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Research Article

Instrumentation of a High-Shear Mixer: Evaluation and Comparison of a New Capacitive Sensor, a Watt Meter, and a Strain-Gage Torque Sensor for Wet Granulation Monitoring

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A high-shear mixer was instrumented with a new capacitive sensor, a watt meter, and a strain-gage torque sensor. The output from the capacitive sensor was split into two channels, which monitor both resistive and capacitive changes during the granulation process. The outputs of the devices were related to properties of the wet granulation. The percentage moisture content related linearly to the amplitude channel response. Yield values provided a rheological property to relate with power consumption and torque measurement. Power consumption and torque furnished a similar map of the granulation process. The amplitude channel of the capacitive sensor appears to be more clearly differentiated between binder levels in hydrous lactose-HPMC granulations than either power consumption or torque measurement, based on particle size distributions.

KEY WORDS: capacitive sensor; power consumption; torque; yield value; granulation monitoring; granulation end point.

INTRODUCTION

Wet granulation has been used extensively in the pharmaceutical industry to improve formulation characteristics. This unit process still requires the knowledge and experience of a formulator to determine an appropriate end point. Over the last few decades many tools have been developed to aid the formulator in determining when the end point has been reached. With the advent of high-shear granulators end-point determination has become even more critical.

Amperage (1), power consumption (2–4), torque (5–8), and motor slip (9–11) have been monitored as translated effects of the granulation process on the mixer. The Diosna-Boots Mixing Probe (12), conductivity (13), capacitance (14–15), and a probe vibrational analysis technique (16,17) directly monitor changes in the wet mass. All of the methods used to monitor this unit operation give a "map" of the granulation process which can be used for quality control to establish reproducibility of the wet granulation or as an aid for formulation development.

Few reports in the literature have focused on relating properties of the wet granulation to the output of the monitoring device. In addition, a limited number of studies to compare the granulation sensors qualitatively have been reported. In the present study a new capacitive sensor, a watt meter, and a strain-gaged mixer shaft were utilized to monitor the granulation process. The objectives of this study are (i) to characterize the outputs from the capacitive sensor with known electrical and chemical properties, calibrate the torque-sensing strain gages, and establish the reproducibility of the instrumentation; (ii) to relate the outputs from each device to properties of the wet granulation; and (iii) to compare qualitatively simultaneous readings from the three devices.

INSTRUMENTATION AND DATA ACQUISITION OF THE MIXER

A 10-liter vertical high-shear mixer (Model W-10-B, Littleford Bros., Inc., Florence, Kentucky) equipped with an impeller was instrumented with a new capacitive sensor through a hole machined into the mixer lid. The current version of the probe utilizes the same sensor as the earlier version (14,15); however, the output has been separated into two components to monitor purely resistive and capacitive changes that occur during the granulation process.

The probe consists of an inductance coil connected in parallel with two sensing electrodes. The inductance coil and electrode combination together with associated electrical components comprise an inductance-capacitance (LC) resonant oscillator circuit. The amplitude and frequency of the oscillator signal are functions of the resistive and capacitive components, respectively, of the load across the probe. A change in resistance across the probe causes a change in the output of the amplitude channel but does not affect the output of the frequency channel. Conversely, a change in the

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Table I. Effect of Various Loads on the Probe Output

Probe load	Amplitude channel, V (dc)	Frequency channel, V (dc)
Baseline	9.00	9.00
82kΩ	7.44	8.19
62kΩ	7.05	8.47
47kΩ	6.31	7.46
39kΩ	5.74	8.27
20kΩ	4.93	8.32
15kΩ	3.19	8.70
10kΩ	2.04	8.90
1 pF	8.75	6.39
2 pF	8.62	4.29
3 pF	8.45	2.68
4 pF	8.32	1.96
5 pF	8.22	<0

	Dielectric value[a]		
DI water	78.5	5.42	<0
Methanol	32.6	7.13	<0
Isopropanol	18.3	7.49	0.20
Chloroform	4.8	8.82	6.65
Triethylamine	2.4	8.91	8.06
Carbon tetrachloride	2.2	8.94	8.12
Pentane	1.8	8.96	8.38

[a] From R. C. Weast. *Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, 1989–1990, pp. E51–E53.

capacity across the probe causes a change in the output of the frequency channel but does not affect the output of the amplitude channel. The amplitude and frequency baseline outputs are calibrated with no load across the probe to tune the probe to the reference resonant frequency. With the probe inserted in the granulation, a load exists across the probe which detunes the resonant circuit. The amplitude of the oscillator signal and the amplitude channel output are proportional to the moisture content of the medium surrounding the probe. The frequency of the oscillator signal and the amplitude of the frequency channel output are proportional to the density or dielectric of the medium surrounding the probe. The amplitude and frequency channel outputs of the probe are direct-current (dc) voltages which are functions of the moisture content and density of the medium surrounding the probe.

