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EFFECT OF GRANULATING METHOD ON PARTICLE SIZE DISTRIBUTION OF GRANULES AND DISINTEGRATED TABLETS. I

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ABSTRACT

The average particle size and distribution of granules were found to be dependent on the granulating method. The slugging method produced the widest particle size distribution and the largest average particle size, while the microgranulating method produced the narrowest distribution and the smallest average particle size. The average particle size of dexamethasone granules produced by wet granulating, microgranulating and slugging methods, were reduced on compaction by fragmentation. Of the three, the granules prepared by the slugging method, exhibited maximal average size reduction on compaction. On the other hand, the average particle size of sulfadiazine microgranulates and sulfadiazine slugs were enlarged by consolidation during compaction.

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INTRODUCTION

The physiological availability of many water-insoluble drugs is affected by their degree of fineness. For example, the particle size of procaine penicillin G, griseofulvin and bephenium embonate must be controlled if their therapeutic activity is to be standardized. The absorption efficiency of griseofulvin is increased two-fold if sufficiently fine powder is used. Potent water-insoluble drugs in finely divided form may, however, show a high degree of toxicity owing to their rapid rate of absorption and hence a controlled particle size may be necessary. For the quality control of these medicaments, chemical assay would only supply part of the information needed for their standardization. Consequently, attention must be given to the particle size of hydrophobic drugs.

A large number of inventions for granulating methods have been reported but not many of these have found universal application. Presently, the popular methods are conventional wet granulation, dry slugging, direct compression with granular excipients, microgranulation, pan granulation and spheronization (1-4).

This report investigates the effect of microgranulating, slugging, direct compression and wet granulating methods on particle size distribution of dexamethasone and sulfadiazine granules before compaction, and after compaction, i.e., disintegrated tablets.

EXPERIMENTAL

Materials - Dexamethasone[1] and sulfadiazine[2] were U.S. Pharmacopeial grade. Excipients used in preparing the tablets were starch[3] USP, acacia[4] USP, lactose[5] USP powder, lactose USP anhydrous

direct tableting grade[6], magnesium stearate[7] USP, talcum powder[8] USP.

Preparation of Granules and Tablets - Dexamethasone containing 0.25 mg per 150 mg tablet and sulfadiazine 130 mg per 150 mg tablet were prepared by using different granulating methods. The excipients were maintained constant in all the granulating methods within practical limitations. Formulations of the experimental dexamethasone and sulfadiazine granules and tablets are given in Tables I and II respectively. Dexamethasone was mixed with excipients by using a geometric dilution procedure in a V-blender[9] of 3 kg capacity.

Wet Granulation - The homogeneous blends of active ingredients and excipients were granulated with starch-acacia paste in a planetary mixer[10]. The wet mass was passed through an oscillating granulator[11] equipped with a No. 8 screen and oven dried overnight at 45°. After dry-screening through a No. 16 screen, the granulations were blended with the remaining dry starch and lubricated.

Microgranulation - The microgranulates were prepared as described by de Jong (1). The drug and excipient blends were granulated with purified water in a mixer. The moist mass was broken down into microgranules by passing it through the granulator equipped with a fine No. 16 screen. The rest of the method, oven drying, dry milling, blending with disintegrant and lubrication were the same as that used for wet granulation.

Granulation by Slugging - The slugs were made using a heavy duty press[12] and 1-inch diameter punches. The slugs were broken down by passing through a dry granulator equipped with a No. 16 screen.

Direct Compression - The active ingredient, binder, disintegrant

TABLE I

Formulations of Experimental Dexamethasone Granules and Tablets[a]

Ingredients mg/tab	Wet Granulation	Micro Granulation	Direct Compression	Slugging
Dexamethasone	0.25	0.25	0.25	0.25
Starch, dry	10.00	11.00	15.00	11.00
Acacia powdered	2.60	3.00	3.00	3.00
Lactose	130.75	130.25		126.75
Lactose, D.C.[b]			127.75	
Starch[c]	1.00			
Acacia powdered[c]	0.40			
Purified Water	18.60	8.00		
Starch, dry[e]	4.00	4.00		4.00
Magnesium Stearate	1.00	1.00	2.00	1.00
Talcum powdered		0.50	2.00	3.00
Magnesium Stearate[f]				1.00
Total, mg/tab	150.00	150.00	150.00	150.00

