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MONITORING THE GRANULATION PROCESS IN A HIGH SHEAR MIXER/GRANULATOR: AN EVALUATION OF THREE APPROACHES TO INSTRUMENTATION

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ABSTRACT

A high shear vertical mixer/granulator was instrumented to monitor power consumption, direct torque and reactive torque. All three methods were used to determine their ability in describing the granulation operation. Of the three methods used, direct torque generated the most descriptive profile of the granulation process.

Two formulations were manufactured making use of direct torque in detailing the massing process. End-points were determined and the granulations produced were shown to yield tablets with acceptable hardnesses. One formulation was intentionally overwetted and the change in direct torque monitored to demonstrate the ability of the transducer to detail the massing process. Large fluctuations in torque, during the terminal phase of granulating, were seen and related to the doughy consistency of the final product.

It was concluded that torque measurements, preferably direct, are needed to more precisely define granulation end-points. These types of measurements are needed to optimize the granulation unit operation during product development.

INTRODUCTION

The unit operation of wet granulation plays an important role in the fabrication of solid pharmaceutical dosage forms (1). It is the properties of the manufactured granules which determine, in-part, the ultimate quality of the solid dosage form. It is interesting that the determination of the amount of granulating fluid required and the powder massing end-point is done, by some, on an intuitive level. Testing the wetted mass by hand is still widely practiced and even considered an artform by many.

Variation in the quality of drug and excipients may require different amounts of granulating fluid to obtain similar granule quality seen with previous batches. Therefore, this operation is often difficult to reproduce and scale up due to the lack of a precise method to detect granulation end-point.

Several approaches have been used to determine the granulation end-point with the most prevalent relying on various electrical measurements of the drive motor. These typically include current, voltage, power consumption and motor speed.

In a series of publications by Leuenberger and associates (2-7), they demonstrated that the agglomeration process could be monitored by power consumption of the mixer. They were able to relate the electrical power consumed by the mixer to the amount of granulating fluid added to the powder mass. A plot of power consumption against the amount of granulating fluid resulted in a profile that was divided into five phases which were used to define the agglomeration process (Figure 1). Phase I represents the moistening of the powder bed without the formation of liquid bridges between individual particles. As Phase II is approached, liquid bridges begin to build. At Phase III, the filling of interparticular voids is noted. As more granulating fluid is added, Phase IV is reached and partial saturation of the interparticular voids is seen. If additional fluid is added, phase inversion is seen and a suspension is achieved. Thus, the powder bed is overwetted and Phase V is reached. Using the above scheme, it should be clear that usable granules are achieved during Phase III of the agglomeration process. The general form of the profile is dependent on the constituents being granulated and the type of mixer used (8, 9).

When making use of power consumption measurements, investigators have mistakenly assumed that it is only a function of current and voltage. However, for the most part, industrial motors are induction motors which make use of alternating current. Therefore, current lags behind the voltage making the expression for power consumption more complex. The expression must include a power factor to represent the angular displacement between current and voltage. This factor can vary

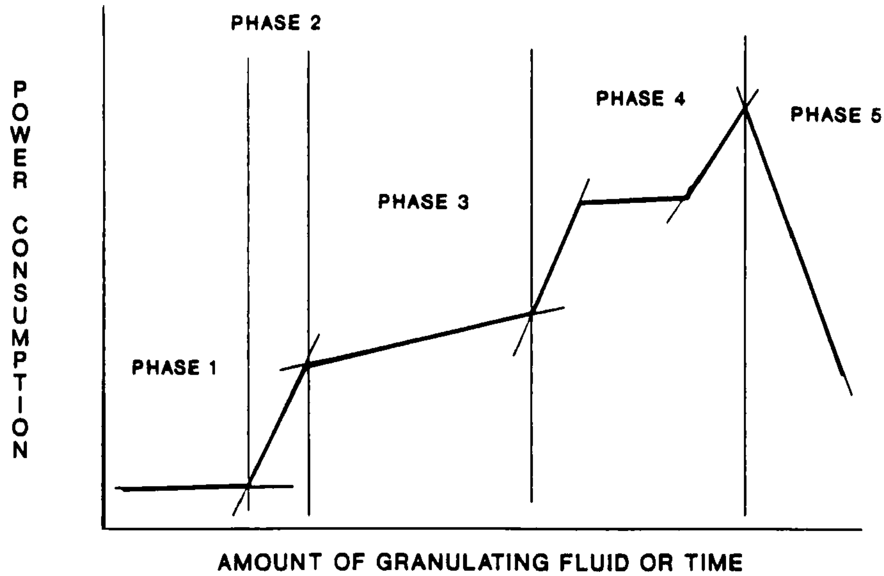

FIGURE 1: Five phases of a power consumption profile.

between 0.1, for low loads, to as high as 0.95 for full loads. It would then appear inappropriate to determine granulation end-point by monitoring current or the combined product of current and voltage (10).

