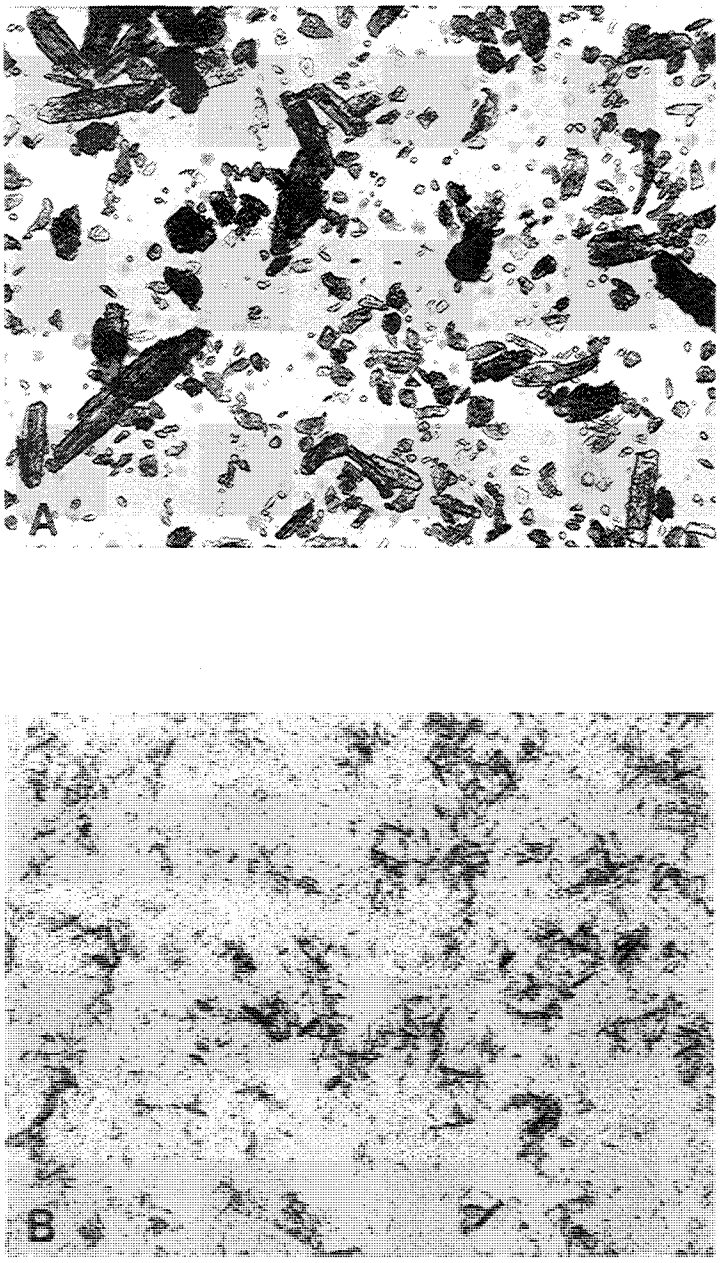

Fig. 2. Photomicrographs of the MCC particle suspension (A) before blending and (B) after blending. 100×.

Further characterization of the MCC suspensions was obtained through measurements of slurry viscosity. The viscosity was measured using a Brookhaven Viscometer, at a motor speed of 30 rpm, and an LV-2 spindle.

An important parameter was measurement of the mechanical performance of the blenders used to produce the MCC suspensions. An optical tachometer was used to measure the frequency of rotation of the blender blades, obtained under unloaded and loaded conditions. The typical uncertainty in the blender speed measurements was estimated as 200 rpm, associated with blade speed fluctuations which were visible in the tachometer readings during the measurement periods.

