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USE OF A MOTOR LOAD ANALYZER TO MONITOR THE GRANULATION PROCESS IN A HIGH INTENSITY MIXER

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ABSTRACT

A motor load analyzer instrumented to a high intensity mixer was examined for its ability to monitor the granulation process with varying formulation and processing parameters. A lactose/microcrystalline cellulose blend with povidone as the binder was used as the test system.

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The motor load analyzer was able to note chopper operation and liquid addition methods. However, it could not differentiate between povidone addition as an aqueous solution or as part of the lactose microcrystalline cellulose blend, followed by massing with water. The compression characteristics of the granulations depended upon chopper usage, and povidone and liquid amounts, and their methods of addition.

INTRODUCTION

The granulation process in a high intensity mixer has generated a large amount of interest over the years from both characterization and instrumentation veiwpoints. A number of studies have been reported which attempt to correlate equipment variables with granulation characteristics for the purposes of end-point detection.

In a mixing efficiency study, a possible relationship between power input to the plow motor and development of the granulation was suggested.[1] Examination of the granulation process in several different mixers,

including a high intensity type, attempted to correlate power consumption with intragranular porosity, binder amount, and time to develop a suitable mass.[2] Subsequently, it has been suggested that the correlation of power input to the plow motor and granulation characteristics appears to be dependent upon the type of materials being processed.[3]

Other studies[4,5] have used the differential of the power consumption signal in controlling the amount of binder in an uncritical process. A means of determining the uncritical quantity of granulating fluid using power consumption measurements for planetary mixers has been shown adaptable to high intensity mixers.[6-10]

The use of a target probe to detect changes in particle momentum with varying formulation and process characteristics has been successfully demonstrated under a production atmosphere.[11,12] The recording of amperage to the plow and chopper motors has also been applied to monitoring the granulation process.[13]

Recently, measurement of plow motor rotational rate changes via an optical incremental encoder has been made.[14] Rotational rate changes have been correlated with granule size distribution when other process and formulation parameters are held constant.[15,16]

The use of a capacitive sensor[17-19] to measure distribution of aqueous based binder systems has shown promise in monitoring the granulation process and determining optimum water quantities.

In summary, depending upon formulation and process variables, it may be possible to design a granulation monitoring/endpoint detection system to meet specific applications. No single system currently available appears universally acceptable.

In a previous communication,[20] the use of a commercial device, a motor load analyzer, which monitors motor slip characteristics, has been suggested as a means of monitoring the granulation process in a high intensity mixer. This report describes studies conducted to define its suitability for this application.

EXPERIMENTAL

Instrumentation: The plow motor of a high intensity mixer[1] was instrumented with a motor load analyzer,[2] as previously described.[20]

Test Materials: The test system consisted of a blend of 8 kg of lactose[3] and 2 kg of microcrystalline cellulose[4] with varying amounts of povidone[5] added either as an aqueous solution or as part of the blend followed by massing with Purified Water, USP. Magnesium stearate[6] was added to the dried milled granulations for the compression studies.

Test Methods: Granulations were processed for a total of fifteen minutes with liquid addition occurring five minutes into the run. All studies were performed with a high speed plow. If the chopper was implemented during the granulation process, it was activated approximately five seconds after liquid addition was initiated.

Binder solutions which were added in a single large increment (dumped) were added via an orifice in the lid of the mixer.

Binder solutions which were sprayed[7] were added over a 5 ± 0.25 minute interval unless otherwise noted.[8] The solution atomization pressure was 30 psi.

The wetted granulations dried in a hot air oven[9] set at about 60°C until their moisture contents were less than one percent. A representative 10 g sample maintained at 69°C for 10 minutes[10] was used for the moisture determinations.

Dried unmilled granulations were examined for their bulk densities[14] and particle size distributions.[15] A 50 g representative sample was used for the particle size measurements.

Dried granulations were passed through a hammer mill[11] fitted with a 0.079" (2.0 mm) round hole screen[12] and operated at high speed with knives forward. The reduced granulations were blended with 0.5% w/w magnesium stearate for two minutes in a twin shell blender.[13]

Compression studies were conducted on a suitable tablet press[16] fitted with 7/16" (11.1 mm) standard concave tooling.[17] Target tablet weight was 700

mg. Tablets were tested for weight,[18] hardness,[19] and thickness.[20]

RESULTS & DISCUSSION

A motor load analyzer (MLA) is designed to measure the slip characteristics of an alternating current single speed motor.[21] Its instrumentation to a high intensity mixer has been discussed.[20] MLA output is recorded in percent horsepower (% HP). The area under the percent horsepower - time profile is the percent power consumption (% HP - minutes) for the massing process.

Two series of experiments were conducted to examine the effects of formulation and processing variables on MLA output. In one series, the 4:1 lactose/microcrystalline cellulose blend was massed with varying quantities of a 5% w/w aqueous povidone solution. A high speed plow with or without a high speed chopper was used. Binder addition was either by spraying or by dumping. In the other series, the processing conditions of high speed plow and chopper along with a liquid volume of 2500 ml were maintained constant.

The povidone concentration ranged from 1% to 2.5% w/w of the lactose/microcrystalline cellulose blend. Its addition was either as an aqueous solution or as part of the lactose/microcrystalline cellulose blend with massing using water. All liquid additions were in a single increment (dumping).

Figure 1 shows typical MLA output profiles for the lactose/microcrystalline cellulose system used in this study. Upon addition of the granulating liquid in a single increment, there was a sharp increase in percent horsepower followed by a plateauing of response as the liquid became more distributed throughout the mass. With liquid addition by spraying, the increase in MLA output was more gradual, reaching a maximum at about the time spraying was terminated.

The effects of liquid volume and chopper operation on MLA response of maximum percent horsepower and percent power consumption are presented in Figures 2 and 3. When the chopper was operated, response was slightly lower than when the chopper was not implemented. This difference is due to a change in mixing characteristics within the vessel resulting in less

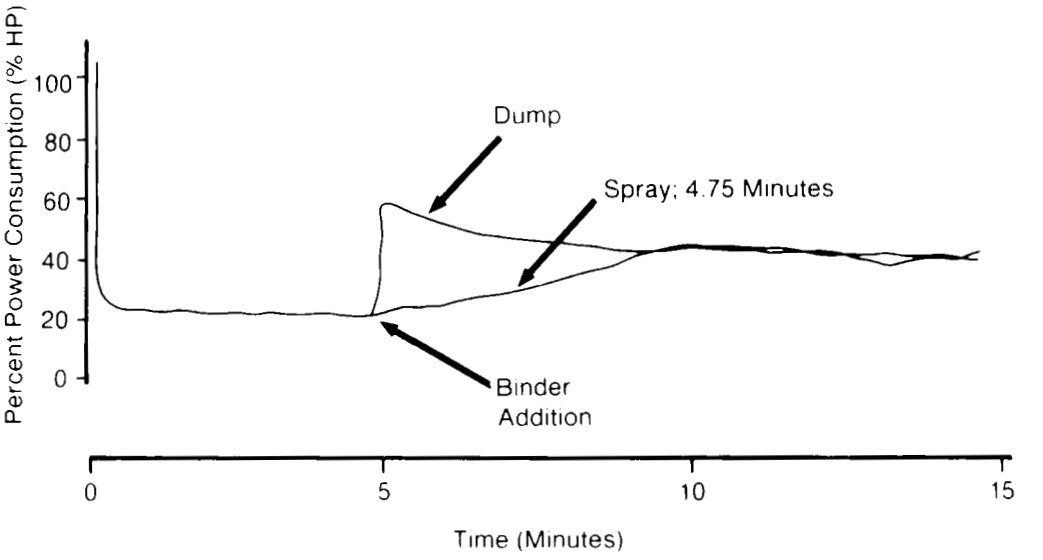

Figure 1

Typical Motor Load Analyzer Output Profile for the 4:1 Lactose/Microcrystalline Cellulose-Povidone System Demonstrating Different Liquid Addition Methods

torque on the plow motor shaft when the chopper was used. The data are similar for liquid addition by dumping and spraying.