To make use of the power factor, devices have been designed to sense the current and multiply it by the measured voltage. From this is calculated the lag of the current or the power factor. A deficiency of this approach is that it assumes the motor and gear assembly efficiencies remain constant over the lifetime of the granulating device. However, this may not be true and becomes a function of equipment condition, age and lubrication.

To avoid many of the problems encountered in measuring power consumption, some investigators have turned to the measurement of torque

(11-13) in determining granulation end-point. Torque, as a general classification, can be broken down into two subclasses: direct and reactive.

Direct torque makes use of the ability to measure shaft strain in a rotating drive shaft. The sensing system is installed, in such a way, that it is not connected to the drive train. Thus, the system operates independent of both power factor and motor efficiency. The main problem encountered with this design is in getting the signal from a moving part, where torque is measured, to a remote, stationary data acquisition site. There are many techniques available to accomplish this and include the use of slip rings, radiotelemetry and inductive coupling. Perhaps the most common approach is to make use of slip rings because of their cost effectiveness and long service life.

Reaction torque senses the motor's reaction to the produced shaft torque. This method is also independent of the power factor and motor efficiency but dependent on the efficiency of the mechanical drive train system. However, this will only represent approximately 1% variation in the data. The major advantage of this design is that the sensor is fixed thereby eliminating the need for slip rings or other data transmission accessories.

It was the intent of this study to instrument a high shear mixer/granulator with devices to measure power consumption, direct torque and reactive torque for monitoring the granulation process. All methods will be compared to determine the potential of these sensing devices in describing the granulation process.

EXPERIMENTAL

MATERIALS

Mixer/Granulator

The mixer/granulator instrumented was a Machines Collette (Towaco, NJ) Gral 75. The mixer is a dual speed unit with an overhead mixer and chopper blade shaft. The mixer will run at 306 rpm at 7.5 horsepower and 203 rpm at 5 horsepower. The chopper blade can run at either 1500 rpm or 3000 rpm in conjunction with the main mixer. The mixer has a 75 liter bowl capacity with a 50 liter working capacity. The mixer drive train consists of two sets of tooth belts and a reducer set of pulleys that provide the speed reduction from the motor to the mixer blade. The mixer motor is located at the rear of the mixer with a 1360 mm long drive train between the motor and the mixer blade shaft. The electricity supplied to the mixer motor is three phase, at 440 volts and 60 Hertz. The mixer is explosion proof and utilizes a pressurized electrical box to house the controls that are located in the mixer room.

Granulation

It is not important to specify the exact composition of the granulations employed other than to delineate their general composition. Two test systems were used with the first consisting of three different actives mixed with a filler and binding agent. The binding agent is a non-ionic water soluble cellulosic polymer which swells in the presence of water (Formulation A: 15.5 kg). The powders were mixed and granulated with

2.64 kg of a hydro-alcoholic (1:1.2) solution for a given period of time. The main mixing impeller was operated at low speed (203 rpm) throughout the granulating process. During the last 30 seconds of granulating, the chopper was operated at low speed (1500 rpm) to aid in densification of the produced granules.

The second test system consisted of two different actives mixed with fillers and a binding agent which is a 1-vinyl-2-pyrrolidinone polymer. This polymer is soluble in water and alcohol. The powders (16 kg) were mixed and granulated with a hydro-alcoholic (1:3) solution (4.4 kg) for a given period of time. The main mixing impeller was operated at high speed (306 rpm) throughout the granulating operation. As the granulating fluid was added, the chopper was operated at high speed (3000 rpm) for the duration of the granulating process (Formulation B). This process produced granules with the desired characteristics.

Instrumentation

The mixer/granulator was instrumented by three methods: power consumption, reactive torque and direct torque. Power consumption of the motor was measured making use of a power cell that senses the amperage, phase angle and voltage consumed by the motor. This produces an analog output which is proportional to the power consumed.

The direct and reactive torque measurements were determined by strain-gauge-based transducers. These transducers react to the torque being delivered to the main mixer impeller. Both transducers provide an analog signal that is proportional to the torque in the drive train at the location of their installation. The reactive torque transducer measures the torque at the motor while the direct torque transducer measures torque at the mixer impeller shaft.