RESULTS AND DISCUSSION

Effect of the Blending Process on the Physical Properties of MCC

Typical particle size distributions for a MCC sample are illustrated in Fig. 1, with data being presented for both the unblended and the blended material. The size distribution of the unblended material was seen to be dominated by particles having average diameters in the range of 40 to 300 μm. After blending according to the compendial method (1), few particles were found in this size range. It is evident that the blending process produces a much finer particle size distri-

Table I. Effect of Blending Time on the Properties of Microcrystalline and Powdered Cellulose

Sample	Blending time (min)	Particle mean diameter (μm)	Viscosity (cP)	Identity test result
MCC A	0	45	—	—
	5	11	380	Pass
	10	10	620	Pass
MCC B	0	56	—	—
	5	13	270	Fail
	10	11	470	Pass
MCC C	0	53	—	—
	5	13	330	Pass
	10	11	675	Pass
MCC D	0	52	—	—
	5	13	260	Pass
	10	11	380	Pass
Powdered cellulose	0	33	—	—
	5	30	30	Fail
	10	27	60	Fail

bution, with all particles being smaller than 100 μm. These findings were noted for all lots of MCC studied, demonstrating that the main effect of the blending step is to reduce physically the average particle size of the material being tested. This finding is not surprising, considering that MCC is classified as a semibrittle material with respect to crack propagation and fracture mechanics (2).

Further verification of this finding was obtained through studies of the particle morphologies associated with unblended and blended materials. The photomicrographs shown in Fig. 2 clearly indicate that the large crystallites present in the unblended powder are replaced by smaller fibers and crystallite fragments. Very few crystallites with sizes exceeding 100 μm remain intact after the materials are blended. Regardless of the source of MCC, the average particle sizes were observed to decrease from approximately 50–55 to 10–15 μm.

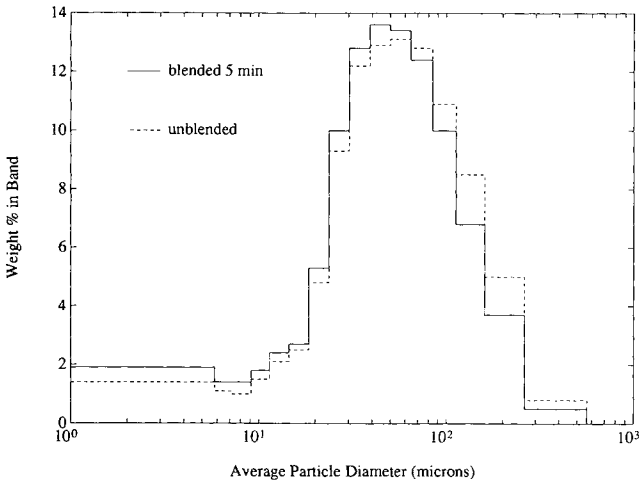

Fig. 3. The lack of effect which blending has upon the particle size distribution of powdered cellulose. The slurry was blended for a period of 5 min, at a blender speed of 16.5 krpm. The equivalent distributions for unblended (dashed trace) and blended (solid trace) materials are shown.

As shown in Table I, the decrease in particle size associated with the blending process is accompanied by a concomitant increase in suspension viscosity. The viscosity of the unblended suspensions increases dramatically, to approximately 250–400 cP, at the conclusion of the blending period.

Effect of Blending on the Physical Properties of Powdered Cellulose

The identity test serves to differentiate MCC from powdered cellulose, since powdered cellulose settles immediately after the blending step. The blending of powdered cellulose according to the NF method does not produce any alteration of the particle size distribution, as illustrated in Fig. 3. The average particle size of this material only decreased slightly when it was processed through the blending step, going from 33 to 30 μm. In addition, only a moderate increase in the viscosity of the suspensions was noted after performance of the test, with a final value of 30 cP being observed (Table I).

These findings indicate that the ability of the suspendability test to differentiate between powdered and microcrystalline cellulose materials is associated with the ability of

Table II. Effect of Loading on Blender Speed[a]

Speed (krpm)	
Unloaded	Loaded
16.6	13.8
19.3	16.5
18.1	15.6
18.0	15.1

[a] The uncertainties in the blade speeds are estimated to be ±0.2 krpm.