Figure 4 shows the effect of spray time on maximum percent horsepower and percent power consumption. There is a slight increasing trend in both parameters with increasing spray time. Even at the longest spray time these data are consistent with the trends presented in Figures 2 and 3. Thus, this suggests

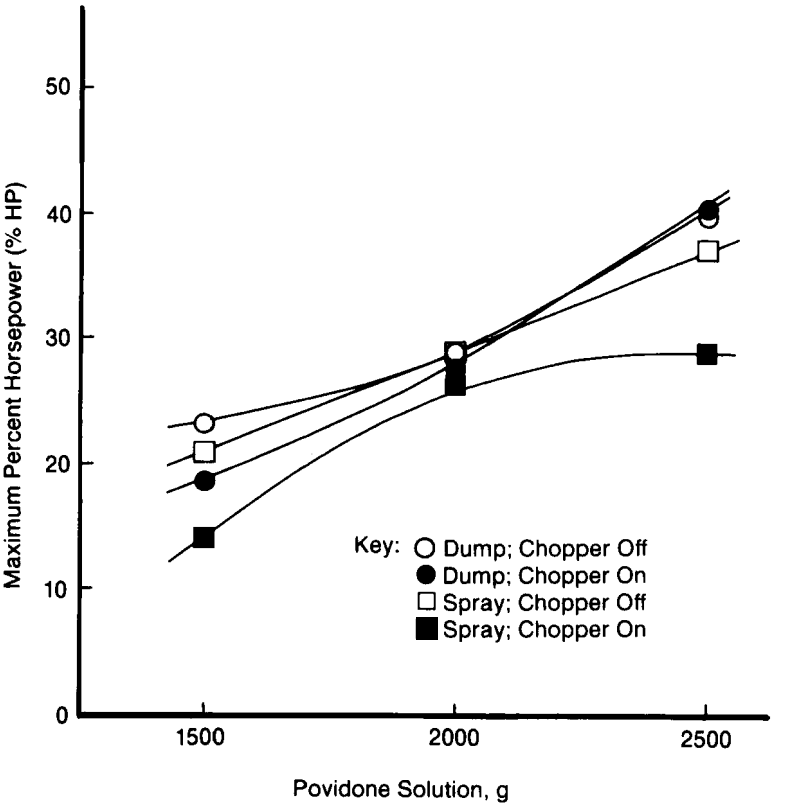

Figure 2

Effect of the Quantity of a 5% W/W Aqueous Povidone Solution on Maximum Percent Horsepower of the Motor Load Analyzer Trace

that the MLA system cannot discern small variations in spray time for this system.

Varying the povidone concentration along with its addition as as aqueous solution or as part of the lactose/microcrystalline cellulose blend does not

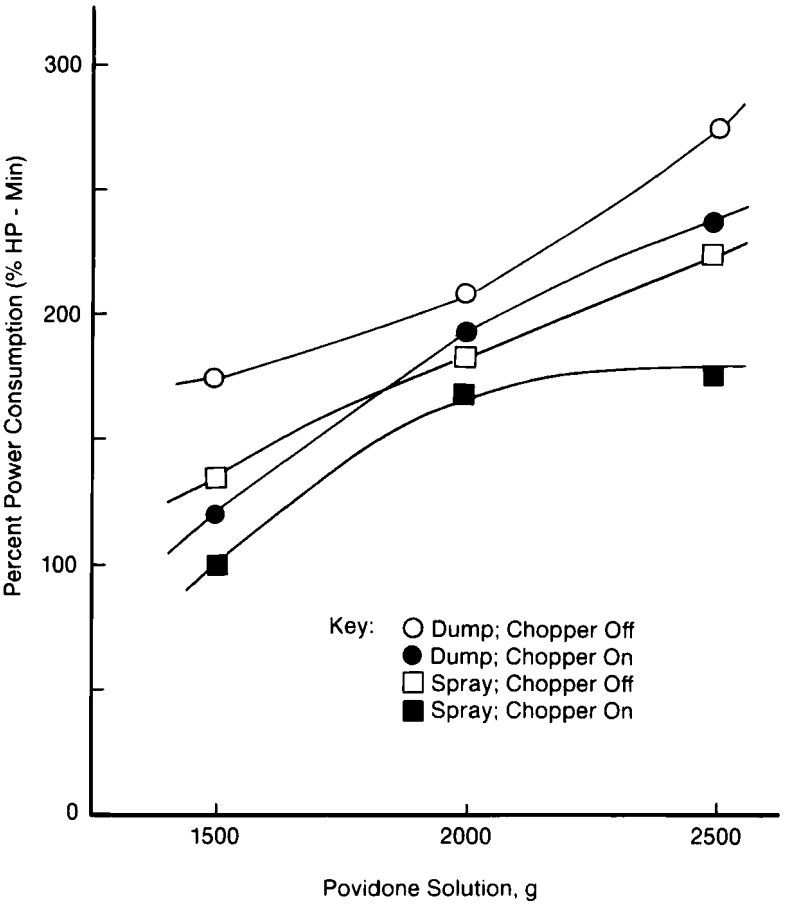

Figure 3

Effect of the Quantity of a 5% W/W Aqueous Povidone Solution on Percent Power Consumption

cause much of a change in maximum percent horsepower or percent power consumption (Figure 5). Here again, the MLA instrumentation is not capable of detecting differences in the order of addition of materials or small variations in concentration of excipients.