An alternating-current (ac), three-phase, three-wire watt transducer (Model PC5-023D, Ohio Semitronics, Inc., Columbus) utilizing two Hall Effect sensors was wired into the mixer to monitor power consumption. The output from the watt meter is proportional to the real average power.

Hall Effect sensors sense the magnetic field generated by the current and multiply the current and voltage via a vector multiplication to obtain power. This vector multiplication accounts for the power factor (Cos θ), which is the angular displacement between the current and the voltage resulting from variable inductive and capacitive effects present in an ac motor. Changes in motor efficiency and frictional losses in the drive train can have an effect on the power consumption. In the present studies all granulations were preceded by a 5-min dry mix time to allow for changes in viscosity of the grease seals and frictional losses to the drive train. The watt meter generates a 0- to 10-V dc output with a factory-determined calibration factor of 6 kW per 10 V dc.

Direct torque was measured by mounting two pairs of strain gages (Type EA-06-062TW-120, Micro-Measurements, Raleigh, North Carolina) 3 in. below the impeller aligned at 45° from the normal axis on a machined mixer shaft 180° apart and wired in a Wheatstone bridge configuration that maximizes torque sensitivity and minimizes temperature and bending effects. The strain-gage wiring terminates on a slip ring assembly (Model S4; Michigan Scientific Corp., Charlevoix, Michigan) at the end of the mixer shaft. The bridge is excited and the signal is amplified and filtered through an amplifier recorder (Recorder 2200S, Gould Inc., Cleveland, Ohio). A 1-Hz filter was used to eliminate low-frequency fluctuations induced by the belt-drive system.

The analog signals from all three devices are processed by a PC 80386 (IBM, Armonk, New York) in conjunction with an analog-to-digital (A/D) converter (Model DT2801-A, Data Translation, Inc., Marlborough, Massachusetts). The data acquisition program used in all experiments has the capability of sampling up to four channels simultaneously, with an option to change the number of A/D conversions per data point. In these studies, each data point is the average of 300 A/D conversions, resulting in a 1.38-sec sampling rate for four channels.

Table II. Manufacturing Parameters

Parameter	Dical	MCC 102	MCC 101	MCC 101	Lactose
Figure(s)	2	3	4, 5	6	7, 8
Dry binder	PVP K 29/32	NA	NA	NA	HPMC
Dry binder (%)	5	0	0	0	2, 4, 6, 8
Mixer charge (kg)	2.5	1.0	0.9	0.9	2.0
Mixer speed (rpm)	500	500	500	500	400
Dry mixing (min)	5	5	5	5	5
Pump on (sec)	20	20	20	20	20
Granulating fluid	DI water	DI water	DI water	DI water	DI water
Amount of fluid (%)	23.1	See Fig. 3	See Fig. 4	209.9	16.8
Addition rate (g/min)	216	169–422	211	212	177
Wet massing time (sec)	30	0	0	0	20

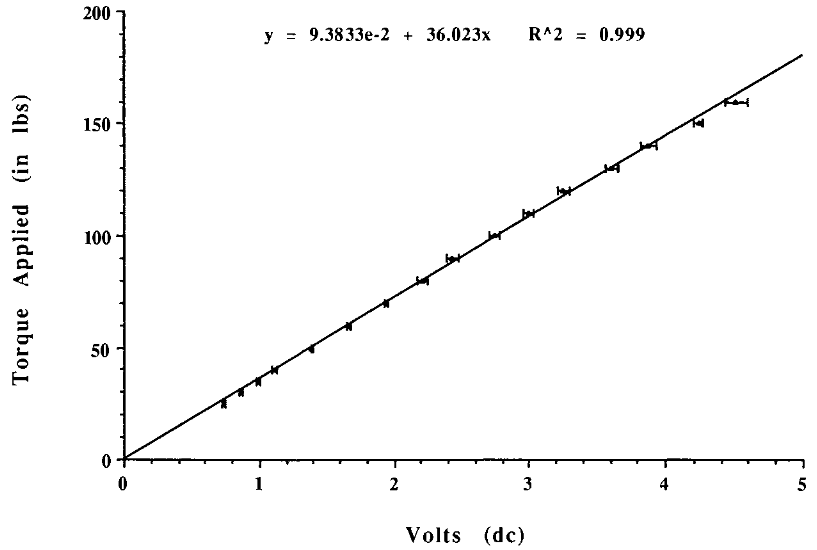

Fig. 1. Calibration of strain gages for torque measurement.