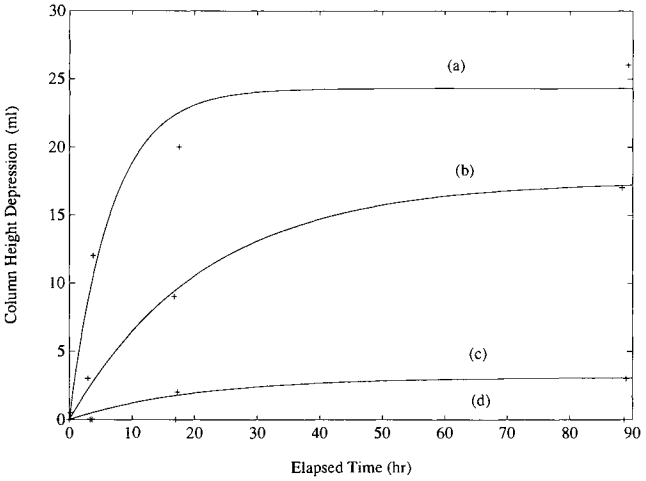

Fig. 4. Column settling heights, measured as a function of the blender speed, during the identity testing of microcrystalline cellulose. Blender speeds of (a) 13.8 krpm, (b) 15.1 krpm, (c) 15.6 krpm, and (d) 16.5 krpm were used. No settling was observed for the trial conducted at 16.5 krpm.

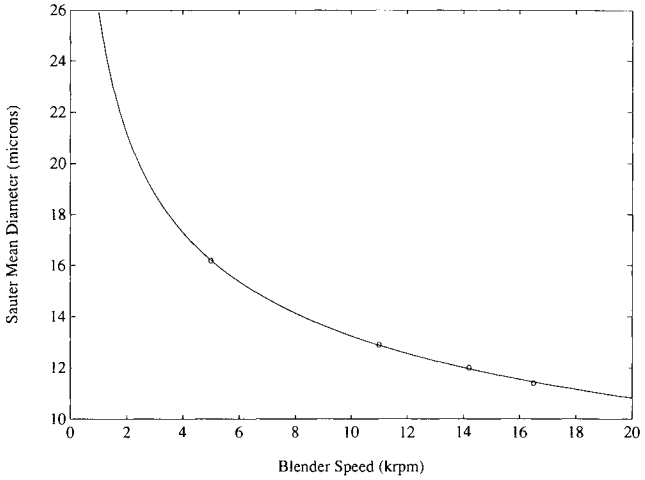

Fig. 5. Dependence of the mean particle size on the blender speed used to conduct the identity test. The particle sizes are shown in terms of their Sauter mean diameters.

the MCC particles to fracture under the conditions of the test. In addition, the large viscosity increments which are associated with the MCC suspensions also contribute to the performance of the test, since particles are less likely to settle out of a more viscous solution.

Effect of Blending Time on the Properties of MCC

Since the USP test specifies a blending time of 5 min, it was important to investigate the effect of blending time on the probability that a given sample will pass the identity test. Several MCC samples were blended at constant speed (approximately 16.5 krpm under loaded conditions) for both 5 and 10 min, with the mean particle size and suspension viscosity being measured. The results of this work are collected in Table I. It was found that doubling the blending time from 5 to 10 min yielded further increases in the viscosity of the suspensions. At the same time, relatively little change in average particle sizes was observed. This finding indicates that the full reduction in particle size is complete very early in the blending process. It is very significant to note that all samples of MCC pass the identity test when blended for the longer period of time, implying that the viscosity increase is essential to the performance of the material.

Continued blending of powdered cellulose yielded a very small decrease in particle size and a small increase in the viscosity of the suspension. This material still failed the MCC identity test, indicating that insufficient particle size reduction and increase in suspension viscosity had taken place.

Effect of Blender Speed on the Properties of MCC

Since the NF test method specifies that the blender be run at 18 krpm when loaded, the effect of blender speed on test performance was studied next. In the previous studies, it was demonstrated that the viscosity of a suspension increased significantly during the blending process, and this phenomenon would certainly affect the velocity of the blender blades. Using a tachometer which was positioned to measure the spindle speed of the blender, it was found that the loaded blender speed was significantly lower than the unloaded speed. The differences are summarized in Table II, and examination of the data reveals that the loss of blender speed upon loading the blender (which is very nearly constant over a wide range of unloaded speeds) is approximately 3 krpm.