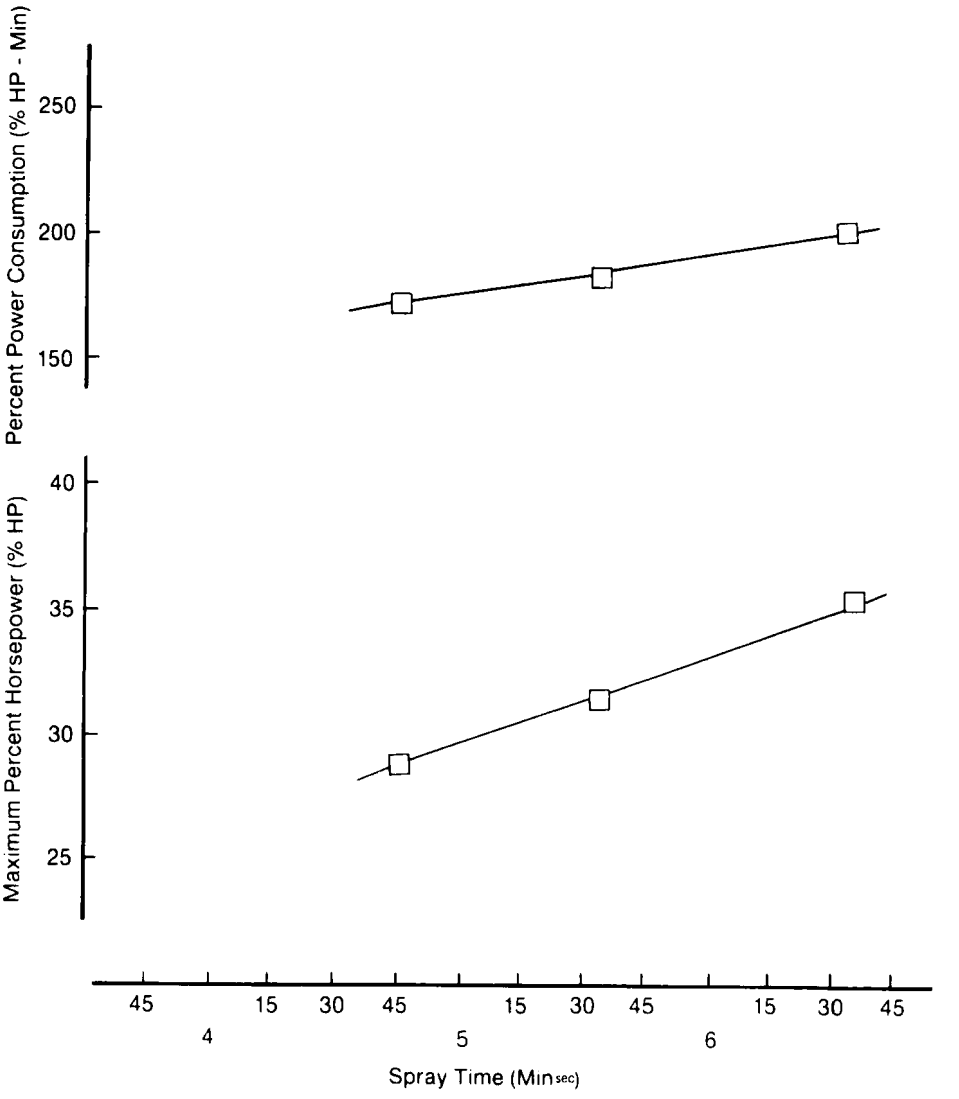

Figure 4

Effect of Spray Time on Percent Power Consumption and Maximum Percent Horsepower of the Motor Load Analyzer Output for 2500 g of a 5% W/W Aqueous Povidone Solution and Chopper On

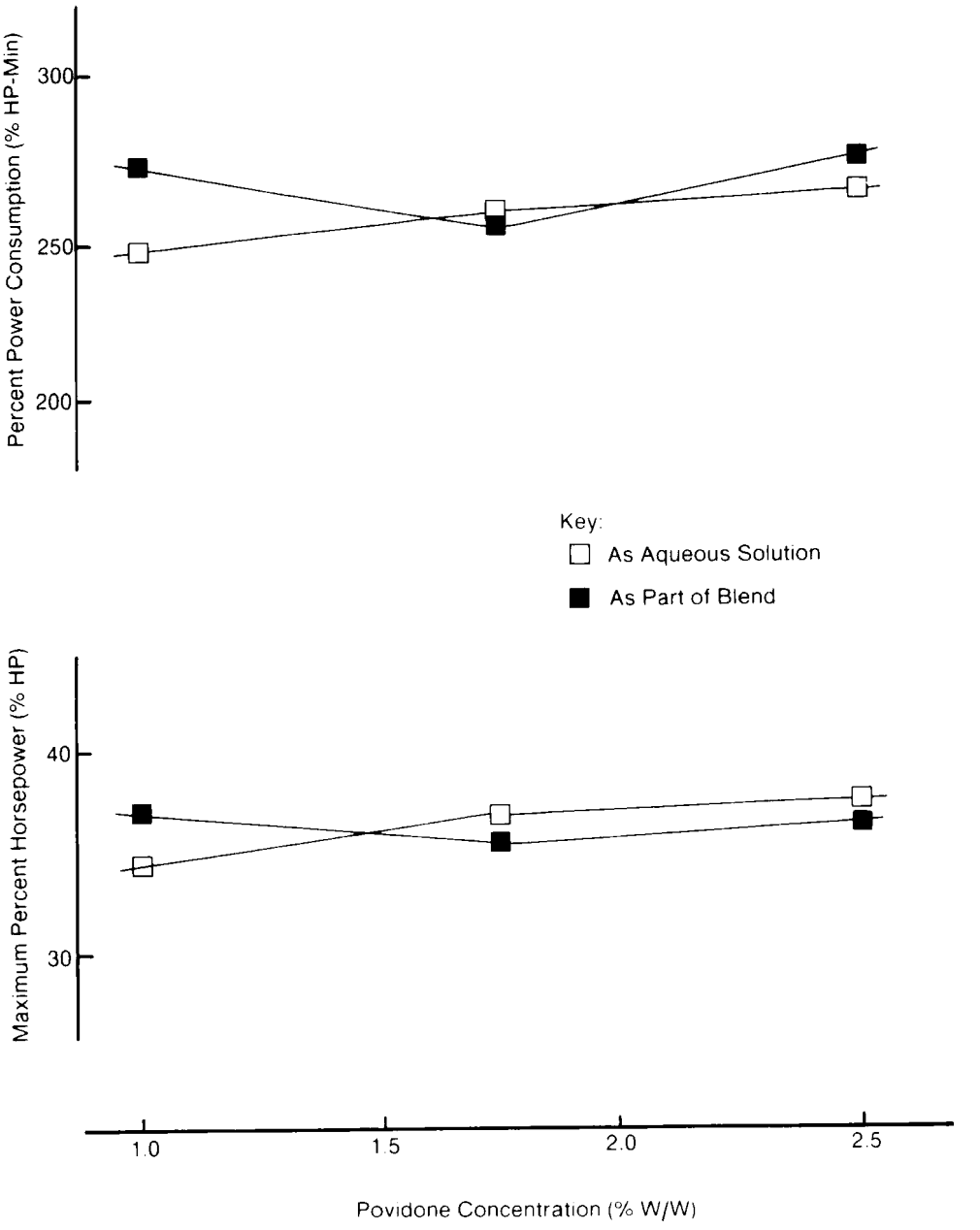

Figure 5

Effect of Povidone Addition Method on Maximum Percent Horsepower and Percent Power Consumption of the Motor Load Analyzer Trace