MATERIALS AND METHODS

Characterization of the Capacitive Sensor Outputs, Calibration of the Torque-Sensing Strain Gages, and Establishment of Reproducibility

Resistors and capacitors of known value were placed across the probe in parallel. In addition, the capacitive sensor was submerged in solvents of known dielectric value. Table I lists all resistors, capacitors, and solvents used in this experiment. The voltages displayed in Table I are the final values reached while under a given load.

A torque wrench (Craftsman Microtork Wrench, Sears, Roebuck and Co., Chicago, Illinois) with a 25- to 250-in. lb (inch pounds) range was used to calibrate the strain-gage system.

The reproducibility of the monitoring devices was established by granulating dicalcium phosphate anhydrous (Di-

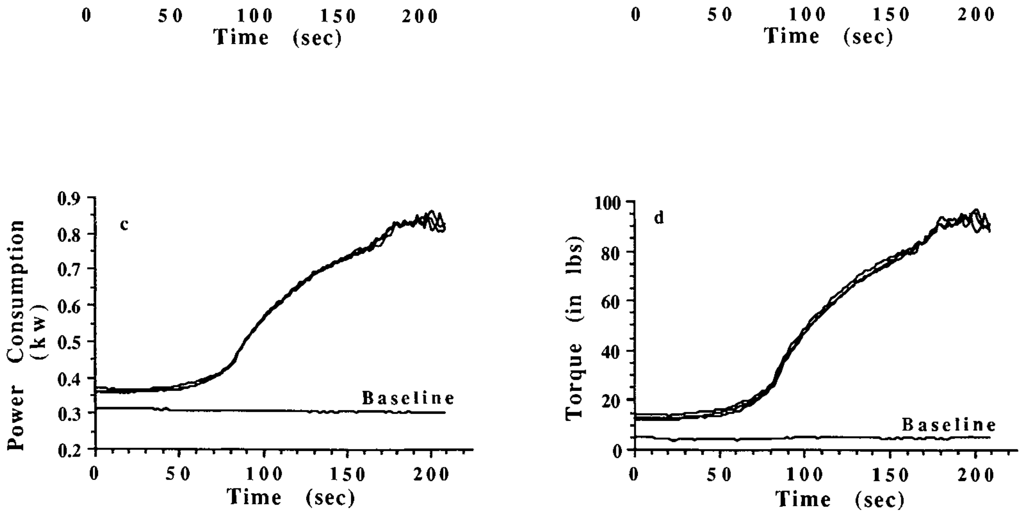

Fig. 2. Instrumentation response to the granulation of Dical with 5% PVP K 29/32 as a dry binder in triplicate: (a) amplitude channel, (b) frequency channel, (c) watt meter, and (d) strain-gage torque sensor.

cal) (Rhone-Poulenc Basic Chemicals Company, Shelton, Connecticut) and 5% Plasdone K-29/32 (PVP K 29/32) (GAF Chemicals Corp., Wayne, New Jersey) as a dry binder using deionized water (DI water) as the granulating fluid metered with a peristaltic pump (No. 7553-00, Cole Parmer, Chicago, Illinois). Table II lists the granulation parameters, excipients, and percentages used based on the total charge weight. To eliminate variability, all excipients used in these studies were from the same manufacturers' lot.

Relationship Between Instrumentation Outputs and the Wet Granulation

Granulations of microcrystalline cellulose (MCC 102) (Avicel PH102, FMC, Newark, Delaware) were prepared as per Table II to correlate the moisture content with the amplitude channel. DI water was metered at varying rates over the same period of time for seven granulations of MCC 102. The granulator was immediately stopped when water addition ended. Samples of the granulation were assayed for the percentage moisture content using an automated Karl Fisher titrator (K-F Accessory Model 392, Titrimeter Model 395, Fischer Scientific, Pittsburgh, Pennsylvania).

