DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(12), 1931-1944 (1990)

EFFECT OF BINDER CONCENTRATION AND METHOD OF ADDITION ON GRANULE GROWTH IN A HIGH INTENSITY MIXER

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ABSTRACT

A model system consisting of microcrystalline cellulose and povidone was used to study the effect of binder concentration and method of addition on granule growth in a high intensity mixer. The methods of binder addition include blending the dry binder with the excipient prior to granulating with water and granulation of the excipient with an aqueous solution of the binder. When the binder was dry-mixed with excipient prior to wetting, a good correlation was obtained between granule size and binder level. The growth of granules prepared by this method also appears to be related to the mechanical "resistance" encountered by the mixing blade during wet massing. In general, granules prepared by the addition of aqueous binder solutions are smaller than granules prepared with corresponding concentrations of dry binder and demonstrate a lesser degree of granule growth with respect to increasing binder level. For the wet addition method, the mechanical resistance was found to be essentially constant with respect to binder level.

INTRODUCTION

The use of binding agents in tablet formulations has been well documented. However, relatively little attention has been paid to their ability to influence granule formation and growth (1-3).

Several studies have been reported concerning the effect of binder concentration on granule growth when the binder is added as an aqueous solution (3-6). An enhancement of granule size was observed with gelatin in a binder comparison study (3). Granules prepared with gelatin solution may exhibit growth because the viscosity of the gelatin solution results in a high degree of densification.

In the last decade, much interest has been directed toward monitoring the granulation process. Several reports deal with the measurement of the power consumed during granulation (7), relative dynamic torque (8) and probe vibrational analysis (9). These methods are primarily concerned with the detection of granulation endpoint, process optimization or validation. In one study, a torque rheometry apparatus was used to assess differences in the rheological behavior of granulations prepared with two chemically different binding fluids (10).

Only a few investigations have been reported which address the significance of the method of binder addition on granule growth. In a factorially designed experiment, the method of binder addition, among other process variables, was observed to have a significant influence on the particle size of a lactose-corn starch-povidone formulation (11).

In this study, the effect of binder concentration on granule growth was examined, as well as the method of binder addition for a simple system. An instrumented technique for monitoring the granulation process is also described and was used to evaluate the process conditions.

EXPERIMENTAL

Materials

The granulations consisted of 1 kg Microcrystalline Cellulose, USP, (MCC; Avicel PH 101, FMC Corporation, Philadelphia, PA) with varying levels of Povidone, USP (PVP; Plasdone K 29-32, GAF Corporation, Wayne, NJ). The granulating solvent for all experiments was 1000 mL distilled water. When the binder was added as a dry powder, distilled water was used as the granulating liquid. For experiments involving the aqueous addition of binder, povidone was dissolved in the water prior to addition. The concentration range of povidone utilized in this study was approximately 1-5 % which is commonly recommended for tablet formulations (12). For additional comparison, a control batch containing no binder was prepared.

Lactose (Foremost Whey Products Company, Baraboo, WI), dicalcium phosphate (Stauffer Chemical Company, Westport, CT) and MCC were used to calibrate the sensitivity of the granulation monitoring technique.

Equipment

A 10 liter capacity high intensity mixer (Baker Perkins Chemical Machinery, Ltd., Stoke-on-Trent, England) configured with a variable speed main impeller (plow) and side chopper, was used to process the granulations. The granulating liquid was added using a peristaltic pump (Model 501 S, Watson Marlow, Ltd., Falmouth, England).