TABLE II

Formulations of Experimental Sulfadiazine Granules and Tablets[a]

Ingredients mg/tab	Wet Granulation	Micro Granulation	Slugging
Sulfadiazine	130.00	130.00	130.00
Starch, dry	7.00	10.00	10.00
Acacia powdered	2.50	4.00	4.00
Starch[c]	3.00		
Acacia powdered[c]	1.50		
Purified Water	96.00	60.00	
Starch, dry[e]	6.00	6.00	9.00[d]
Magnesium Stearate	2.00	2.00	2.00
Talcum powdered			1.00
Magnesium Stearate[f]			2.00
Total, mg/tab	152.00	152.00	158.00

[a] Batch size for each method was 10,000 tablets. [b] Direct Compressible lactose. [c] Used as starch-acacia paste. [d] Higher proportion was added to compensate for higher amount of lubricants needed. [e] Added to the dry granules. [f] Added for the final compression.

and anhydrous lactose were blended in a V-blender following geometric dilution. The blend was lubricated before compression.

Tablets were compressed on a rotary machine[12] operating at 26 rpm and using only 4 stations equipped with 5/16 in. diameter, flat punches.

Determination of Particle Size Distributions - Particle size analyses were performed on samples of the powder before granulation, after granulation and after compaction and disintegration, using a nest of sieves and an electromagnetic sieving machine[13]. The particle size distribution of the granules after compaction were determined by the method of Khan and Rhodes (5), using methanol and benzene as the disintegrating medium for dexamethasone tablets and sulfadiazine tablets respectively.

RESULTS AND DISCUSSION

Particle size distribution and average particle size were obtained from the plots of cumulative weight percent on an arithmetic scale versus particle size on a logarithmic scale. The log normality of the distribution plots were checked by comparing the geometric standard deviations.

The size distribution and average particle size were shifted to different extents by the different granulating methods (Table III). The slugging method produced the widest particle size distribution and the largest average particle size (Figures 1 and 2), while the microgranulating method produced a narrow range of size distribution and the smallest average particle size (Figures 3 and 4). The latter method caused very little change of size distribution and

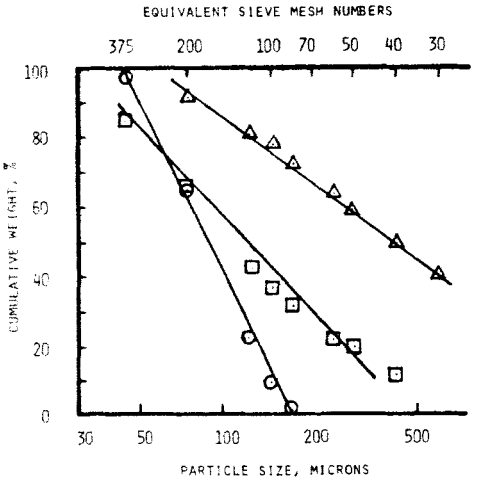

FIGURE 1

EFFECT OF THE SLUGGING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF DEXAMETHASONE TABLETS. KEY: ○, POWDER BLEND; △, GRANULES; □, DISINTEGRATED TABLETS.

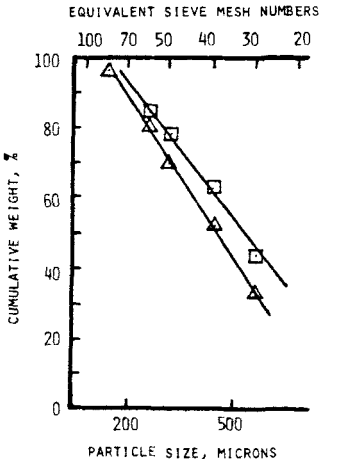

FIGURE 2

EFFECT OF THE SLUGGING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF SULFADIAZINE TABLETS. KEY: △, GRANULES; □, DISINTEGRATED TABLETS.