METHODS

Transducer design and installation

Reactive torque transducer

Reactive torque measured the torque driving the mixing impeller at the motor. The method employed was to construct a torque sensing motor bracket instrumented with foil strain gauges. The motor bracket suspends the drive motor between two shafts aligned with the axis of the motor. One shaft was the power shaft of the motor, the other shaft was installed at the rear of the motor and mounted to the motor housing. The two shafts were mounted to the mixer frame through roller bearings (Figure 2). This arrangement allowed the body of the motor to rotate about its axis freely and to have a torque response to the power being delivered by the motor. The actual motor drive torque measurement was made through the shaft at the rear of the motor. The torque required to hold the body of the motor stationary through this shaft was equal and opposite to the torque being delivered by the motor's drive shaft.

The torque in the shaft at the back of the motor was measured by a strain gauge based torque cell. The torque cell was mounted between the shaft at the rear of the motor and the stationary frame that was mounted

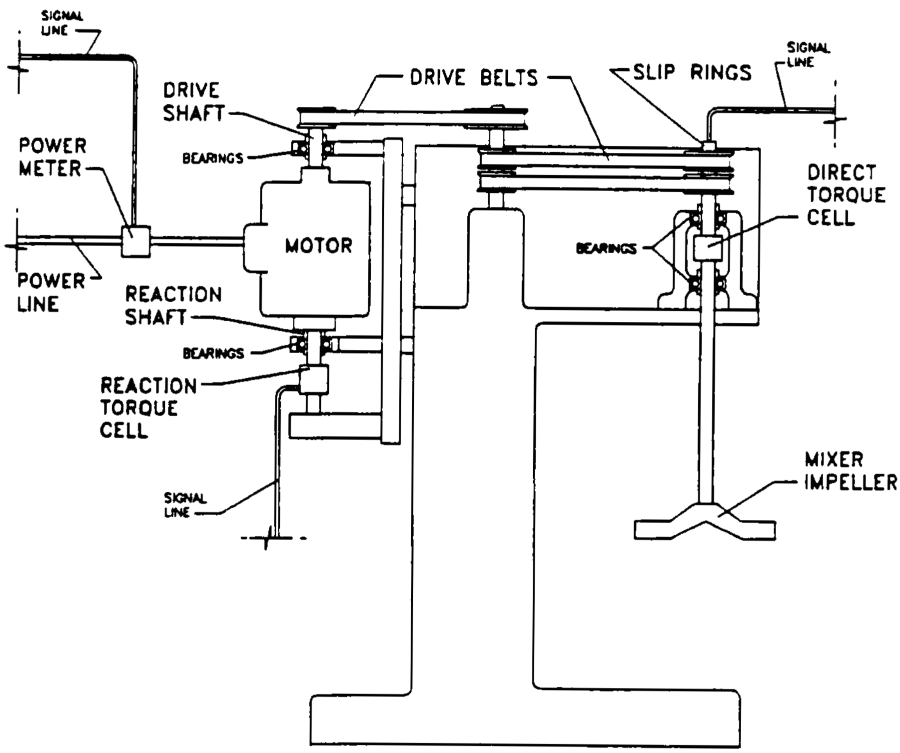

FIGURE 2: Schematic of Gral 75 depicting location of torque devices and power meter.

to the mixer body. The cell was constructed using 350 ohm foil strain gauges in a full Wheatstone bridge bonded to a torsional spring element. The motor bracket was constructed with an adjustable overload protection device. The overload protection could be adjusted to carry all the load above the safe range of the torque cell. This protected the torque cell from potential damage from such events as high initial start-up torques of the mixer. The advantage of the overload protection was to allow the use of a highly sensitive torque cell matched to the operating torque of interest. This avoided the use of a high capacity low sensitivity cell designed to allow for short term overloading. Provisions were made to allow for quick removal of the torque cell while retaining the operation of the mixer. The torque cell was designed to allow for increased torque cell sensitivity by trimming the spring element without reconstructing the torque cell in the event increased sensitivity was required.

Direct Torque

Direct torque measured the torque driving the main mixer impeller at the mixer impeller shaft. The design employed was to replace the entire mixer shaft with a torque sensing strain gauge based transducer. The direct torque transducer was constructed of a single shaft of hardened stainless steel with the sensing elements located mid-way between the two support roller bearings. This transducer was a rotating part and transferred its torque signal to the stationary mixer frame. The electrical connections to the transducers passed through a slip ring assembly mounted to the top of the impeller shaft. The wires leading to the slip ring assembly from the torque sensing element passed through a hole bored through the center of the transducer. The resulting shaft functions identical to the original drive shaft.