The ammeter for the impeller blade, located on the instrument panel of the mixer, was connected to a strip chart recorder (Linear Instruments, Inc., Las Vegas, NV) providing an electrical output signal that was used to monitor the granulation process. Prior to granulation, the recorder was calibrated to 100 mV full scale using a known input from a potentiometer (Model 8690, Leeds & Northrup, Philadelphia, PA). The response from the recorder was adjusted to correspond to a calibrated range (0-100

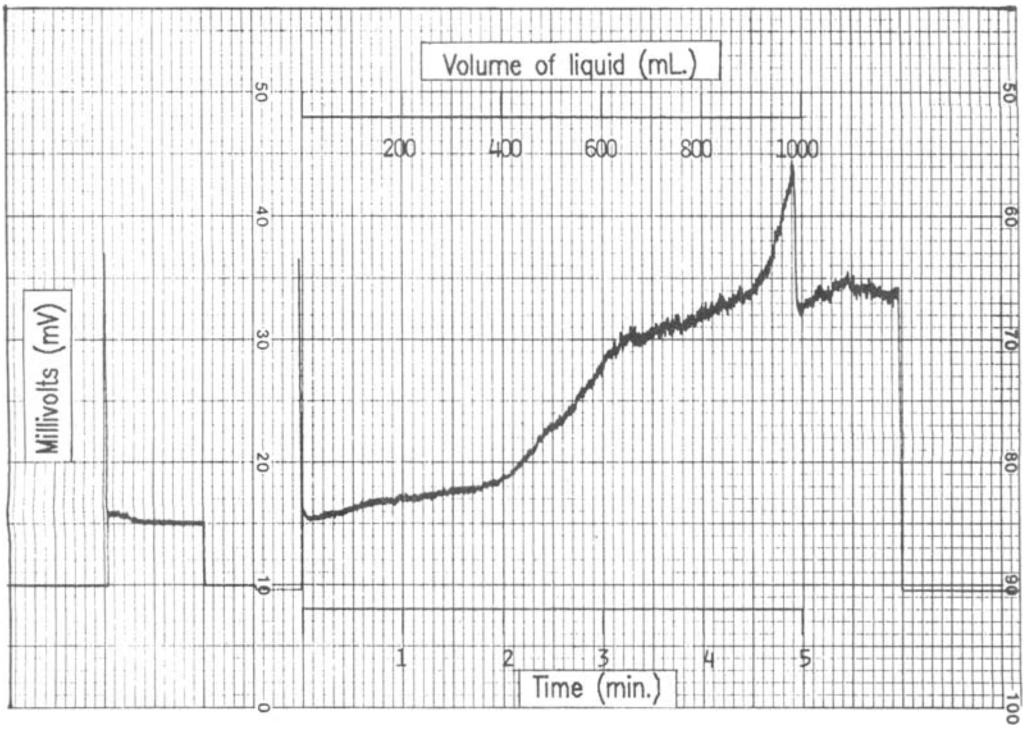

FIGURE 1

A typical tracing of resistance obtained during granulation in the high intensity mixer.

mV). This enabled the ammeter dial reading to be quantitated in units of millivolts. A typical tracing obtained during liquid addition and wet massing is depicted in Figure 1.

As seen in Figure 1, the ordinate axis of the tracing represents changes in the interparticulate forces involved in the formation of moistened granules during wet massing. Because the granulation liquid was added at a constant rate, the process can be monitored as a function of time or liquid level.

Calibration

Calibration of the monitoring technique was necessary to determine if values from the recorded profiles could be

