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EFFECT OF RAW MATERIALS AND PROCESSING ON THE QUALITY OF GRANULES PREPARED FROM MICROCRYSTALLINE CELLULOSE-LACTOSE MIXTURES

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ABSTRACT

Wet granulation, using lactose as an excipient, is widely used in the pharmaceutical industry. The use of microcrystalline cellulose, as part of the excipient, may offer several advantages. The purpose of this work is to investigate the effect of ingredients and processing variables on granule quality. For these studies, only two-component systems granulated with water in a planetary mixer were considered. The variables studied included the volume of granulating solution, type of lactose, dissolved material (other than binder) in the granulating solution, massing time, mesh size for wet screening and drying technique (oven and fluidized bed drying).

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INTRODUCTION

Wet granulation experiments on simple two-component systems using only water as the granulating agent were carried out to study the mechanism of the agglomeration process. Effect of the composition of granulating liquid, characteristics of the components and process variables for a lactose-boric acid binary mixture has been studied by Opakunle and Spring (1-3).

The results of variation in raw materials and of changes in several important processing variables are described in the present paper. Much of the data documents what one might predict. The most dramatic results, however, show that there is a difference between oven dried and fluid bed dried granules. It was also necessary to find a way to monitor lactose dissolution to attempt to explain the granule characteristics when the lactose dissolves to form its own binder.

MATERIALS AND METHODS

Wet granulations containing microcrystalline cellulose (Avicel PH-101, FMC Corp., Philadelphia, PA) and lactose (25:75) were prepared using only purified water as a granulating liquid. Two different types of lactose were included to study the effect of variation in raw material (particle size, crystal shape, solubility, etc.); i.e., regular lactose or a direct compression lactose.

The powders were dry blended for four minutes in a planetary mixer operating at 140 rpm (Kitchen Aid Model K 5 SS -

Hobart). The granulating liquid was added and granulation proceeded for either eight or fifteen minutes. The effect of the wet milling operation on granule quality was studied using either 8 or 12 mesh screens. Batches were oven dried (Stokes Model 38C) at 40 degrees celsius or fluidized bed dried (Aeromatic Column); residual amount of water was held lower than 4%.

The granule properties investigated include size distribution, friability and bulk, and tapped volume. Granule friability was determined by subjecting 10 g of granules (250 um - 590 um fraction) together with 200 glass beads (average diameter 4 mm) to falling shocks for 10 minutes in an Erweka Friabilator fitted with an abrasion wheel. Sieve analysis and bulk and tapped volumes were determined by standard techniques.

Dissolution rates for the two different types of lactose were determined using a 250 g MCC-lactose blend in 500 ml water in a planetary mixer operating at 140 rpm. The refractive index was used to monitor the amount of lactose dissolved as a function of time.

RESULTS AND DISCUSSION

Effect of the quantity of granulation solution on granule properties

Varying quantities of water were used to granulate a 3 kg blend of microcrystalline cellulose and direct compression lactose (25:75). The wet granulation step was followed by coarse milling (by hand) through either an 8 or 12 mesh screen. In each case, one-half of the batch was oven dried and one-half was dried in a fluidized bed.

As shown in Table I, a decrease in total amount of granulation liquid resulted in significant increase in friability. When the amount of granulation liquid was decreased from 45% to 35% of dry weight of powder material, the friability doubled independently of the drying technique or wet milling conditions. This would be expected due to incomplete granulation at lower liquid levels, and these simple measurements may represent a method to optimize one's granulation process.

Effect of Sieve Size

The choice of wet screen aperture affects particle size distribution, as expected; a greater number of medium and coarse particles are produced with the larger (8 mesh) screen (Table I). For the same type of granulation, however, bulk volume does not seem to be affected by the choice of the wet screen aperture. By observing and monitoring the extrusion behavior of a wet granulation through different sieve sizes, one can evaluate the granulation liquid level and the state of liquid distribution in his granulation.