Power Cell

The operating power of the mixer drive motor was determined by the use of a Load Controls Incorporated (Sturbridge, MD) PH-3A power cell. The power cell measured the current passing through each of the three phase line by the use of Hall Effect sensors. The voltage in each of the three lines were monitored by a direct connection to the lines. From these inputs, the power factor was determined by the power cell and used with the voltages and amperages to determine the power consumed by the motor. The power cell produced a zero to 10 volt output up to the full range of the unit. The power cell had an adjustable frequency response of one to 17 Hertz and was set to 4 Hertz.

Strain Gauge Transducer Signal Conditioning

Both the direct and reactive torque cells were strain gauge based transducers and, when excited by a voltage, would produce a millivolt level analog signal in response to a load. The millivolt signal was amplified and filtered prior to conversion to a digital value by the computer. The electronic installation in the mixer room conformed to a Class 1 Division 1 environment.

Intrinsically safe signal conditioning was installed for each of the strain gauge channels. The signal conditioning modules provided a pulsed excitation and reading of the transducers ninety times a second over a constant current output of 4 to 20 milliamps with a frequency response of 4 Hertz. The modules provided gain and zero adjustment through pots in the module's case. The units were adjustable to work with transducers with a one to 3 millivolt per volt output at full scale. To convert the constant amperage signal to a voltage, the output line was connected to ground through a 500 Ohm resistor. This provided an output signal voltage of two volts at zero torque and 10 volts full scale torque.

Transducer Installation

The installation of the instrumentation involved extensive disassembly and minor modification of the original mixer. The installation of the direct torque required replacement of the mixer drive shaft with the torque transducer. This was accomplished by removing the mixer shaft bearing housing, pressing out the original shaft, pressing in the new transducer and re-installing the housing. The transducer was installed with the slip ring assembly and the associated wiring contained under the original mixer cover guard.

The installation of the reaction torque transducer included the removal of the motor's mounting bracket and the installation of the instrumented motor bracket. The wires from both strain gauge based transducers entered the pressurized electrical box through liquid tight connectors. The transducer signal conditioning modules were installed in the pressurized box along with the power cell. The high level transducer signals exited the box via a sealed conduit that terminated in an adjacent room where the computer was installed.

Computer and Software

The instrumentation system installed was designed to work with a SMI (Pittstown, NJ) PC-30 computer based data acquisition and analysis system. Flexibility exists to use the instrumentation with more conventional data recording devices (ie. strip chart recorder). The minimum computer system requirements were a 286 microprocessor, 287 math co-processor, an

EGA monitor and a 10 megabyte hard drive. The computer used was a Gateway (N. Sioux City, SD), IBM compatible 386 computer, with a math co-processor operating at 33 megahertz. The computer was equipped with two floppy drives, a 200 megabyte hard drive and a VGA monitor. The digital and analog inputs were made through a Metrabyte (Taunton, MA) DAS-20 data acquisition board installed in an expansion slot on the computer.

The data acquisition and analysis software was the SMI PC-30 Proprietary Mixer/Process Data Acquisition System. Menu driven screens provide real time monitoring of the mixing/granulating process torque, peak torque, root mean square and area under the curve along with analysis of collected process data.

The software provided statistical analysis on user selected segments of the process data. The analysis included maximum, minimum and average torque, root mean square, area under the torque/time curve and Fast Fourier Transform of the user selected segments. Root mean square is a measure of the degree the torque values vary from the average torque. Fast Fourier Transform is an analytical process that identifies the simple sinusoidal wave frequencies and their magnitudes. The software also allowed for process termination control through a user defined truth table that monitored the magnitude of the operating parameters of peak torque, root mean square or area under the torque/time curve.

RESULTS AND DISCUSSION

Calibration

Prior to operating the instrumented mixer/granulator, the transducers were calibrated. The power cell was calibrated at the factory. The two strain gauge load cells and their signal conditioning were calibrated on the mixer. The method of calibration was to mechanically lock the motor shaft to the motor housing and then apply a known static load to the mixer shaft while monitoring the output of the transducers through the signal conditioners. The torque was applied by a 12 inch moment arm fastened to the shaft. The perpendicular load applied to the moment arm was monitored by a 500 pound load cell traceable to the National Institute of Standards and Technology. The transducer amplifiers were tuned to have a full scale output at 150 foot pounds which was monitored on a multi-meter. Though 150 foot pounds was less than the capacity of the mixer and transducers, it represented the maximum value anticipated for the present use of the mixer.