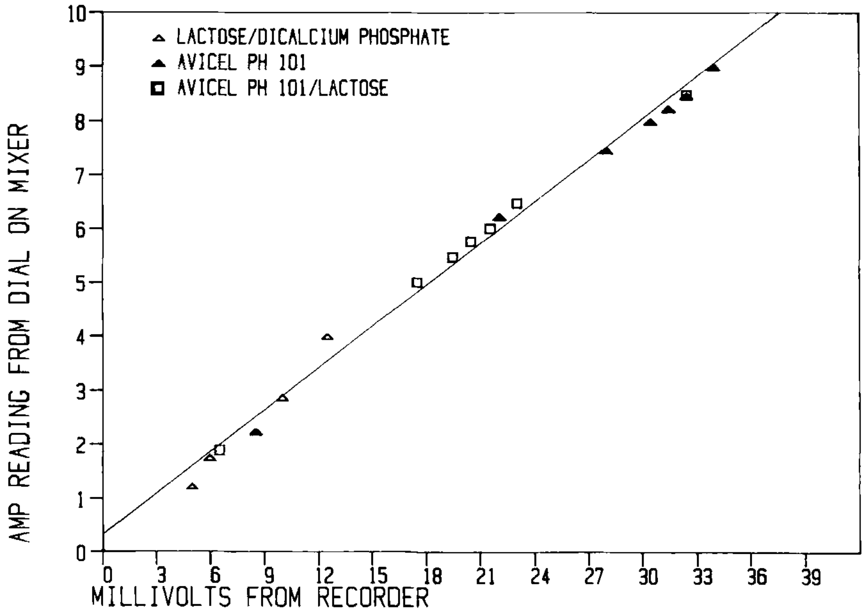

FIGURE 2

Calibration curve for amp dial reading on mixer as a function of millivolts from the recorder.

correlated to the values observed on the ammeter dial during wet massing. Single powder or binary powder mixtures consisting of microcrystalline celluose, lactose and dicalcium phosphate, were wetted by stepwise additions of water. When the recorded signal reached a plateau after each addition of water, the value on the ammeter dial and its millivolt equivalent were noted. The calibration curve is shown in Figure 2.

Granulation and Testing

The dry powders were initially mixed for one minute to remove any aggregates and to obtain a constant baseline of the recorded signal. The main impeller was set to operate at 750 rpm. The granulating fluid was added using the pump at a constant rate (200 mL/min) for 5 minutes through an open port in the lid of the mixer. Following the addition of liquid, the side chopper was operated at a mid-range speed (1500 rpm) to insure complete distribution of the granulating liquid. A separate batch for each concentration of binder was prepared for both methods of addition. The resulting granules were dried in a hot air oven (Stokes Model-38C, Pennwalt Corporation , Philadelphia, PA) for 20 hours at 40°C. For these studies, a dry milling step was omitted because it was important to observe changes in particle size during granulation.

The particle size distribution was determined by sieve analysis using a representative sample. The geometric mean granule diameter (d'_g) and geometric standard deviation (σ_g) were determined using a log-probability relationship as discussed by Martin (13).

RESULTS/DISCUSSION

The recorded profiles generated during the granulation process exhibited the characteristic shape shown in Figure 1. As the granulating liquid was added to the powder or powder blends, there was a noticeable rise in the recorded signal from the baseline prior to wet massing. With increasing quantity of granulating liquid, the recorded tracing during mixing ascends to a maximum value. After 5 minutes, the profile descends because the additional mixing force of the chopper reduces the resistance of the wet mass. For comparison, the area under the profile or curve (AUC) for the 5 minute wet massing period was calculated using the trapezoidal rule and expressed in units of millivolt-seconds for each binder level. These AUC values can be used to indicate the mechanical "resistance" encountered by the impeller plow during wet massing.

Dry Addition Method

Granule growth was enhanced when PVP was added in the dry state, as depicted in Figure 3. The size distributions for all

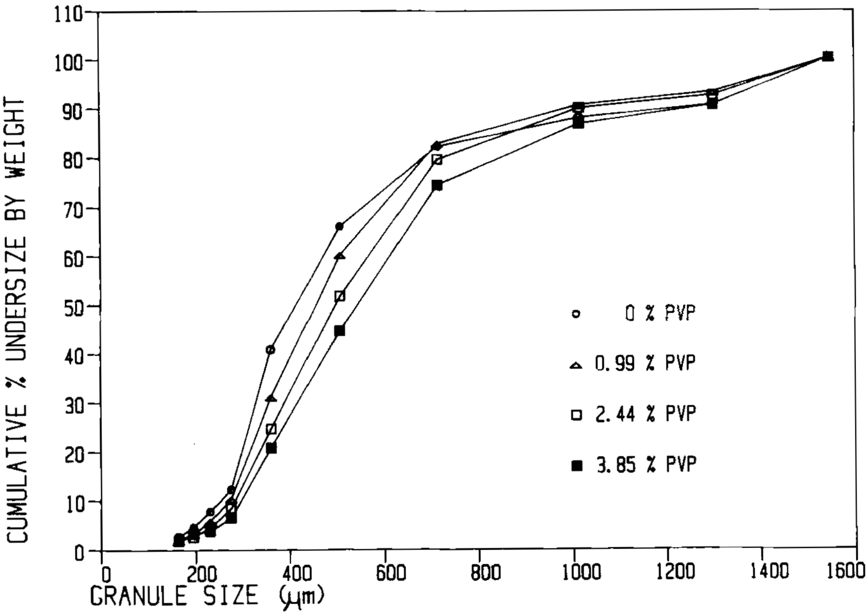

FIGURE 3

The effect of varying the concentration of dry binder on the granule size distribution.