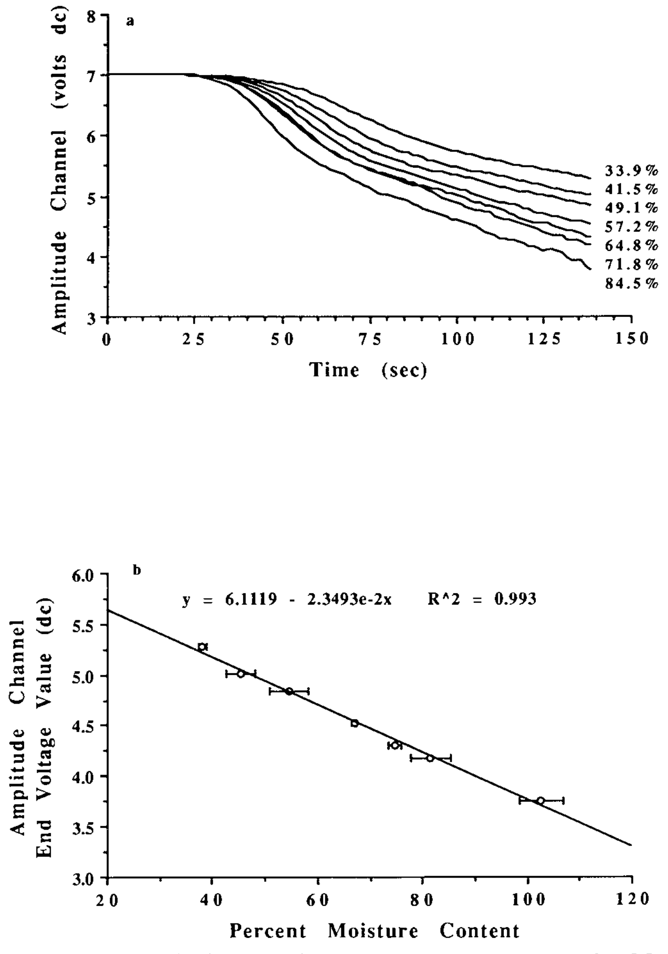

Fig. 3. (a) Amplitude channel response to the granulation of MCC 102 with varying amounts of water. (b) Relationship between the end voltage value of the amplitude channel response for the granulation of MCC 102 with varying amounts of water and the percentage moisture content.

Granulations of microcrystalline cellulose (MCC 101) (Avicel PH101, FMC) were prepared as per Table II to correlate the yield value of the wet granulation to power consumption and torque measurements. DI water was metered at the same rate over an increasing period of time for five granulations of MCC 101. The granulator was immediately stopped when water addition ended. Samples of the granulation were tested using a Haake Rotovisco (Model RV20, Fisons Instruments, Saddle Brook, New Jersey). The Rotovisco was equipped with a PK100 sensor and a PQ2 plate to form a parallel-plate configuration. A low rate of shear was used to alleviate slippage. The Rotovisco was operated with a 1.67-mm gap setting and programmed to increase the shear rate from 0 to 0.08 $\sec^{-1}$ over 5 min. Each sample was equilibrated for 2 min between the parallel plates prior to testing.

Comparison Between Power Consumption and Torque Measurement

MCC 101 was wet granulated as per Table II in duplicate to compare qualitatively the outputs from the watt meter and strain-gaged torque sensor. Data were acquired from each sensor using the current PC-based program and an oscilloscope (Model 420, Nicolet Instrumentation Corp., Madison, Wisconsin). The oscilloscope sampled both devices every 5 msec and fast Fourier transforms were performed on these

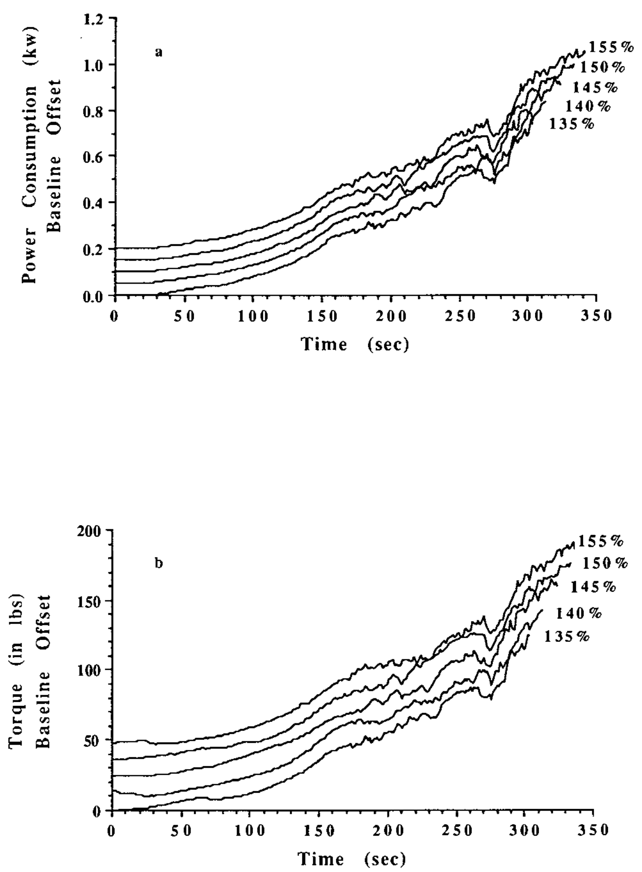

Fig. 4. Instrumentation response to the granulation of MCC 101 with varying amounts of water: (a) watt meter and (b) strain-gage torque sensor.

outputs. The strain-gage signal was unfiltered in the oscilloscope study.