Effect of Drying Method

Granule friability was generally twice as high for oven dried granules as compared to fluidized bed dried granules. The

Table I

Physical Properties of Granules

Influence of Granulating Liquid Level, Coarse Milling and Drying Method

	Oven drying				Fluidized bed drying			
Amount of water expressed as % dry weight	35 %		45 %		35 %		45 %	
Wet sieve size (mesh)	8	12	8	12	8	12	8	12
Particle size (micrometers)	**% weight**							
Less than 250	14.6	14.3	6.7	6.9	28.1	24.6	9.2	16.1
250 - 590	49.2	68.5	27.1	30.0	22.2	54.8	26.3	34.7
Larger than 590	36.2	17.2	66.2	63.1	49.7	20.6	64.5	49.2
Friability (%)	45	55	22	20	20	20	6	10
Volume (ml)								
Bulk	63	64	63	61	52	55	53	54
Tapped	48	49	54	51	45	46	49	47

oven dried granules were also larger. This phenomenon could be explained if more fines were produced during the fluidization step in drying, so that the remaining granules were smaller, but harder and less friable (Table I). Fluidized bed drying also yielded lower bulk volumes than oven dried granules since the fines could exhibit closer packing.

Influence of Raw Materials

Similar granulations were prepared with either regular lactose or direct compression lactose. Table II lists the properties for granules prepared with identical quantities of granulating solution and the same drying technique. For the same quantity of granulating solution, the mixture with D.C. lactose produced less friable granules with a more narrow particle size distribution. See Figures 1(a) and 1(b).

Influence of Massing Time

An increase in the granulating time from 8 to 15 minutes dramatically reduced the friability of MCC-lactose granules, especially in the case of fluidized bed dried granules. It also appears to narrow the particle size distribution (Table III and Figure 2). There are less coarse particles produced, but the amount of fines seems to be less affected. This could be explained if one postulates a more homogenous distribution of the granulating solution during the process with a longer massing time.

Table II

Influence of Lactose Type on Granule Properties

	Lactose D.C.				Lactose Regular			
	Oven dried		Fluid bed dried		Oven dried		Fluid bed dried	
Wet sieve size (mesh)	8	12	8	12	8	12	8	12
Particle size (micrometers)				**% weight**				
Less than 250	6.7	6.9	9.2	16.1	8.7	6.3	14.2	18.0
250 - 590	27.1	30.0	26.3	34.7	34.1	48.5	32.8	51.0
Larger than 590	66.2	63.1	64.5	49.2	57.2	45.2	47.0	31.0
Friability (%)	22	20	6	10	35	40	35	40
Volume (ml)								
Bulk	63	61	53	54	65	63	55	51
Tapped	54	51	49	47	53	47	49	44

45% Liquid level, 8 minute massing time.