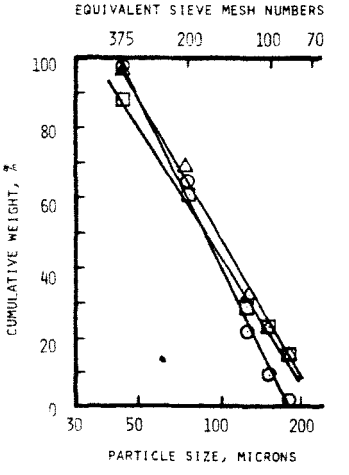

FIGURE 3

EFFECT OF THE MICROGRANULATING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF DEXAMETHASONE TABLETS. KEY: ⊙, POWDER BLEND; △, GRANULES; □, DISINTEGRATED TABLETS.

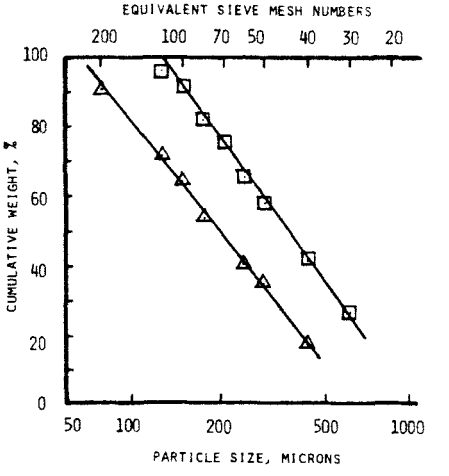

FIGURE 4

EFFECT OF THE MICROGRANULATING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF SULFADIAZINE TABLETS. KEY: △, GRANULES; □, DISINTEGRATED TABLETS.

TABLE III

Average Particle Size of Powder Blends, Granules and Disintegrated Tablets Prepared by Different Methods

Drug	Processing Stage	Granulation Methods Wet	Micro	Slugging	Direct
Dexamethasone	Powder Blend	88[a]	88	88	120
	Granules	315	100	400	-
	Disintegrated Tablets	235	90	120	120
Sulfadiazine	Granules	390	200	435	
	Disintegrated Tablets	300	355	540	

[a] Micron

average particle size from that of the starting material used. The wet granulating method also produced a broader size distribution, but was less than that by the slugging method (Figures 5 and 6).

Compaction has a significant influence on the particle size of the granules, either increasing their size by consolidation (6), or decreasing their size by fragmentation (5). In case of the dexamethasone tablet formulations, granule particle size reduction was noted by three methods, i.e., slugging, microgranulating and wet granulating. Granules of the same materials produced by different granulating methods when compressed into tablets at the same compaction pressure, yielded different average particle size and size distributions A very significant compaction behavior of dexamethasone granules produced by the slugging method was noted. The size distribution returned close to that of the original size distribution before compaction (Figure 1). This effect of compaction was not so pronounced in case of the granules prepared by the wet granulating method (Figure 5). Directly compressible granules did not show any change in particle size distribution on compaction (Figure 7). This was anticipated from the high values for the compressibility factor.

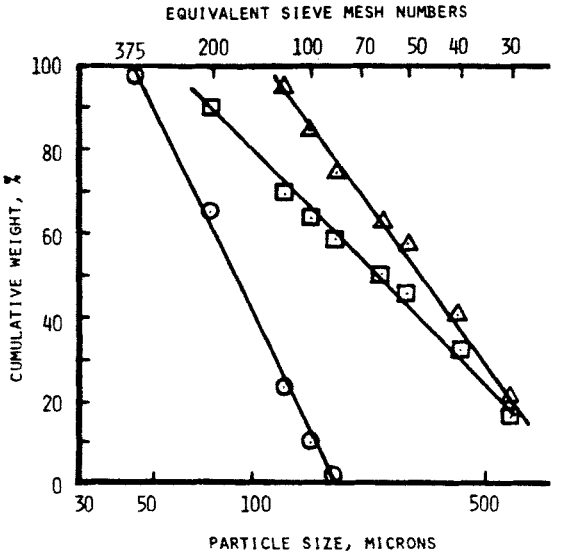

FIGURE 5

EFFECT OF THE WET GRANULATING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF DEXAMETHASONE TABLETS. KEY: ⊙ , POWDER BLEND; △ , GRANULES; ⊡ , DISINTEGRATED TABLETS.