Comparison Among All Four Outputs

Granulations were prepared in duplicate using hydrous lactose (No. 80M, Sheffield Products, Memphis, Tennessee) and varying amounts of hydroxypropyl methylcellulose (HPMC) (Methocel E15-LV Premium, Dow Chemical, Midland, Michigan) as a dry binder as per Table II under identical manufacturing conditions. The hydrous lactose–HPMC dry binder formulations were immediately dried without wet screening in a fluid bed drier (Model WSG3D, Glatt Air Techniques Inc., Norwood, New Jersey). The dried granules were sieved through a 10-mesh screen (U.S. Standard Sieve Series, Fischer Scientific, Springfield, New Jersey) in order to obtain a usable range of granules since this mixer is not equipped with a chopper. Particle size distributions of the dried granules smaller than 10 mesh were determined in triplicate using a sieve shaker (CSC Scientific Sieve Shaker, CSC Scientific Company Inc., Milford, Connecticut) and standard screens. The percentage greater than 10 mesh ranged from 20 to 25% of the total dry granule yield and was considered approximately equivalent for all granulations.

RESULTS AND DISCUSSION

Characterization of the Capacitive Sensor Outputs, Calibration of the Torque-Sensing Strain Gages, and Establishment of Reproducibility

Table I shows the effect of resistors, capacitors, and solvents placed across the probe in parallel. As resistance decreases, an increase in the amplitude modulation of the oscillating signal occurs, resulting in a larger dc voltage drop. Conversely, an increase in resistance results in a decrease in the change of the amplitude modulation of the signal. The addition of water simulates the effect of lowering resistance. The response to resistors by the frequency channel can be attributed to the small amount of capacitance a resistor contains. Increasing the capacitance placed across the probe causes a change in the frequency modulation, which results in a proportional drop in voltage for the frequency channel. The dielectric medium or density of the granulation in contact with the probe simulates the effect of capacitors. The amplitude channel is only slightly influenced by capacitors due to the extremely high resistance they possess.

The effect of solvent or dielectric value on the amplitude

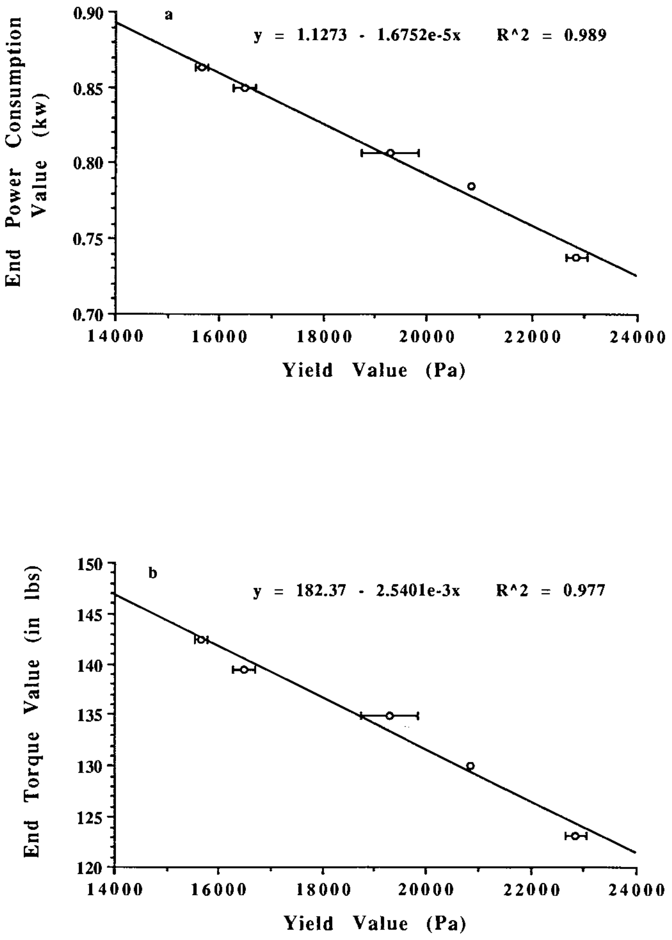

Fig. 5. Relationship between (a) end power consumption value and (b) end torque value for the granulation of MCC 101 with varying amounts of water and the yield value for the MCC 101 granulations.

and frequency channels confirms the resistive and capacitive data. A linear relationship exists between the frequency channel voltage change and the dielectric value of the solvents (regression equation, $y = -0.204 + 0.494x$ $R^2 = 0.999$). The dielectric values of methanol and DI water were outside the frequency channel operating range.

Calibration of the strain-gage mixer shaft was performed using a torque wrench. Figure 1 shows the voltage output from the strain gages versus the applied torque. The values indicated in Fig. 1 are the averages of 10 replicate loads, with the standard deviations indicated by error bars.