batches followed rank order with respect to binder concentration. Because the powders were uniformly blended prior to water addition, the granule size distributions would be expected to shift towards a larger granule size with increasing binder concentration. This assumes that an adequate liquid level is present to initiate the potential binder activity.

These results are further supported by the values obtained for resistance using the dry addition method. In Figure 4, the resistance values for the wet kneading stage of granulation are plotted against the concentration of binder. The results indicate that a strong relationship exists for these parameters and that the resistance measurements are sensitive to small changes in binder level.

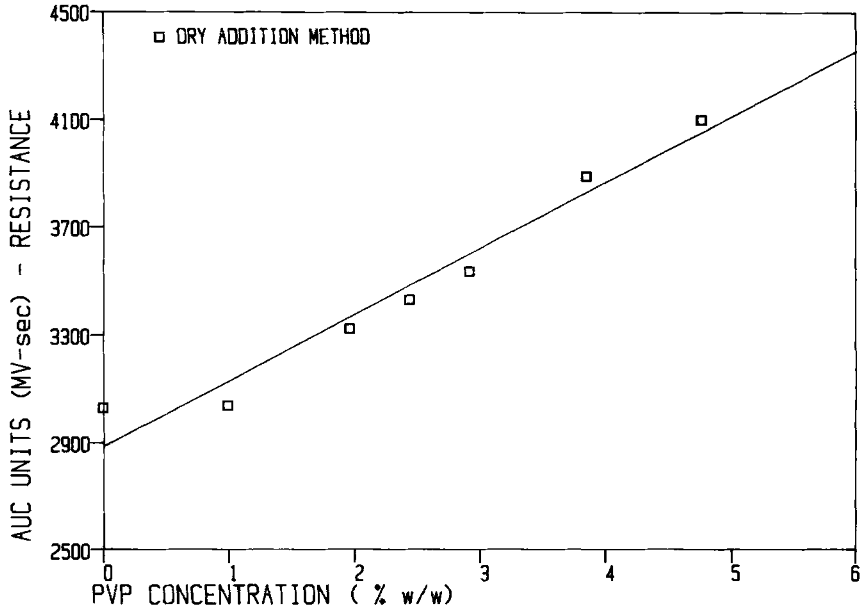

FIGURE 4

Mixer resistance in AUC units as a function of binder level for the dry addition method of PVP.

TABLE 1

Granule Size Distribution Parameters for some Batches Prepared by the Dry Method of Binder Addition

Povidone Concentration (% w/w)	Geometric Mean Granule Diameter (d'_g)	Geometric Standard Deviation (σ_g)
0	410	1.76
0.99	458	1.61
2.44	498	1.58
3.85	535	1.60