The direct torque transducer demonstrated excellent linearity, hysteresis and return to zero. The reactive torque cell demonstrated excellent linearity and good return to zero. Though the reactive torque transducer exhibited excellent hysteresis when calibrated off the mixer, the mechanical friction present in the mixer drive train caused a hysteresis error of 4% full scale when installed.

Granulation Process

A three-pen strip chart recorder was used in conjunction with the computer data acquisition system to record the output from the three transducers installed on the mixer/granulator. The computer system was designed to monitor only one channel, while the strip chart recorder could monitor all three. Thus, the strip chart recorder would provide a direct comparison between the different sensing devices during the granulation operation. The computer was used to highlight only one of the transducers; usually the direct torque.

Figure 3 represents the granulation process for Formulation A. The tracing was compressed to highlight the beginning, middle and end of the process. The initial plateau represented the dry mixing process for the powders charged into the bowl. A torque of approximately 8 ft/lbs was noted which represented the force needed to blend the powders. The mixing process ran for approximately 5 minutes. Between 5 and 7 minutes, the granulating fluid was added and a steep increase in torque was noted. The wetted mass was allowed to mix and the process monitored. Another plateau was noted between approximately 9 and 13 minutes. This represented the time needed for the granulating fluid to distribute over the powder and for the binder to hydrate. Once this occurred, the powders continued to mass until a peak torque of approximately 72 ft/lbs was reached. As the mass was further granulated, the torque decreased demonstrating breakdown of the granules and subsequent drying of the product.

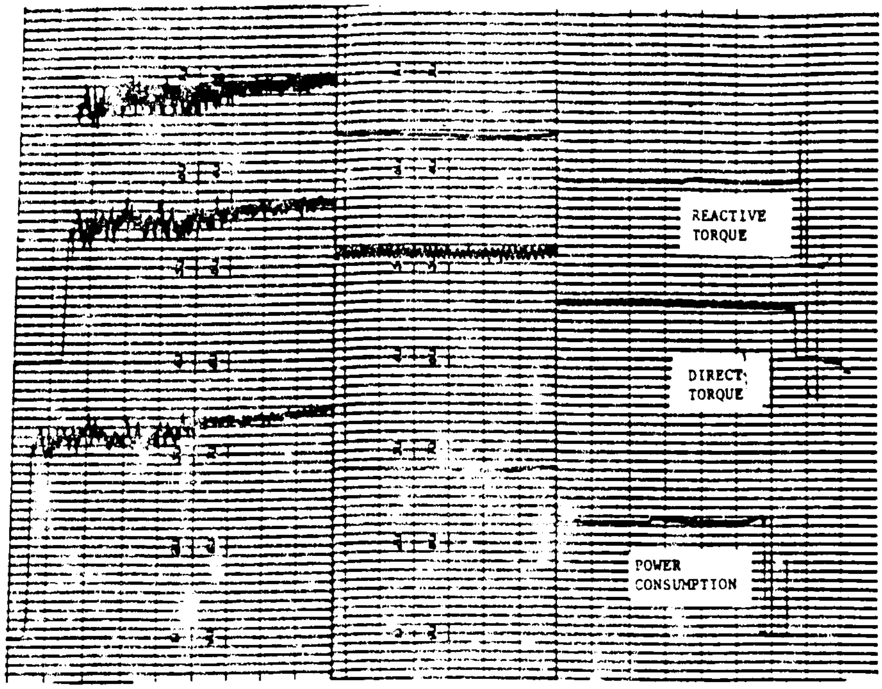

FIGURE 3: Compressed strip chart recording of the change in torque, as measured by power consumption, direct torque and reactive torque, during the granulation of Formulation A.

From Figure 3, it is seen that all three traces parallelled each other and gave similar profiles. However, a closer investigation of the generated profiles revealed that the mixer transducer (ie. direct torque) followed the granulating process more closely. It showed the change in torque more clearly which was apparent by its saw-tooth tracing. The other two, power and reactive torque, did not exhibit the detail that was seen with direct torque. This suggested that the closer the sensing device was to the site of action, the more detailed and more descriptive the profile would be of the process (ie. direct torque).