Figures 2a, b, c, and d establish the reproducibility of the amplitude channel, frequency channel, watt meter, and strain-gage torque sensor, respectively, for the granulation of Dical with 5% PVP K 29/32 as a dry binder in triplicate. The unloaded signal from each device with the mixer running is superimposed on each graph as a reference point. The variability associated with the frequency channel in Fig. 2b is to be expected since this component of the signal responds to the density of the granulation which is flowing randomly around the probe.

Relationship Between Instrumentation Outputs and the Wet Granulation

Figure 3a represents the response of the amplitude channel to seven granulations of MCC 102 with varying levels of water metered over the same period of time. Figure 3b shows a linear relationship between the end voltage value of the amplitude channel and the percentage moisture content of the MCC 102 samples determined by Karl Fischer titration. Each sample was titrated in triplicate. The discrepancy between the percentage of water added and the amount determined by titration is due to the initial moisture content of MCC 102, which was determined prior to granulation to be 5.1%. In addition, at higher moisture contents (i.e., 71.8 and 84.5%), as granule formation begins, granules adhere to the walls of the mixer, removing these granules from significant further water addition and leaving the free-flowing granules with a disproportionate amount of moisture. The capacitive sensor is positioned in the mixer to monitor the free flowing granules. In an earlier publication, Fry *et al.* (15) showed a linear relationship between the percentage of water added to lactose granulations and the end voltage value from the capacitive sensor.

A few reports have appeared in the literature which have attempted to establish a correlation between rheological properties of the wet granulation and instrumentation outputs. Parker *et al.* (18–20) and Hancock *et al.* (21) have developed a mixer torque rheometer to establish a correlation between the viscosity of MCC granulations in the capillary region of liquid saturation and torque measurement.

During wet granulation material is undergoing agglomeration and deagglomeration. Power consumption and torque measurements increase throughout this process as a result of the resistance the granulation presents to the impeller. This resistance is due to the material coming into contact with the impeller and undergoing deformation in the wet state. Therefore, yield values were thought to be an appropriate rheological parameter of the wet granulation to relate to the outputs of the watt meter and torque sensor. Five granulations of MCC 101 were prepared using increasing amounts of DI water metered at the same rate. Figures 4a and b show the watt meter and strain-gage torque sensor output for these granulations, respectively. The baseline is offset in each figure so a visual distinction can be made between the granulations. At the end of each granulation samples were evaluated using the Haake Rotovisco. The yield values of the MCC 101 granulations decreased as the water level increased in each of the five granulations. The yield value indicates the value of shear stress τ [pascals (Pa)] at which the material yields under a given shear rate D (sec^{-1}). Figures 5a and b show the relationships between the mean yield value ($n = 3$) and the end power consumption and torque sensor output, respectively. For practical measurement using the Rotovisco, the MCC 101 granulations had a moisture content in the capillary region of liquid saturation (22) similar to that of Parker *et al.* (18–20) and Hancock *et al.* (21).

Comparison Between Power Consumption and Torque Measurement

Figure 6a shows the voltage output for the watt meter and torque-sensing devices while continuously adding DI

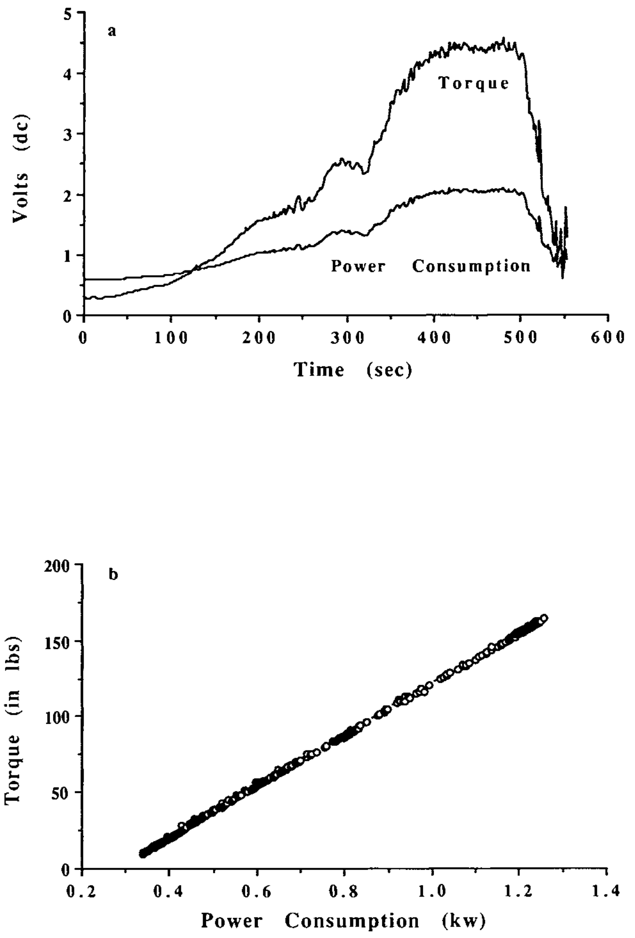

Fig. 6. (a) Power consumption and strain-gage torque sensor response to the granulation of MCC 101 with water. (b) Relationship between torque and power consumption for the granulation of MCC 101 with water.