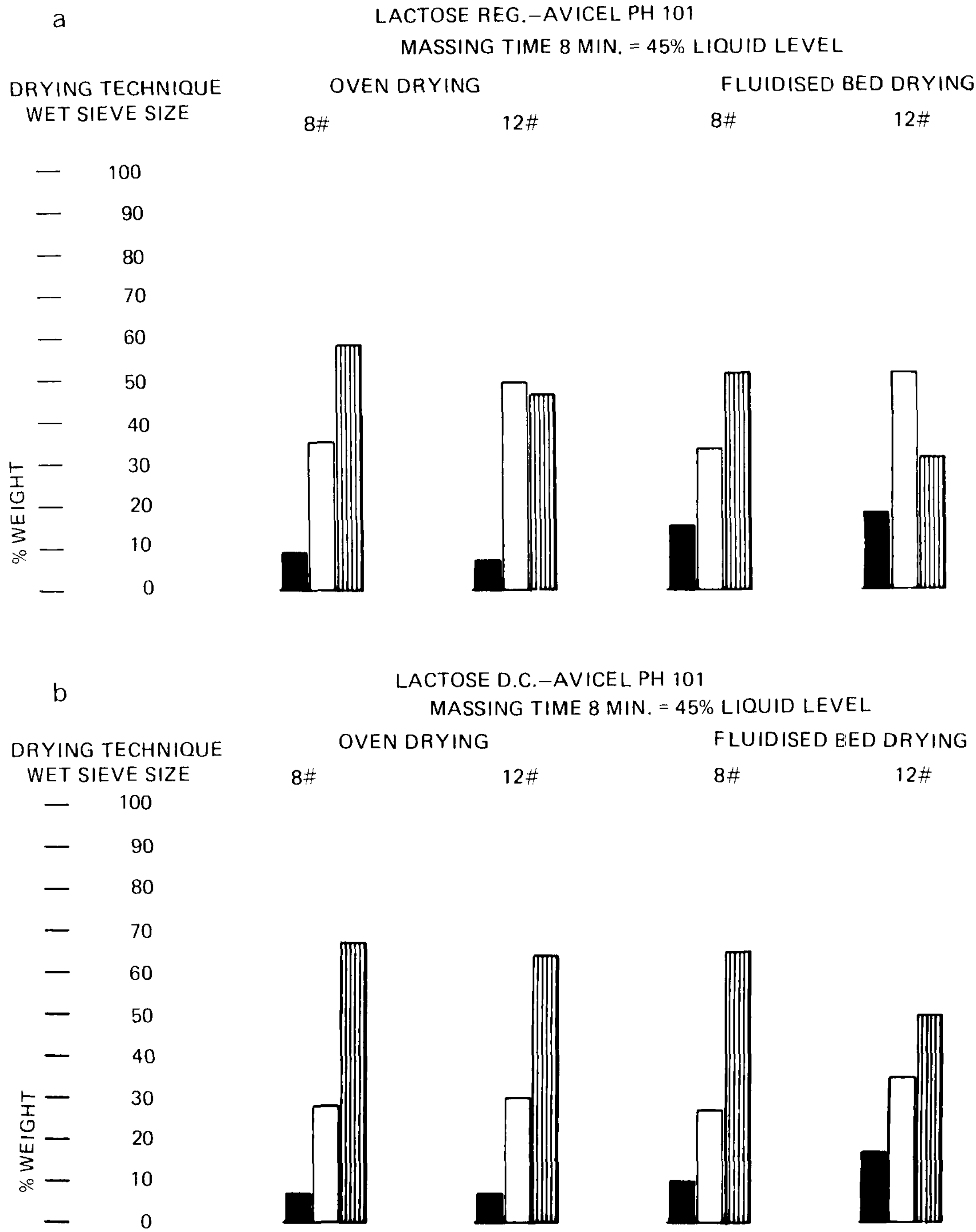

Figure 1 - Histograms representing Particle Size Distributions under various processing conditions: (a) Conventional Hydrous Lactose and (b) Direct Compression Lactose

Key: < 250 um
250 - 590 um
> 590 um

Table III
Granule Properties

	Oven dried		Fluidized bed dried	
Wet sieve size (mesh)	8	12	8	12
Particle size (micrometers)	**% weight**			
Less than 250	4.4	5.5	16.4	20.0
250 - 590	62.3	80.7	50.5	66.2
Larger than 590	33.3	13.8	33.1	14.8
Friability (%)	26	28	15	20
Volume (ml)				
Bulk	66	65	59	55
Tapped	56	49	55	46

45% liquid level, 15 min massing time.