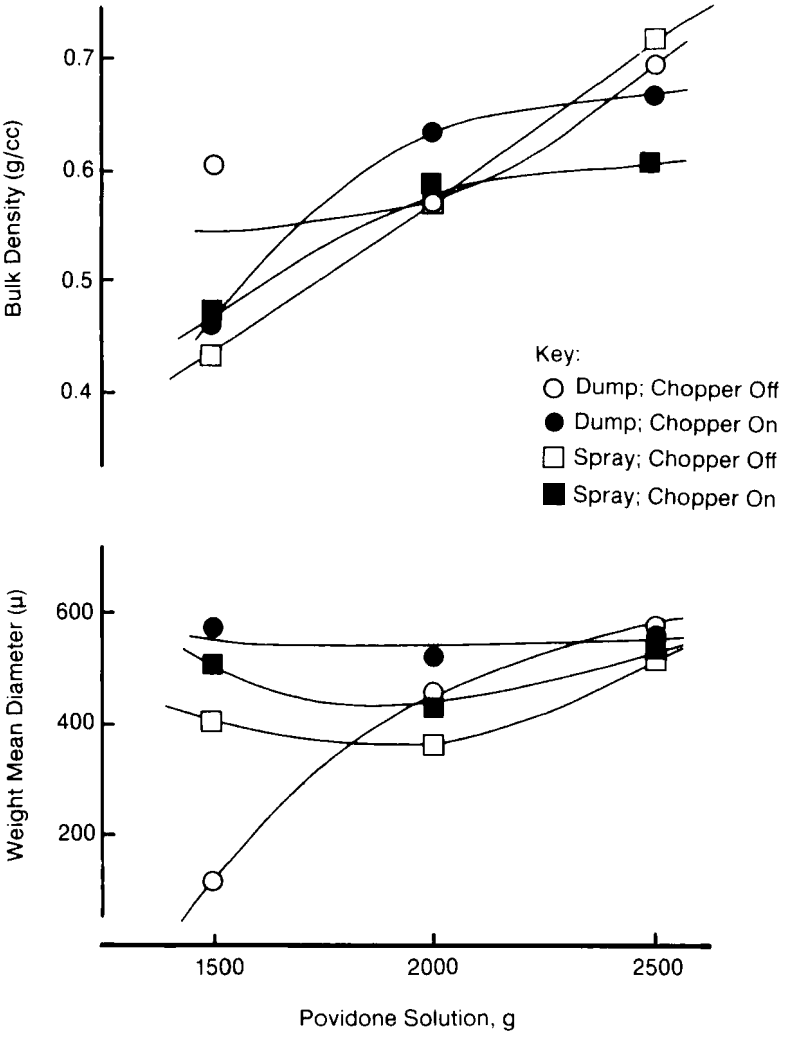

Figure 6

Effect of the Quantity of a 5% W/W Aqueous Povidone Solution on Granulation Bulk Density and Average Particle Size

To further evaluate our system, the granulations were processed through a battery of physical characterization tests. Changes in bulk density of the granulations with formulation and processing modifications are given in Figures 7-9. Results show an increase in bulk density concurrent with increasing liquid volume. As the quantity of povidone is increased at a given liquid volume, there is a slight decrease in bulk density. There does not appear to be much difference in bulk density with changes of binder addition methods; wet versus dry, or spray versus dump. Also, a chopper effect could not be detected.

Only when the chopper was not used was there an apparent change in average particle size and particle size distribution with increasing liquid quantity. At a constant liquid volume there was a slight decreasing trend in particle size with increasing povidone amount (Figures 7-11).

The average compressibility of the granulations are given in Tables I and II. The values reported represent the slopes of the linear relationships between tablet hardness and compression force. Table III report the capping force for the

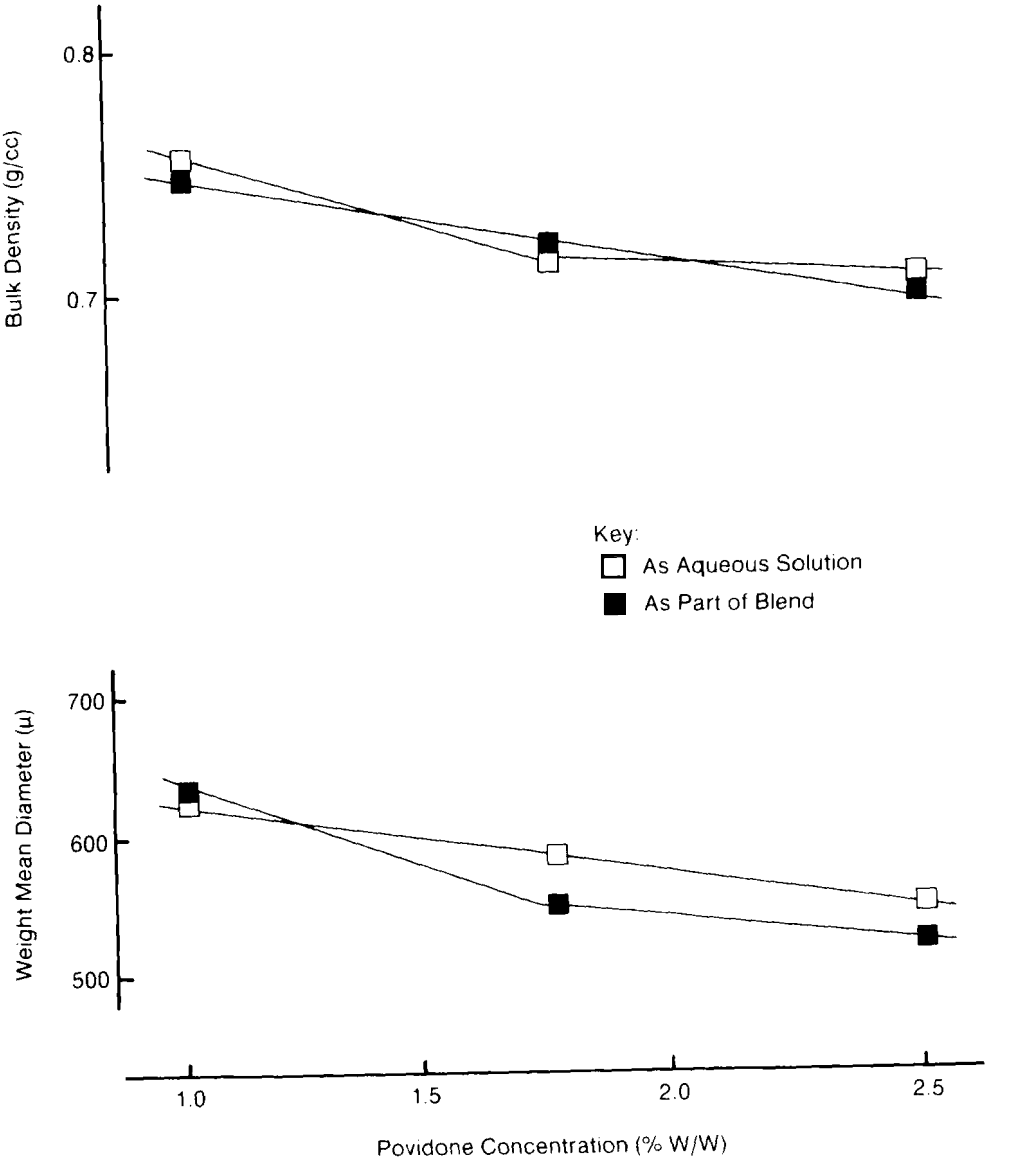

Figure 7
Effect of Povidone Addition Method on Granulation Bulk Density and Average Particle Size