This finding implies that a blender must be capable of running at an unloaded speed of approximately 21.0 krpm to ensure that it will be capable of operating at the 18.0 krpm

Table III. Effect of Blender Variables on the Physical Properties of MCC

Loaded speed (krpm)	Blending time (sec)	Particle mean diameter (μm)	Slurry viscosity (cP)	Total number of revolutions (N_{rev})	Normalized energy input ($\Delta E'$)
16.5	15	17.7	ND	4,125	1.6 ± 0.2
16.5	30	15.4	41	8,250	3.3 ± 0.4
16.5	60	14.3	68	16,500	6.5 ± 0.8
16.5	300	11.4	380	82,500	33 ± 4
16.5	600	10.2	620	16,500	65 ± 8
5.0	300	16.2	44	25,000	3.9 ± 0.3
11.0	300	12.9	109	55,000	16 ± 1
14.2	300	12.0	225	71,000	29 ± 4

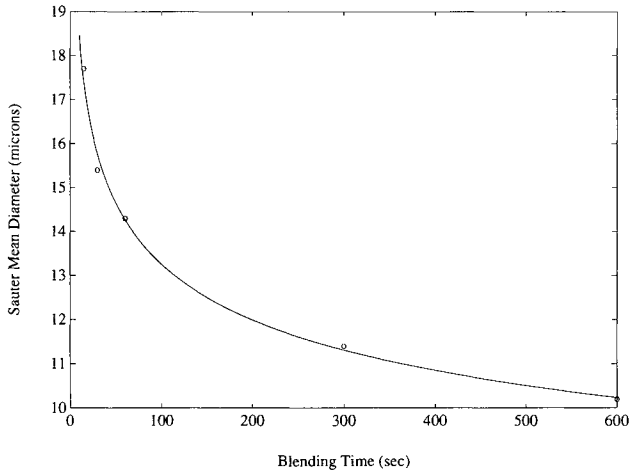

Fig. 6. Dependence of the mean particle size on the blending time used to conduct the identity test. The particle sizes are shown in terms of their Sauter mean diameters.

required by the compendial test. In examining the various blenders on hand, it was found that units which had been heavily used could only achieve velocities in the range of 18 to 19 krpm. These findings indicate that proper performance of the compendial method requires continual replacement of the blender.

Further studies relating the effect of blender speed with the conditions of the MCC identity test were conducted. In one study, several samples of the same MCC lot were blended at loaded speeds ranging from 16.5 down to 13.8 krpm and evaluated according to the compendial suspendability test. The volume of clear fluid appearing at the head of the suspension was monitored as a function of time, and plots of these settling data are presented in Fig. 4. The results clearly demonstrate the effect of decreasing blender speed on the MCC settling rates. For this particular sample, only a loaded blender speed of 15.6 krpm would permit this material to pass the identity test. Running the same acceptable sample at lower blender speeds (i.e., in an inferior blender) would cause the material to fail the test. Another

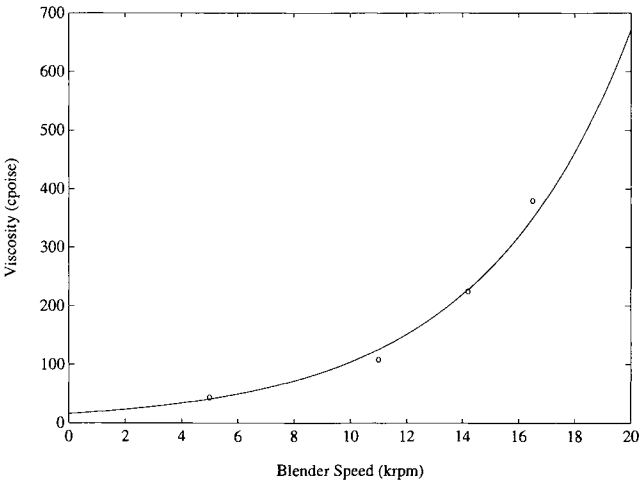

Fig. 7. Dependence of slurry viscosity on the blender speed used to conduct the identity test.

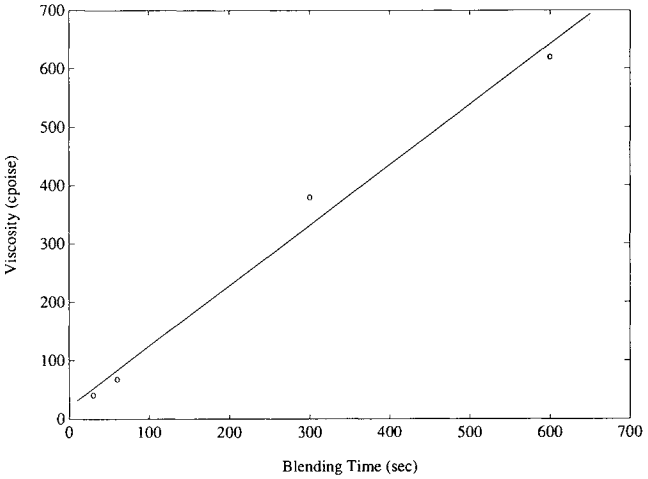

Fig. 8. Dependence of slurry viscosity on the blending time used to conduct the identity test.