water until the MCC 101 was overgranulated. The curves of both devices are remarkably similar. A similar observation has been reported previously by Beir *et al.* (4). Figure 6b relates the power consumption (kW) curve to the torque (in. lb) curve shown in Fig. 6a. The data presented in this granulation study were obtained with the PC-based data acquisition program described earlier. A repeat of the previous MCC 101 granulation, using a digital oscilloscope for data acquisition without filtration of the torque signal, revealed outputs similar to those of the PC data acquisition system. The watt meter and strain-gage torque sensor outputs were then subjected to fast Fourier transforms (FFT). FFT indicate the magnitude and distribution of events occurring at different frequencies. FFT analysis revealed that direct torque measurement sensed higher-frequency events due to material impacting on the impeller. However, the increased sensitivity detected by FFT of the torque sensor did not provide any advantage for interpretation of the granulation process over the watt meter in this study.

Comparison Among All Four Outputs

Hydrous lactose–HPMC granulations were prepared in duplicate to compare qualitatively the outputs of all three devices. By varying the dry binder level and keeping the amount and rate of water addition the same, a system was developed which alters the water available to the granulation and also changes the rheology of the granulation.

As the binder level increases, the same amount of water will cause the binder to hydrate and/or swell to a lesser extent, therefore causing a decrease in the availability of water to the granulation since it is tied up in the hydrating and/or swelling process. If there is less water for the granulation to utilize with increasing binder level, then the electrical resistance of the granulation should increase. Figure 7a demonstrates this effect, as seen by a decrease in the rate and extent of the amplitude channel output as the binder level increases. The watt meter and torque sensor shown in Figs. 7b and c respond to the same process; however, in this case the differences are attributed to the rheological changes that occur as a result of the inability of the binder to function well at higher levels without an increase in water level. The frequency channel output in Fig. 7d is not as clear, since this component of the resonating signal changes due to alterations in the capacitance or density of the granulation flowing around the probe.

The important features to note when comparing the outputs from the amplitude channel, watt meter, and strain-gaged torque sensor are the initial and final stages of water addition and the wet massing phase. The initial stage of water addition (up to 100 sec) shows a similar differentiation among the binder levels for all three outputs in rank order. During the final stages of water addition the three devices begin to differ in their response to the granulations. Power consumption and torque curves converge on the same approximate response at about 120 sec and diverge slightly