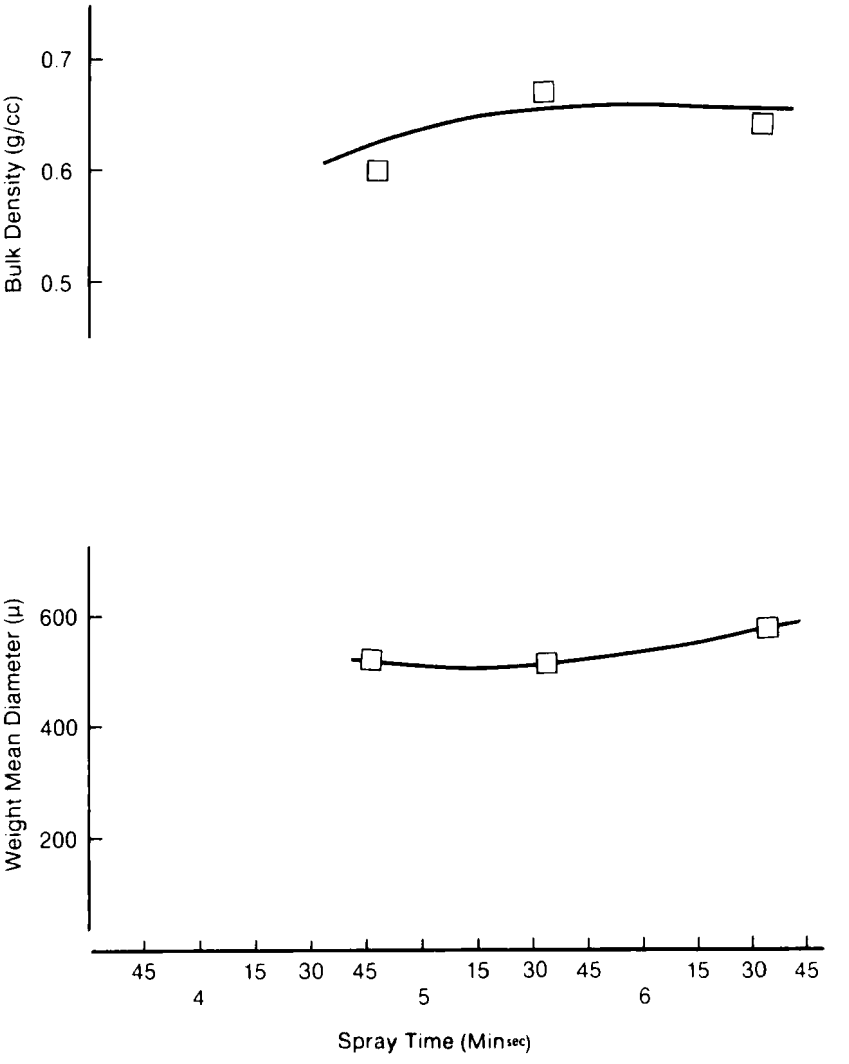

Figure 8

Effect of Spray Time on Granulation Bulk Density and Average Particle Size for 2500 g of a 5% W/W Aqueous Povidone Solution and Chopper On

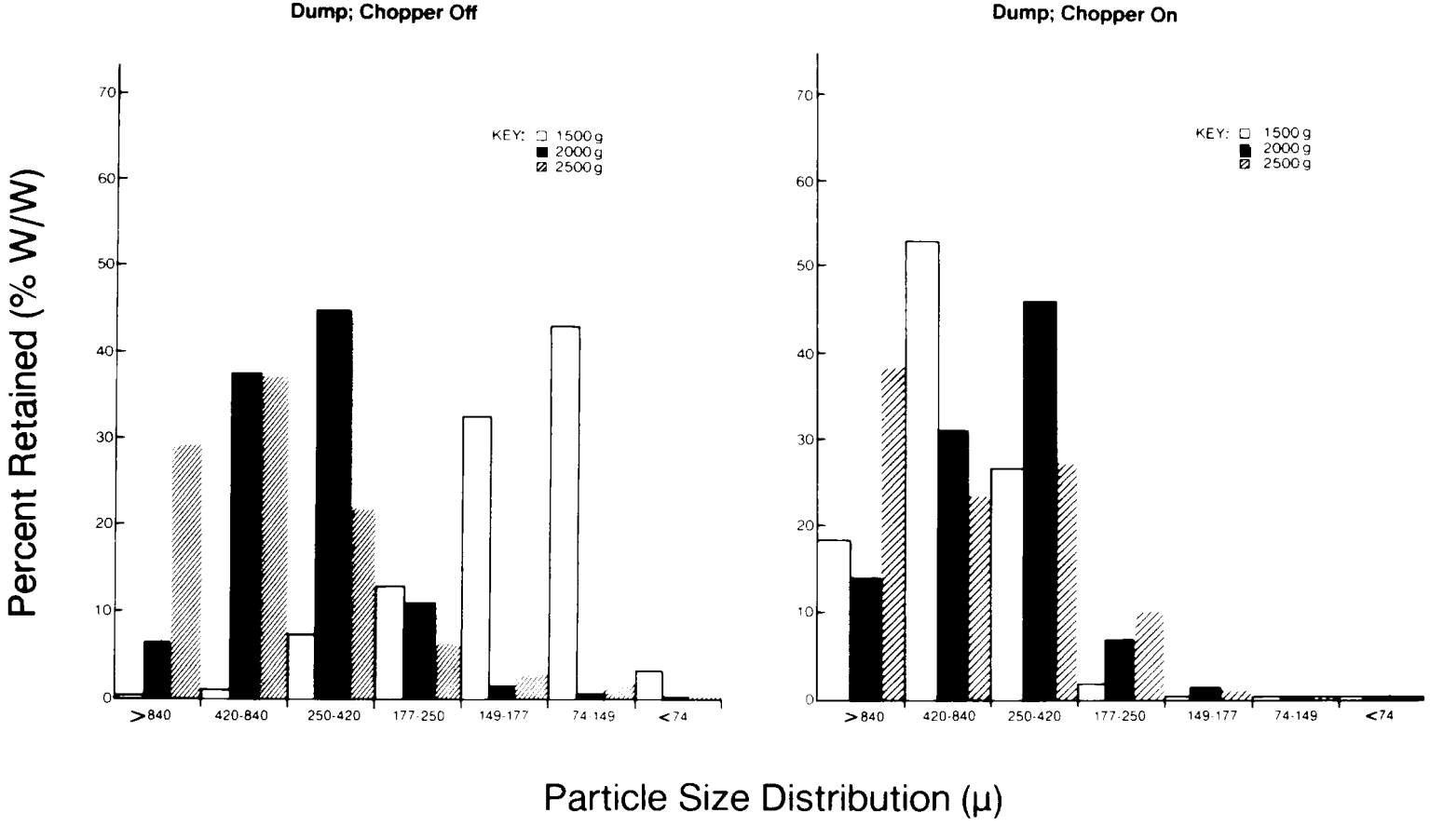

Figure 9

Effect of the Quality of a 5% W/W Aqueous Povidone Solution on the Particle Size Distribution of the 4:1 Lactose/Microcrystalline Cellulose System