A related observation raised an important question about the lactose activity during the process. It was observed that granules prepared with direct compression lactose exhibited lower friability values than did granules prepared with regular lactose. This could be explained if the direct compression lactose yielded a faster rate of solution than did regular lactose, and could therefore act as a more efficient binder. This hypothesis was tested experimentally, and the results in Table IV and Figure 3 show that differences can

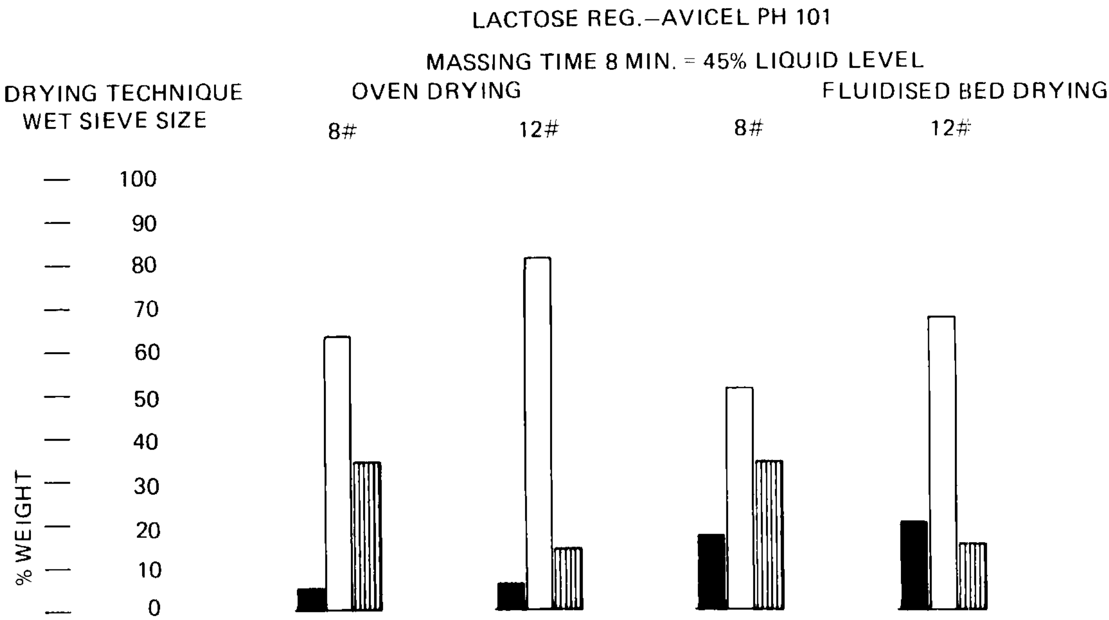

Figure 2 - Histograms representing Particle Size Distributions with increased granulation time

Key: < 250 um
250 - 590 um
> 590 um

Table IV Dissolution Profiles for Lactose

Time (min)	Lactose dissolved (% W/V) Lactose D.C.	Lactose regular
2	9.78	8.46
4	9.92	8.74
8	10.04	8.88
12	10.22	9.00
16	10.30	9.14

Experiments were performed with a 250 g of MCC-lactose blend (25:75) in 500 ml of water in a planetary mixer at 140 rpm.