MCC sample was found to pass the test when blended at 15.0 krpm but also failed when blended at 14.7 krpm. Different samples of MCC exhibit differing responses to the blender speed, depending on the nature of the forces causing the particles to adhere to each other.

Relation of Total Energy Input and Properties of MCC

All results obtained in the preceding sections indicate that the performance of a given sample of MCC during its identity test are affected both by the blender speed and by the blending time. For samples of MCC which failed their initial test increasing either factor was found to permit passage of the material.

It was also determined that a large drop in blender speed was obtained when the system was loaded by the mixture of water and MCC. This implies that the blender motor is operating to deliver a constant power output, as opposed to a constant blade velocity. The decrease in blender speed un-

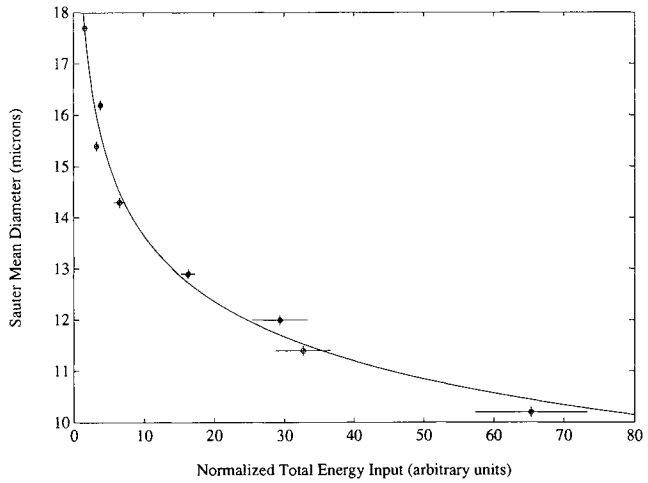

Fig. 9. Dependence of the mean particle size on the normalized total energy input. The filled circles indicate the trials conducted at constant blender speed, while the open circles indicate trials conducted at constant blending time. The curve through the data represents the overall variation of the particle size with $\Delta E'$ for all trials.

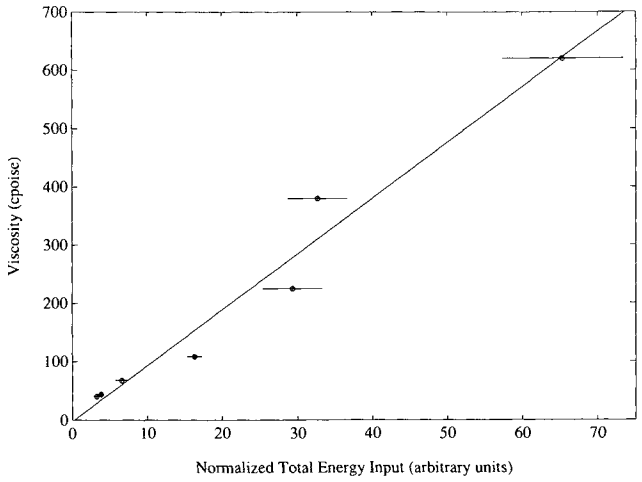

Fig. 10. Dependence of slurry viscosity on the normalized total energy input. The filled circles indicate the trials conducted at constant blender speed, while the open circles indicate trials conducted at constant blending time. The curve through the data represents the overall variation of viscosity with $\Delta E'$ for all trials.

der load is due to an approximately constant power dissipation by the blender system (i.e., a constant loss of rotational kinetic energy per revolution).

It is impossible to define uniquely all of the mechanisms acting upon the system which serve to dissipate the mechanical energy delivered by the motor. The presence of nonconservative forces is implicated by the observed temperature increases of 20–30°C which can be observed in the slurry upon blending. The most obvious forces which would lead to such phenomena include (i) the energy required to break up the aggregate particles, (ii) viscous drag forces acting upon the slurry (as well as the blades), and (iii) cavitation effects due to rapid decompression as the blades spin. While an analytical model of the phenomena taking place in the system is unavailable, it is not difficult to estimate the total mechanical energy dissipated by the system.