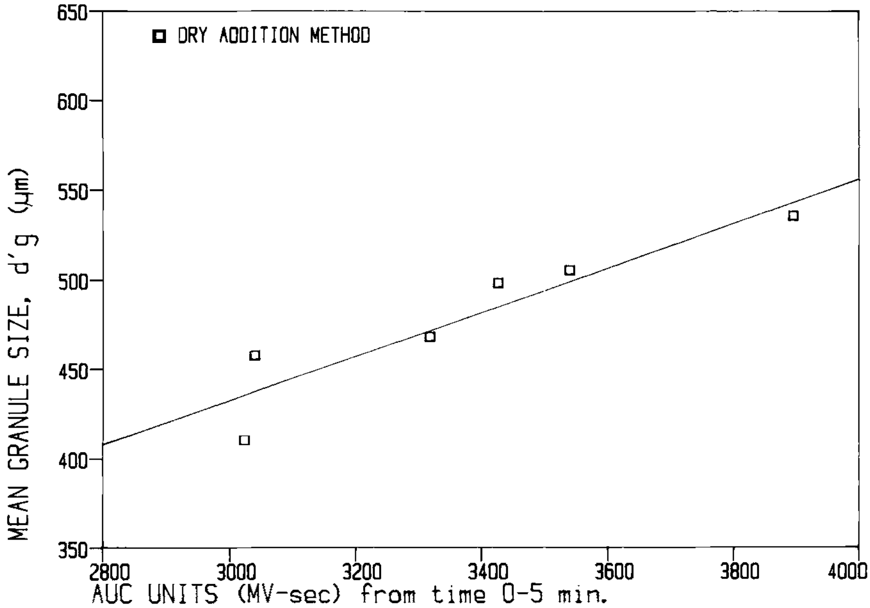

FIGURE 5

Relationship between mixer resistance and granule size for the dry addition of binder.

The geometric mean diameter was used as a means of characterizing granule growth since the granulations exhibited a narrow particle size distribution, as evidenced by the small values obtained for geometric standard deviation (see Table 1).

In Figure 5, the geometric mean granule size was plotted against mixer resistance, in an attempt to relate impeller resistance with granule growth in the mixer. The data appear to indicate that a good relationship exists between mean granule size and AUC for the dry method of binder addition. These results are supported by the premise that changes in torque or power consumption of a mixer occur as the result of changes in the cohesive forces of the agglomerates in a moistened powder bed (14). In addition, a recent study by Lindberg (15) reported that

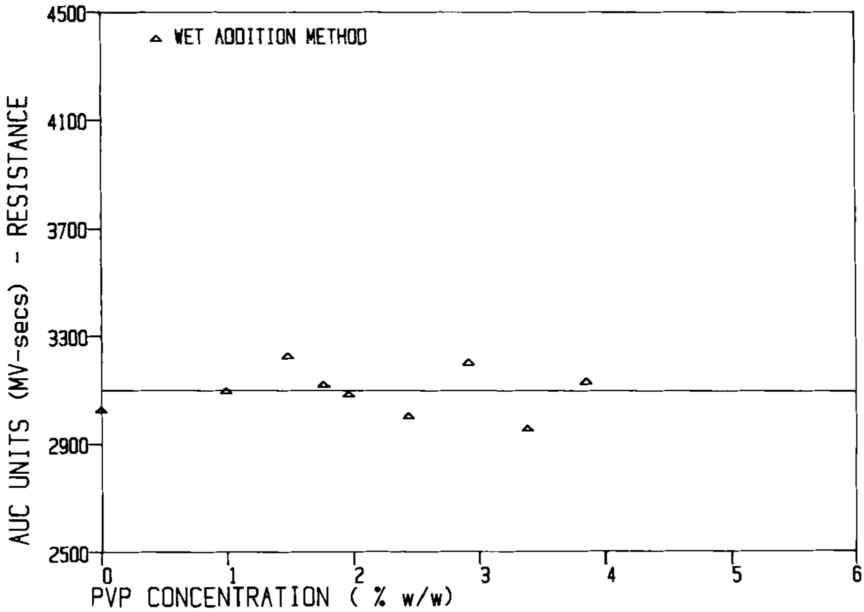

FIGURE 6

Mixer resistance in AUC units as a function of binder level for the wet addition method of PVP.

the torque applied to the arm of a planetary mixer can be used as an indication of granule size for lactose granulated with water.

Wet Addition Method

When PVP was added as an aqueous solution at various concentrations, the mixer recordings exhibited much different results. The resistance values of the mixer, expressed in AUC units, were fairly uniform within this narrow range (Figure 6). In addition, these values were lower than for comparable granulations prepared by the dry method of binder addition. The lower resistance values for the experiments with aqueous binder solution could be explained as a lubrication effect (16).