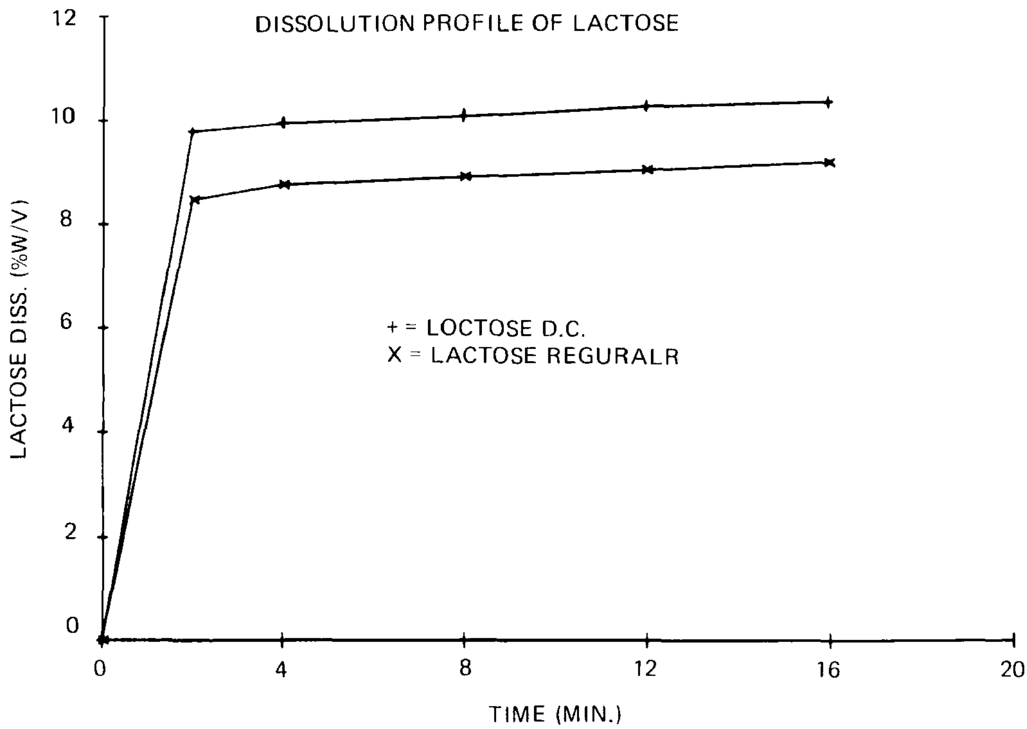

Figure 3 - Dissolution Profiles for Lactose

be observed and could support the explanation; i.e., regular lactose does not dissolve as rapidly.

Influence of Dissolved Lactose

To further support the concept that lactose may provide important binder activity, it was decided to investigate the influence of dissolved lactose on granule properties. One kg batches of the same 25:75 mixtures were granulated with a 10% lactose solution. The quantity of lactose in the dry blends was reduced accordingly in order to keep the overall amount of lactose

Table V
The Effect of Pre-dissolved Lactose on Granule Properties

	Lactose D.C. oven dried	Lactose D.C. fluid bed dried	Lactose regular oven dried	Lactose regular fluid bed dried
Particle size (micrometers)	**% weight**			
Less than 250	0.6	1.6	0.5	0.5
250 - 590	28.9	30.8	37.3	34.8
Larger than 590	70.5	68.1	62.1	64.7
Friability (%)	12	4	17	4
Volume (ml)				
Bulk	61	55	64	56
Tapped	55	53	56	53

8 min granulation time, 8 mesh wet sieve size.

constant and equal to the previous experiments. The resulting granule properties are listed in Table V.

Comparison of the data from Tables II and V shows that the amount of lactose in solution affects both the particle size distribution and the friability of the resulting granules. Dissolving a part of the lactose in the granulating fluid increased the particle size, yielding less fines and more coarse particles. Granule friability was lower in all cases. This indicates that differences in ingredient solubility, in general, may affect the granulation process, and these results may serve as guidelines for formulators.

CONCLUSIONS

For the specific mixture involved in these studies, which contains only microcrystalline cellulose and lactose, the changes in granulation conditions have produced some changes in granule characteristics which can be used to guide general processing development with respect to wet granulation.

As expected, increases in granulating fluid volume and wet sieve aperture yielded larger granules with reduced friability. Increased granulation time produced granules with reduced friability but a more narrow particle size distribution with less coarse particles.

In general, these results indicate that the selection of drying method can influence granule characteristics. It appears that the activity in a fluid bed drier, with these formulations, produces smaller and less friable granules than those from a drying oven. The bed density of these granules is greater, and although not tested, perhaps granule density is also greater. It appears that granules surviving the fluid bed treatment are smaller but more robust. A similar conclusion was reached with spheronization work in these laboratories where drying by fluidized bed produced a more smooth surface and slightly rounder beads (4).

These results also document that the rate of solution of an ingredient in a wet granulation formulation (lactose) can affect granule characteristics. Data show that D.C. lactose dissolves more rapidly than regular lactose and produces much less friable granules. In addition, dissolving the binder to make a granulating solution produced larger, less friable granules. Formulators may be able to apply these observations in the case of soluble additives or active ingredients.

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