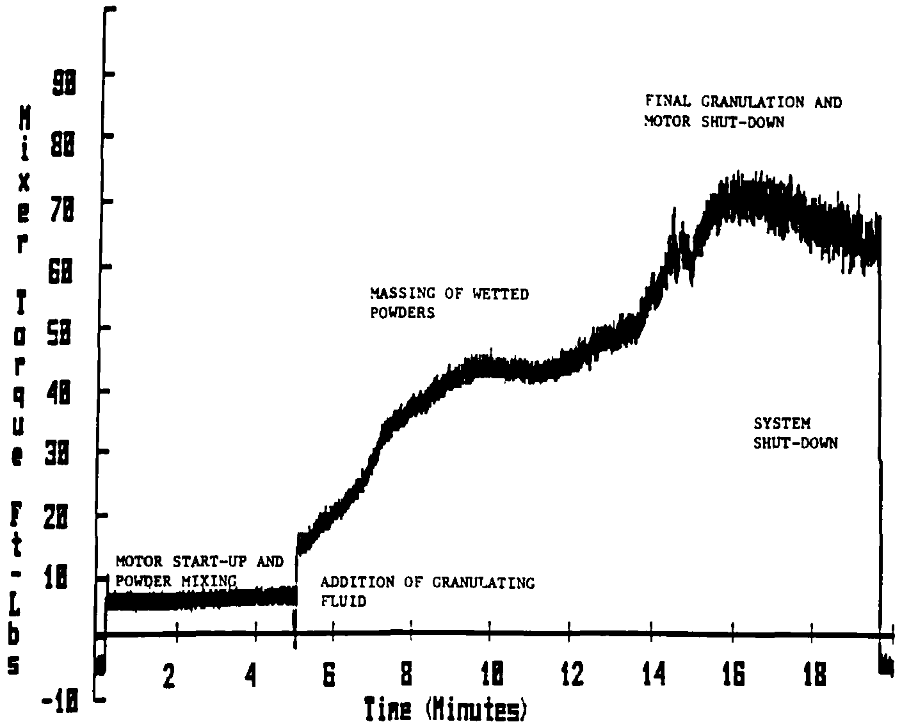

FIGURE 4: Plot of direct torque (ft/lbs) versus time for Formulation A.

The oscillations at the early part of the granulation process (0-5 minutes) may have represented the mixing pattern established as the powders were blended and their impaction on the main mixing impeller. As granulating fluid was added, the powder massed and the oscillations expanded and elongated. The oscillations were more pronounced and showed the agglomeration of powder into large granules.

Figure 4 is the granulation profile, for Formulation A, traced by the computer data acquisition system using the mixer transducer. Note that the massing endpoint was seen at approximately 17 minutes for the amount of granulating fluid added. Thus, the computer data acquisition system was capable of monitoring the granulating process while providing real time torque measurements. It should be noted that the end-point was initially thought to be at 12-13 minutes. When tablets were manufactured with material granulated to this point, non-acceptable tablet hardnesses were noted (8-10 Strong-Cobb Units (SCU)). However, if the granulation process was allowed to proceed to 17-18 minutes, tablets with acceptable hardnesses were achieved (15-18 SCU). Thus, time was needed for the binder to effectively hydrate which in-turn yielded harder tablets. Therefore, the end-point was determined to be between 17 and 18 minutes for this product. After approximately 18 minutes, torque decreased due to drying of the granulation by the heat generated during prolonged mixing.

Figure 5 shows the effect of doubling the amount of granulating fluid for Formulation A. The powders were mixed for approximately 5 minutes after which the granulating fluid was added. Note that the torque needed for mixing was still 8 ft/lbs. This gave some indication of the reproducibility for the monitoring system with this granulation. The addition of the fluid was over a two minute period. The powders rapidly massed to achieve a torque of approximately 70 ft/lbs. There was a sharp drop in the torque reflecting localized wetting and massing with subsequent distribution of the granulating fluid throughout the powder mass. As time progressed, torque rose sharply again to approximately 70 ft/lbs reflecting the quick and rapid hydration of the binding agent and massing of the