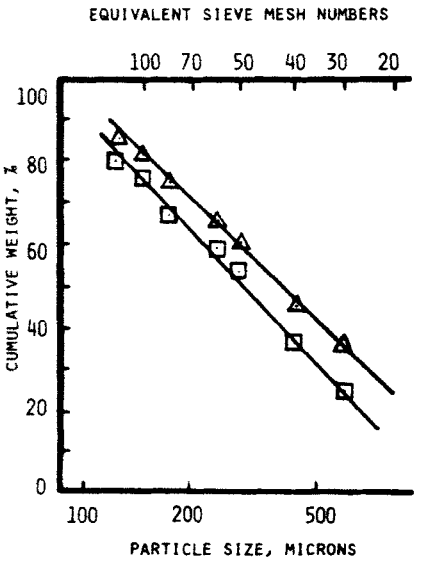

FIGURE 6

EFFECT OF THE WET GRANULATING METHOD ON THE PARTICLE SIZE DISTRIBUTION OF SULFADIAZINE TABLETS. KEY: △ , GRANULES; ⊡ , DISINTEGRATED TABLETS

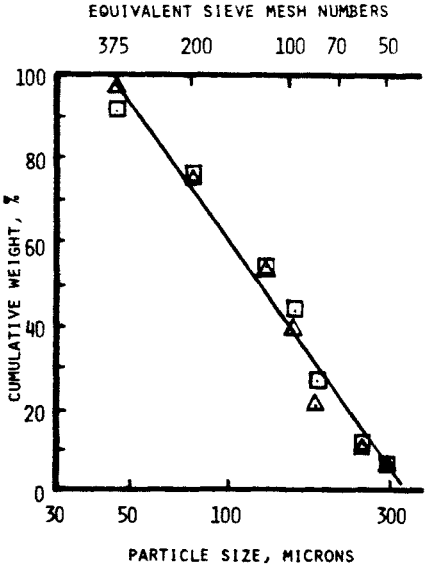

FIGURE 7

EFFECT OF THE DIRECT COMPRESSION METHOD ON THE PARTICLE SIZE DISTRIBUTION OF DEXAMETHASONE TABLETS. KEY: △ , POWDER BLEND; ⊡ , DISINTEGRATED TABLETS.

The result of compaction behavior of sulfadiazine microgranulates and slugs was size enlargement, whereas the opposite effect was observed with tablets prepared from granules obtained by the wet granulating method. This compaction behavior may have a significant influence over the tablet dissolution rate. Particle size of granules is considered an important parameter from the dissolution point of view, but now it appears that the particle size of the disintegrated tablets is more important for tablet dissolution than the particle size of the initial granules. This could explain the slower dissolution rate of some granules as compared with tablets.

The compaction behavior of dexamethasone and sulfadiazine wet granules was similar (Figures 5 and 6). In both cases, the particle size of the disintegrated tablets was reduced and there were minimal changes in size distribution. This indicated that even though in all methods the binder was the same type and quantity, the wet granulating method produced harder granules which were less susceptible to change under a compressional force. It may be concluded therefore that compaction behavior is dependent on the granulating procedure used.

ACKNOWLEDGEMENTS

The authors thank Professors Henry Eisen and Parshotam L. Madan for valuable suggestions.

FOOTNOTES

[1] N. V. Organon, Oss, Netherlands.

[2] American Cyanamide Co., Pearl River, N.Y.

[3] CPC International Inc., New York, N.Y.

[4] S. B. Penick and Co., New York, N.Y.

[5] Samrak Chemical Co., New York, N.Y.

[6] Sheffield Chemical Co., Union, N.J.

[7] Mallinckrodt Chemical Co., St. Louis, Mo.

[8] Whittaker Clark Daniels Co., South Plainfield, N.J.

[9] Patterson Kelly Co., Inc., East Stroudsburg, PA.

[10] Hobart Manufacturing Co., Troy, OH.

[11] Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

[12] Model DS-3 used for slugging & model RB-2 used for compressing tablets F.J. Stokes Company, Philadelphia, PA.

[13] Geoscience Instrument Corp., Mt. Vernon, N.Y.

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