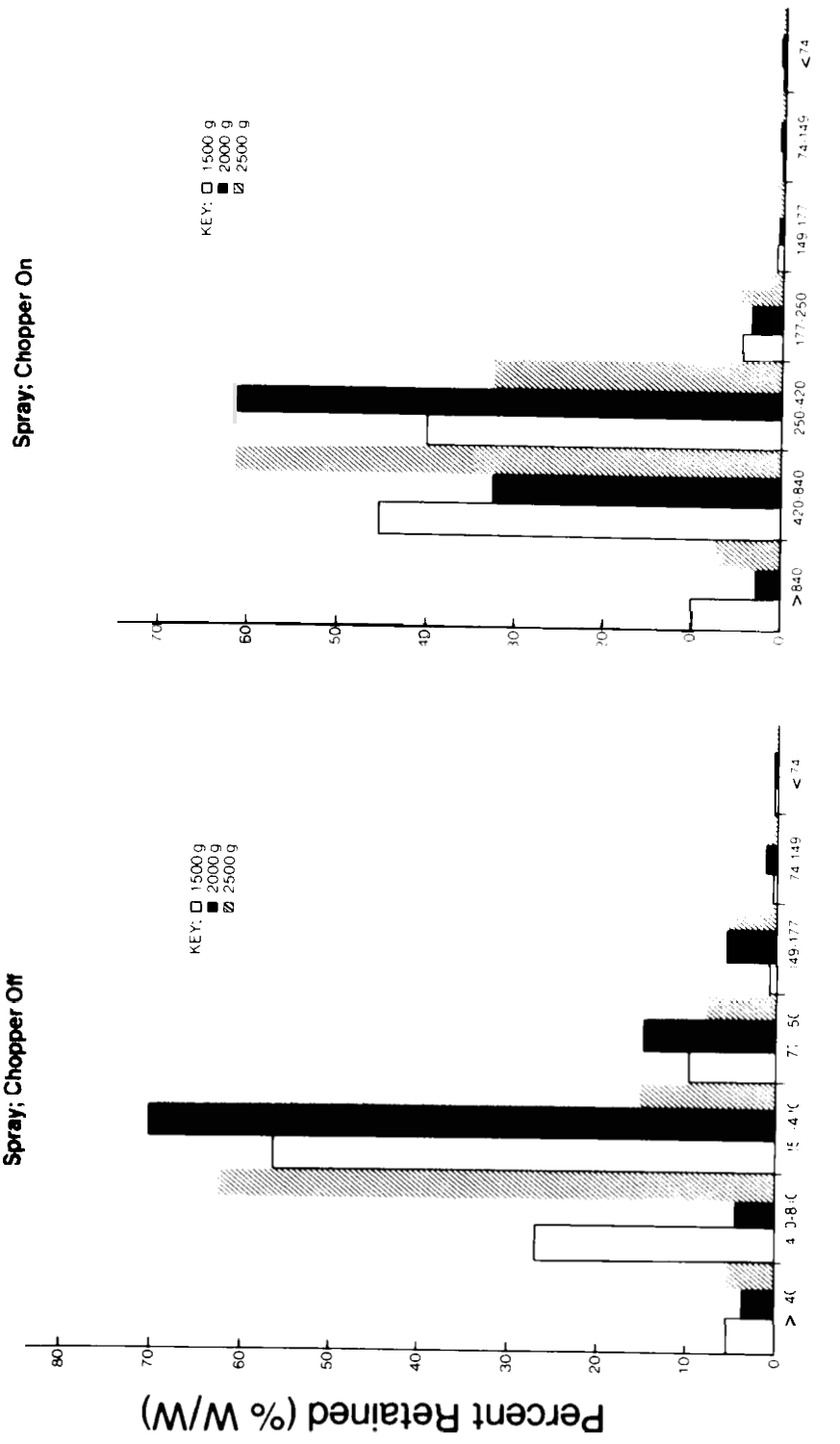

Figure 9 continued.