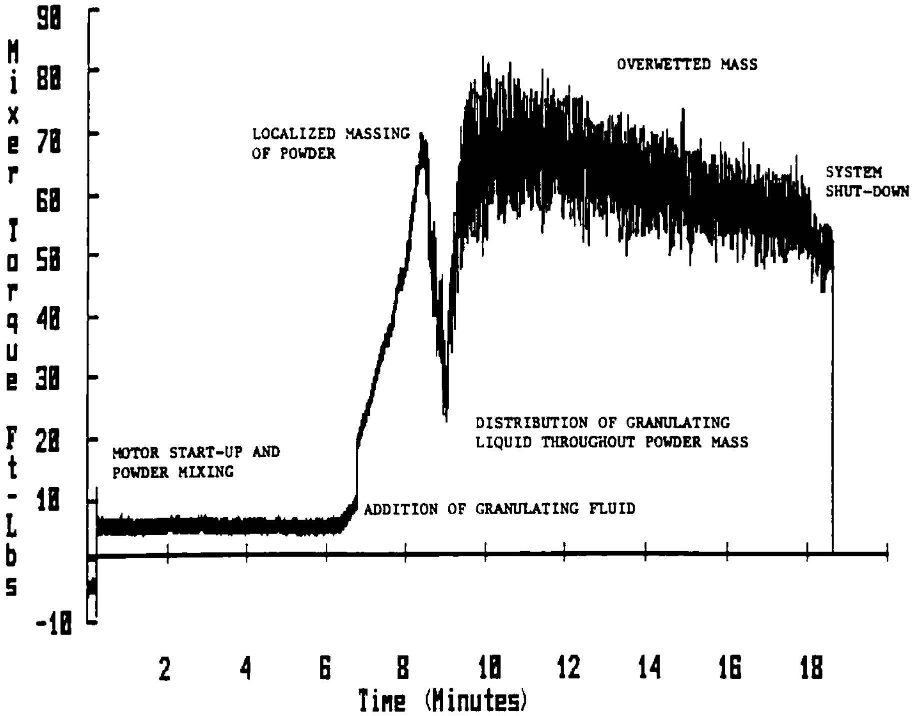

FIGURE 5: Plot of direct torque (ft/lbs) versus time for Formulation A doubling the amount of granulating fluid.

powders. When the torque reached steady-state, the granulation achieved a doughy consistency. The terminal phase of the curve showed large oscillations which was indicative of the divergent range in particle size and granule consistency at this point in the granulation cycle. As time progressed, torque slowly decreased, again showing drying of the mass. It was interesting to note however, that the peak torque was still at roughly 70 ft/lbs as seen earlier. However, the time to peak occurred sooner due to excessive wetting of the powders.

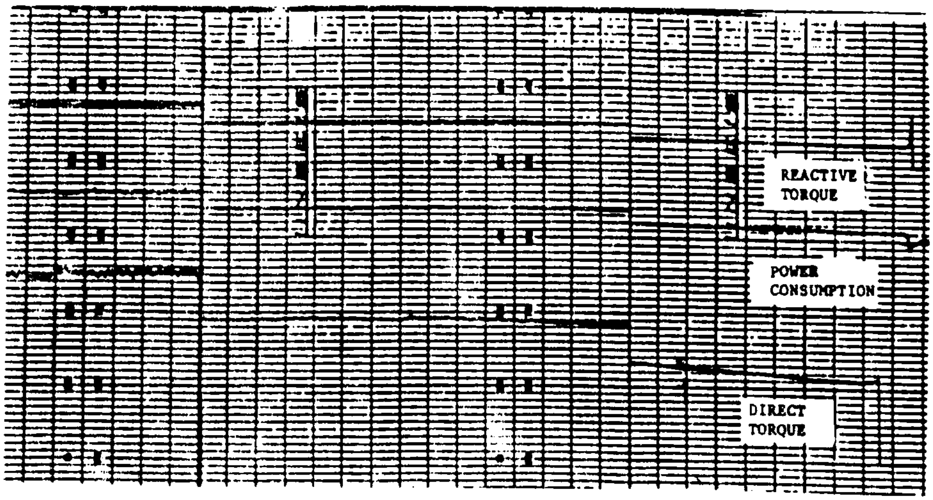

FIGURE 6: Compressed strip chart recording of the change in torque, as monitored by power consumption, direct torque and reactive torque, during the granulation of Formulation B.

Figure 6 shows the compressed strip-chart recording generated during the granulation process of Formulation B. Again, all three plots followed the granulation operation with direct torque providing a more detailed description of the process. The irregular oscillations at the terminal phase represented the impaction of the multi-particulate granulation against the mixing blade, sides of the mixing bowl and between each other.