Since the ability of a given sample of MCC to pass the identity test requires a drastic reduction in material particle size, it can be assumed that the majority of the energy input into the blender system is used to break up the particle aggregates. In that case, there should be a correlation between the MCC particle size after blending and the total energy input into the system to effect that particle size reduction.

The rotational kinetic energy of the motor-blade assembly is given by the quantity:

$$KE_{rot} = (\tfrac{1}{2})\,(I\omega^2) \tag{1}$$

where I is the moment of inertia of the rotating assembly, and ω is the angular frequency of rotation. If the angular frequency drops from ω_1 to ω_2, the total loss of rotational kinetic energy is given by

$$\Delta KE_{rot} = (\tfrac{1}{2})\,I\,(\omega_1^2 - \omega_2^2) \tag{2}$$

It is not necessary to know the value of I exactly, since the approximate approach taken here obviates the need for such precision. In addition, the value of ω is a function of position for the material inside the blender, as the mixture cannot be expected to be in a state of solid rotation with the blades. The energy lost per revolution may be assumed to be equal to the energy difference between the loaded and the unloaded cases and normalized to the condition of $I = 2$.

Under these conditions, the normalized total energy dissipated during a blending experiment ($\Delta E'$) is calculated as

$$\Delta E' = |(\omega_1^2 - \omega_2^2)|N_{rev} \tag{3}$$

where N_{rev} is the total number of revolutions executed by the blades. The units of energy dissipation are now to be regarded as arbitrary. By measuring the unloaded speed, the loaded speed, and the total blending time, a fairly accurate estimate of $\Delta E'$ can be obtained for a blending experiment.

To test this simple model, a single lot of MCC was subjected to a series of experiments, in which either blending time or blender speed was varied while the other was held constant. Measurements of both mean particle size and viscosity were made on the suspensions in order to characterize the effects produced by blending under these various test conditions. The quality of the particle size determinations was verified using optical microscopy, and it was determined that the particle size results were accurate. A tachometer was used to measure the actual loaded speed in most of the trials, but for very short blending times it was physically impossible to make the blender speed measurements. In those instances, a decrease in speed of 3 krpm was assumed for the loaded condition.

The results of these studies are presented in Table III. The data indicate that particle mean diameter decreases with increases in both blending speed and time, while the viscosity increases as the test parameters are increased.

The effects of both blender speed and blending time on the MCC mean particle size are illustrated in Figs. 5 and 6. In both instances, the data points appear to be adequately fitted by an exponential function. The effects of both blender speed and blending time on the MCC slurry viscosities are shown in Figs. 7 and 8, respectively. Although the viscosity of the slurries increases in an exponential manner with respect to blender speed, the viscosity exhibits a linear increase with respect to blending time. The curves drawn through the data in Figs. 5 through 7 were calculated from linear regression analysis.

By plotting the mean particle diameter and viscosity data against the total energy input to the blender system, it was found that the trials conducted with constant blender speed (and variable blending time) or constant blending time (with variable blender speed) all yielded data which could be plotted on the same curve. These plots are given in Figs. 9 and 10 and clearly demonstrate that the mean particle size and slurry viscosity are determined by the total energy input to the system and that it matters little how that energy is fed into the system. There is no real difference in the generated MCC physical properties between slow blending for long time periods and high-speed blending conducted for short periods.

CONCLUSIONS

It has been demonstrated that the NF identity test for microcrystalline cellulose is actually a test of the response of the material to energy dissipation during the process of blending. This response is characterized by disintegration of

the microcrystalline particles and a concomitant increase in the viscosity of the slurry viscosity. These effects cannot be considered as unique functions of either blender speed or blending time. The passage or failure of a given sample of microcrystalline cellulose under the conditions of the identity test is a consequence largely of the test conditions used, and not of the identity of the sample. Any given sample of MCC can be made to pass the identity test if it is blended for a sufficiently long time or at a sufficiently high speed. The test is sufficient, however, to differentiate powdered cellulose from microcrystalline cellulose.

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