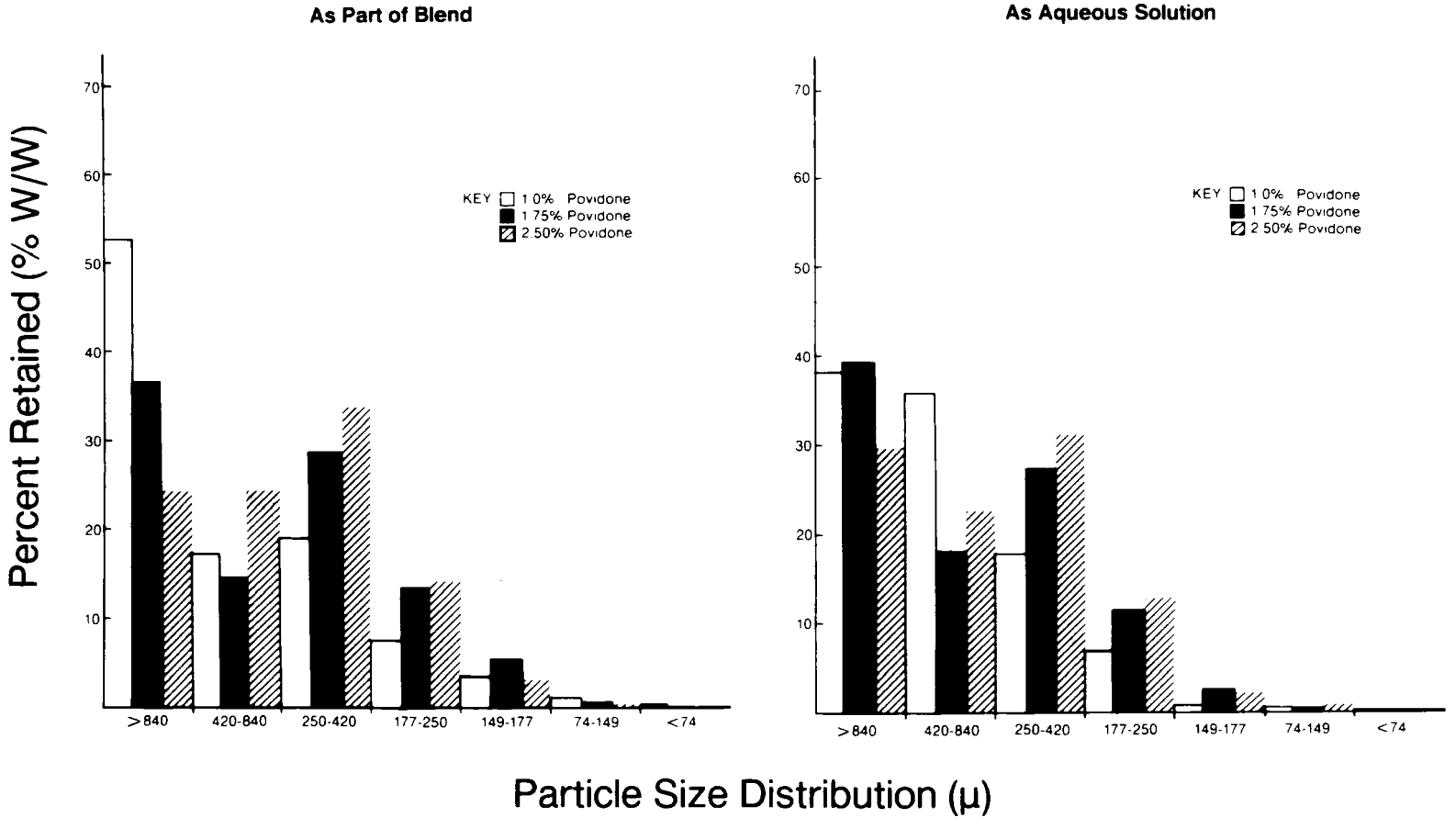

Figure 10

Effect of Povidone Addition Method on the Particle Size Distribution of the 4:1 Lactose/ Microcrystalline System

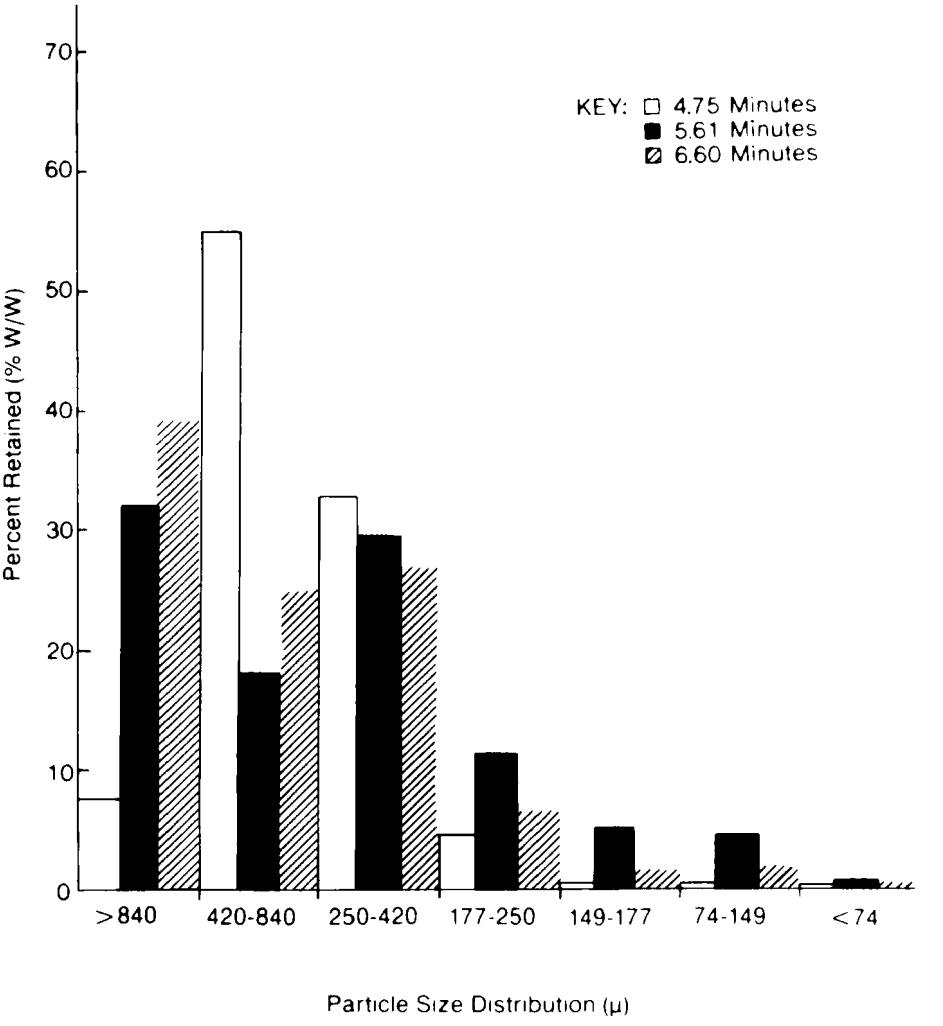

Figure 11

Effect of Spray Time on the Particle Size Distribution of the 4:1 Lactose/Microcrystalline Cellulose System Prepared with 2500 g of a 5% Aqueous Povidone Solution and Chopper On

TABLE I

AVERAGE COMPRESSIBILITIES OF THE 4:1 LACTOSE/MICROCRYSTALLINE CELLULOSE BLENDS GRANULATED WITH VARYING AMOUNTS OF A 5% W/W AQUEOUS POVIDONE SOLUTION

QUANTITY	METHOD OF BINDER ADDITION			
	DUMP		SPRAY[1]	
binder / (g) /chopper	ON	OFF	ON	OFF
1500	2.64[2]	1.88	2.23	3.80
2000	1.97	2.24	1.81	2.73
2500	1.60	1.61	2.63	1.80

[1] Spray time of 5 ± 0.25 minutes.

[2] Slope of the linear portion of the tablet hardness versus compression force profile.

granulations prepared with varying binder quantities. With a liquid volume of 2500 ml and an increasing povidone quantity, the granulation did not show a capping tendency under the experimental conditions employed.

Although the compressibilities were similar, the capping force of the granulations differed.

TABLE II

AVERAGE COMPRESSIBILITIES OF THE 4:1 LACTOSE/MICROCRYSTALLINE CELLULOSE BLENDS GRANULATED WITH VARYING AMOUNTS OF POVIDONE

POVIDONE CONCENTRATION (% W/W)	METHOD OF POVIDONE ADDITION [1]	
	DRY	WET
1	1.54[2]	1.31
1.75	1.58	1.73
2.5	1.72	1.70

[1] Liquid addition by dumping; choppers on.

[2] Slope of the linear portion of the tablet hardness versus compression force profile.

Granulations prepared with the chopper on had a higher capping force than those prepared without the chopper. Also, spray binder addition appears to yield granulations with slightly higher capping force than those prepared with binder addition by dumping.

Tables IV and V present the frictional pressure (ejection force per contact area of tablet in the die)

TABLE III

MAXIMUM COMPRESSION FORCE (kN) BEFORE CAPPING FOR THE 4:1 LACTOSE/MICROCRYSTALLINE CELLULOSE BLENDS GRANULATED WITH VARYING AMOUNTS OF A 5% W/W AQUEOUS POVIDONE SOLUTION

QUANTITY	METHOD OF BINDER ADDITION			
	DUMP		SPRAY[1]	
binder / (g) /chopper	ON	OFF	ON	OFF
1500	20	18	30	20
2000	27	23	28	20
2500	No capping	30	No capping	30

[1] Spray time of 5 ± 0.25 minutes.

per unit of compression force for the various samples. The values represent the slopes of the linear relationships of frictional pressure and compression force, and are an indication of the cohesiveness of the prepared tablets. A cohesive tablet generally has a higher value than a weakly cohesive tablet which tends to laminate on decompression.