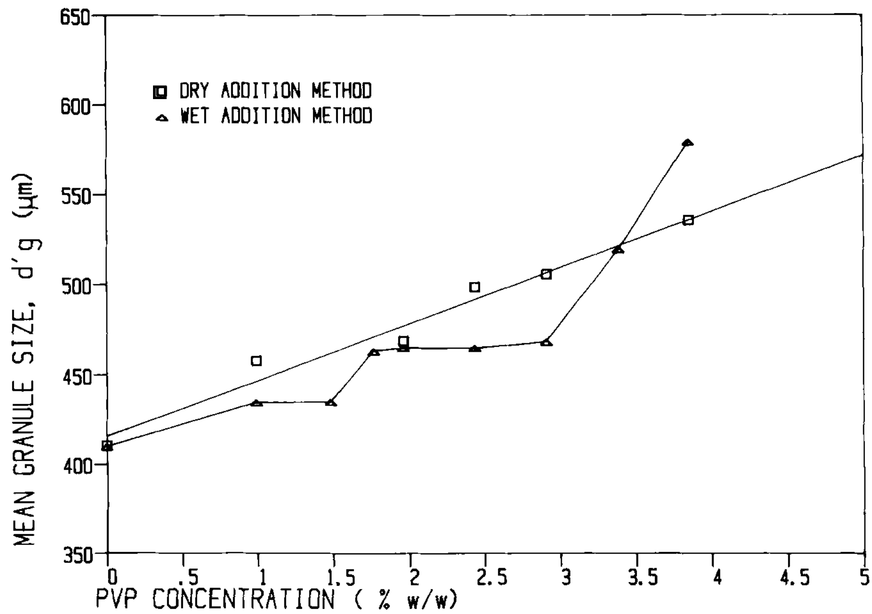

FIGURE 7

The effect of PVP concentration on granule size for two methods of binder addition.

Comparison of Binder Addition Methods

The relationship between granule size and PVP concentration for both methods of binder addition are shown in Figure 7. The granules prepared by the dry method of binder addition indicate a consistent and a greater degree of growth than granules formed by the wet addition method. The use of a dry-mixed binder was found to reduce the percentage of fines and increase the percentage of aggregates for a lactose-PVP formulation (2). Similar findings were reported by Lindberg and Jönsson (11) for a Diosna P25 recording mixer utilizing povidone as the binder. In general, the dry mixing of binder at low levels with this system results in an enhancement of granule size.

TABLE 2

Viscosity and Surface Tension Values for Various Granulating Solutions

Povidone Concentration (% w/w)	Apparent Viscosity * (mPa-sec)	Surface Tension ** (dyne/cm)
0	1	72
0.99	7.7	68
1.96	8.0	66
2.91	8.3	66
3.85	9.4	66
4.76	11.1	65

* Rheomat 15T-FC, Contraves AG, Zurich (25°C)

** Rosano Surface Tensiometer, Roller-Smith, Newark, NJ (22°C)

According to the theoretical considerations of Rumpf (17), the cohesive forces occurring during the wet granulation process originate from the liquid bridges between the solid particles. These cohesive forces which are directly related to the surface tension of the granulation liquid will influence granule formation and growth. Paris and Stamm (18) have shown that the power consumed by a mixer during granulation, which reflects the cohesive forces between particles, is related to the surface tension of the granulating solvent. Ritala et al. (3) have suggested that the viscosity of gelatin solution used as a binder may be responsible for increasing granule size as a result of particulate densification. Therefore, viscosity and surface tension measurements for the granulating solutions in these experiments were determined and are presented in Table 2.

The lower surface tension values determined for PVP solutions could result in smaller AUC values which reflect a reduction in mechanical resistance. On the other hand, at higher binder concentrations, the viscosity of the aqueous binder solutions rises and competes more effectively with the reduced surface tension, leading to a greater degree of granule growth.

CONCLUSIONS

The results of this study indicate that the method of binder addition plays a significant role in the formation of granules prepared by the wet granulation process. By increasing the concentration of binder, granule size was increased, as expected, especially if an excipient with inherent cohesion is utilized. The wet method of binder addition suggests a more complicated situation with regards to the physical properties of the system components and the interactions of those components in the formation of a final granule. Further work is warranted and is in progress.

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