Figure 7 represents the granulation process as monitored by the direct torque strain gauge. Note the initial plateau between approximately one and 6 minutes. This, as seen earlier, represented the torque needed to mix the powders. The granulating fluid was added over a two minute

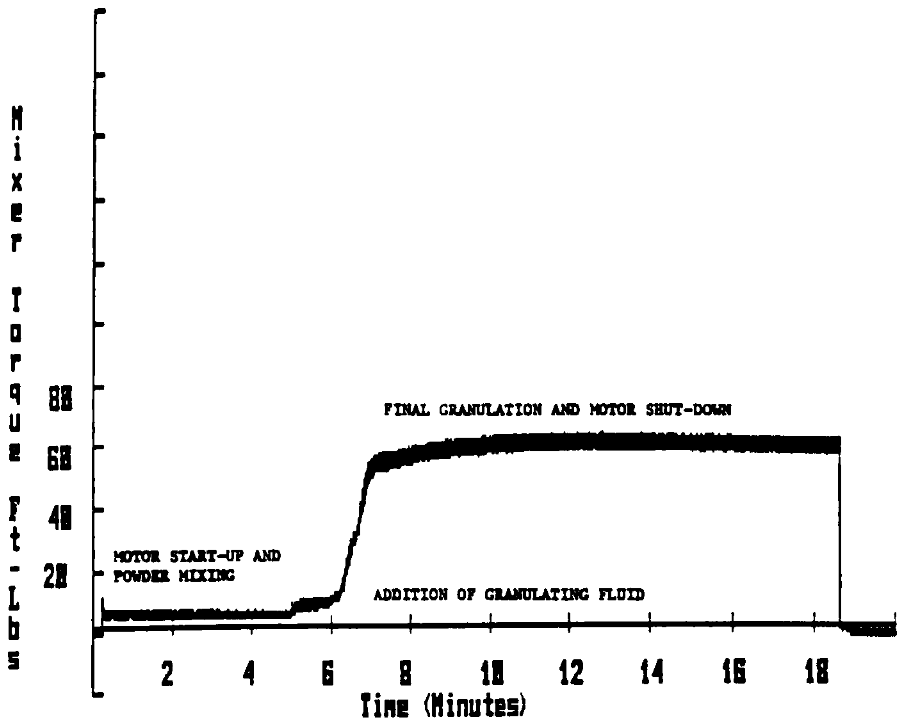

FIGURE 7: Plot of direct torque (ft/lbs) versus time for Formulation B.

period (from 6-8 minutes) and a sharp rise in the mixer torque was noted, reflecting massing of the powders. A plateau was quickly reached after approximately 11 minutes into the granulating process. No further change in the profile was noted up to approximately 20 minutes. Thus, the end-point can be seen to occur at approximately 11-12 minutes into the process. The operation could be terminated at this time with confidence the process was completed. Tablets manufactured from batches manufactured up to 12 minutes and 20 minutes showed no difference in tableting or tablet performance. Both batches demonstrated similar hardnesses which ranged from 18 to 22 SCU. Subsequent batches manufactured gave similar profiles which demonstrated the reproducibility of the monitoring system. Also, when the granulation was terminated after 11-12 minutes, reproducible tablet hardness and performance (ie. dissolution) was observed demonstrating the need to monitor the granulation process. This is especially true in determining the end-point.

When comparing Figures 4 and 7, it was interesting to note that it required approximately 8 ft/lbs to initially blend the powders and that once the granulating fluid was added, a sharp rise in torque was noted. The time and torque observed at the end-point was obviously different and appeared to be dependent on the nature of the binding agent and materials used. With such differences, it should be apparent that monitoring the granulation process, via instrumentation, is necessary to 1) understand the process for a given set of active(s) and excipient(s) and 2) determine when the process is complete for a given level of granulating fluid. As seen earlier with Formulation A, premature termination of the granulating operation can lead to inferior tablet physical characteristics. Also, by having a profile of the granulation process, one is able to establish limits in setting times to reach granulation end-point. For Formulation A, the range was approximately 16-18 minutes while for Formulation B, it was anytime after approximately 11 minutes.

In conclusion, a Gral high shear mixer/granulator was instrumented to follow the change in power consumption, reactive and direct torque during the granulation unit operation. All three methods gave the same general profile for the operation; however, direct torque was more descriptive. This demonstrates that the optimum way to monitor this process is to place the sensing devices as close to the site of mixing/granulating as possible. The further from the source of action the process is monitored, the more diluted the data become while running the risk of missing key changes throughout the operation.

By monitoring the change in torque at the mixer impeller (ie. direct torque) it was possible to obtain a realistic picture of the granulating process. This then provides a way to optimize a granulation operation during product development.

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