TABLE IV

FRICTIONAL PRESSURE (kN/mm^2) PER UNIT OF COMPRESSION FORCE (kN) FOR THE 4:1 LACTOSE/MICROCRYSTALLINE CELLULOSE BLENDS GRANULATED WITH VARYING AMOUNTS OF A 5% W/W AQUEOUS POVIDONE SOLUTION

QUANTITY	METHOD OF BINDER ADDITION			
	DUMP		SPRAY(1)	
binder / (g) /chopper	ON	OFF	ON	OFF
1500	1.51(1)	1.34	1.65	2.43
2000	1.61	1.65	1.98	2.42
2500	1.68	1.73	2.50	2.28

(1) Spray time of 5 ± 0.25 minutes.

(2) $1/mm^2 \times 10^4$; slope of the linear portion of the frictional pressure versus compression force profile.

There is little difference in the frictional pressure/unit of compression force values at the 2500 g binder level for spraying and dumping. However, at the lower liquid levels, 1500 g and 2000 g, the values are greater for binder addition by spraying. (Table IV). There does not appear to be much difference among granulation in which the povidone

TABLE V

FRICTIONAL PRESSURE (kN/mm^2) PER UNIT OF COMPRESSION FORCE (kN) FOR THE 4:1 LACTOSE/MICROCRYSTALLINE CELLULOSE BLENDS GRANULATED WITH VARYING AMOUNTS OF POVIDONE

POVIDONE CONCENTRATION (% W/W)	METHOD OF BINDER ADDITION [1]	
	DRY	WET
1	1.38[2]	1.34
1.75	1.29	1.46
2.5	1.53	1.51

[1] Liquid addition by dumping; choppers on.

[2] $1/mm^2 \times 10^4$; slope of the linear portion of the frictional pressure versus compression force profile.

concentration was added in increasing amounts as part of the preblend or as an aqueous solution (Table V).

Figure 12 shows a plot of frictional pressure per unit of compression force versus capping force for those granulations in which capping was observed. For binder addition by dumping, as the frictional

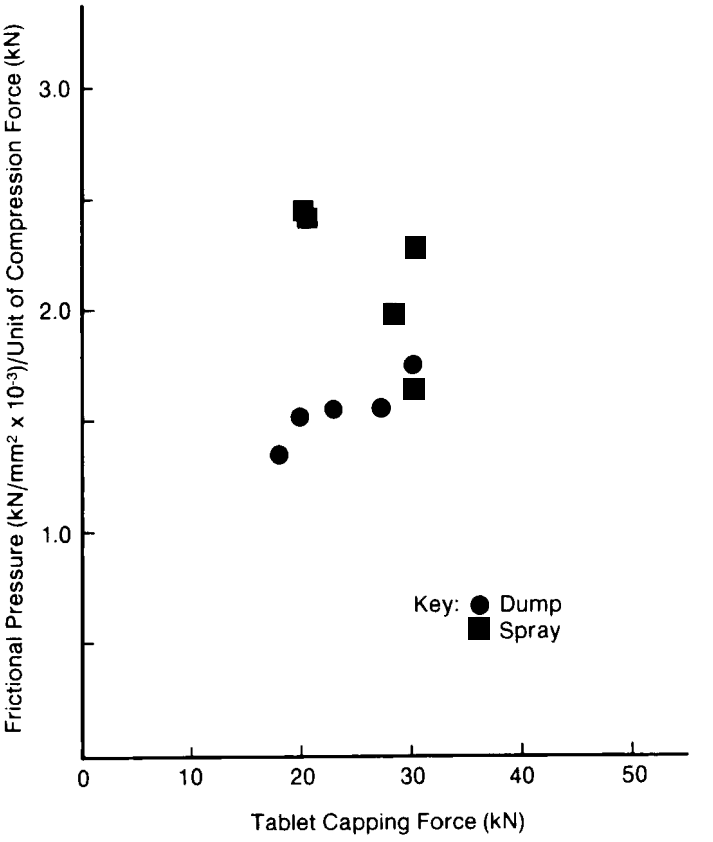

Figure 12

Frictional Pressure/Unit of Compression Force Versus Tablet Capping Force

pressure/unit of compression force increased with increasing liquid volume, so did the capping force. This trend was not observed for spray binding addition. These results are consistent with prior studies on lactose and calcium phosphate granulations which indicated that spray binder addition yields a

more cohesive tablet than binder addition in a single large increment.[22]

In summary, the MLA appears suitable to monitor the granulation process from a routine process control standpoint. It can detect changes of process variables such as binder addition method, and chopper operation. It does not appear capable of detecting subtle formulation modifications such as order of material addition. The physical characteristics and compression properties of the test granulations depended upon binder level, chopper usage, and method of liquid addition.

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Pharmaceutical Sciences, Minneapolis, Minnesota, October 20-24, 1985.

FOOTNOTES

1. Model MGT 70, Littleford Brothers, Inc., Florence, KY
2. Model 2340, Rexnord Instrument Products, Malvern, PA
3. NF, hydrous, regular grind, Foremost Whey Products, Barboo, WI
4. NF, Avicel PH102, FMC Corporation, Newark, DE
5. NF, Plasdone K29-32, GAF Corporation, New York, NY
6. NF, Witco Chemical Company, South Plainfield, NJ
7. Model 1/4 JAV-PM spray gun with a Model 2850 fluid cap and a Model 67228-45 air cap, Spray Systems Co., Wheaton, IL
8. Model 4555-3 pump/controller with Masterflex Model 7018-10 pumphead, Cole-Parmer Instruments, Chicago, IL
9. Model POM-106G Oven, Blue-M Electric Company, Blue Island, Ill.
10. Model 0601, Ohaus Scale Corporation, Union, NJ
11. Model JT Homoloid Mill, Fitzpatrick Company, Elmhurst, IL
12. Fitzpatrick Company, Elmhurst, IL
13. Patterson-Kelly Co., East Stroudsburg, PA
14. Type TP-D Powder Characteristics Tester, Hosokawa Micromeritics Laboratory, Osaka, Japan

15. 8" diameter U.S.A. Standard Testing Sieves (W. S. Tyler, Inc. Mentor, O) on a Type RP 03.001 Pulverit Classification Equipment (Geoscience Instruments, Corp., Mount Vernon, NY) at 50 amplitude.

16. Model LX21, Kilian & Co. GMBH Maschinenfabrik, Köln, West Germany

17. Elizabeth Carbide Die Co. Inc., McKeesport, PA

18. Type 1212 MP Balance, Sartorius GMBH, Göttengen, West Germany

19. Schleuniger Model ZE/106 Tester, Vector Corp., Hiawatha, IA

20. Model 27, B.C. Ames Co., Waltham, MA

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