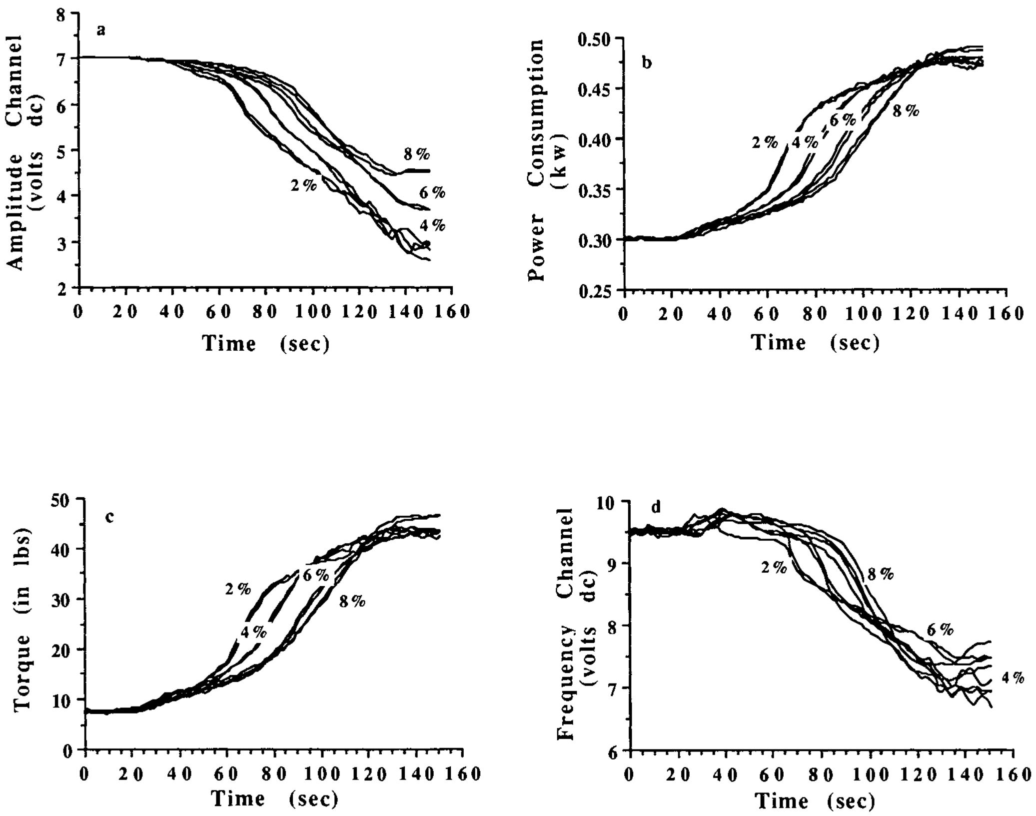

Fig. 7. Instrumentation response to the granulation of hydrous lactose with varying levels of HPMC as a dry binder in duplicate: (a) amplitude channel, (b) watt meter, (c) strain-gage torque sensor, and (d) frequency channel.

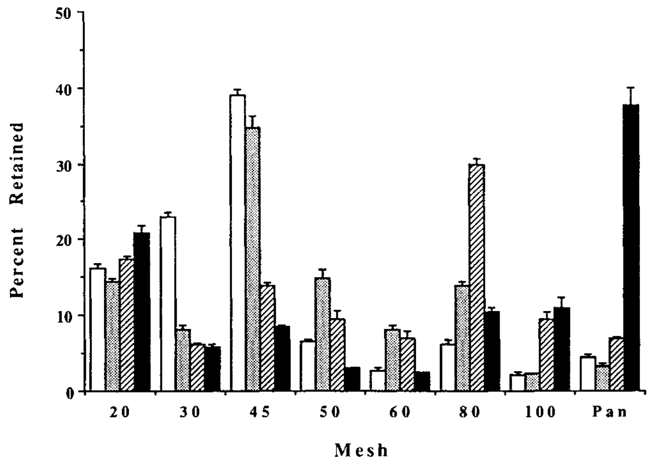

Fig. 8. Effect of HPMC dry binder level on the particle size distributions of hydrous lactose granulations: (□) 2% HPMC; (▒) 4% HPMC; (▨) 6% HPMC; (■) 8% HPMC.

until water addition ends at 130 sec. The convergence of power consumption and torque measurement profiles can be attributed to the competing effects of viscosity and agglomeration. At each binder level the contributions of these effects differ, but overall they present the same resistance to the impellers. The amplitude channel response retained the same rank order for binder level, with the 2 and 4% binder levels converging near the end of water addition. During wet massing power consumption and torque measurements diverged further, with the 8% binder level displaying the highest response value in the end, while the other levels converged to approximately the same value. The amplitude channel response continued to retain rank order throughout the wet massing phase, with the 2 and 4% levels converging.

Sieve analysis in triplicate of the hydrous lactose–HPMC granulations supports the instrumentation data (Fig. 8). A single set of particle size distributions for each binder level is presented. As the binder level increases the particle size distribution shifts to a smaller particle size, indicating that the binder performed more effectively at lower levels. The 2 and 4% binder levels have a similar distribution, with the 4% level shifted slightly to a smaller particle size. At levels of 6 and 8% the particle size distribution continues to shift to a much smaller size. In this experiment, by changing the binder-to-water ratio (which affects the binder function and, ultimately, the particle size distribution), the amplitude component of the capacitive sensor appears to differentiate between binder levels more clearly than either power consumption or torque measurement.

Our experience with the capacitive sensor indicates that the probe is rugged enough to be used in production-scale equipment. The main advantage of this device is that the sensor directly monitors the granulation. Torque and power consumption are dependent on both the mixer and the granulation. The only requirement of the capacitive sensor is that the probe must be positioned in a region of the mixer where the granulation is free flowing.

CONCLUSIONS

The instrumentation of the high-shear mixer used in these studies is reproducible. The amplitude channel monitors moisture content and distribution due to resistive changes. The frequency channel responds to capacitive changes which reflect the density of the granulation flowing around the probe. The variability in the density of the granulation flowing around the probe makes it difficult to evaluate this output.

The yield value is a rheological property of the wet granulation which relates linearly with power consumption and torque measurements in the moisture ranges used in this study. Direct torque measurement taken from the rotating shaft is more sensitive than watt meter measurements, but this sensitivity did not offer any advantage over power consumption in evaluating the granulation process.

Power consumption and torque measurement provided tools to monitor the granulation process which respond to changes in the rheological properties of the wet granulation. In contrast, the amplitude component of the resonating signal monitors water distribution. Since rheological changes are a consequence of water addition, based on the lactose–HPMC granulations, monitoring the water distribution appears to differentiate more clearly between the binder levels than monitoring rheological changes.

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