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EFFECT OF GRANULATING METHOD ON CONTENT UNIFORMITY AND OTHER PHYSICAL PROPERTIES OF GRANULES AND THEIR CORRESPONDING TABLETS. II

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ABSTRACT

Various properties of dexamethasone and sulfadiazine granules and tablets prepared by microgranulation, slugging, wet granulation and direct compression were compared.

The dexamethasone tablets showed comparable disintegration rates by all methods. The sulfadiazine tablets prepared by slugging did not meet the USP XIX limit, whereas those by microgranulating were satisfactory.

It was found that granule-homogeneity was not only dependent on the particle size and distribution, but also dependent on the granulating method. For either drug, the microgranulating procedure gave the best weight and content uniformity.

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INTRODUCTION

The content uniformity test is one of several quality assurance tests carried out by pharmaceutical manufacturers mainly for three reasons: (a) to ensure uniform delivery of drug for desired therapeutic response, (b) to assure safety of highly potent drug, (c) as a simple index of good manufacturing practice. The need for this test was first recognized during the quality assurance program of highly potent steroid drugs. Repeated analyses of different 20-tablet composites of hydrocortisone from the same batch by the same method showed results varying from subpotent to superpotent. The weights of the tablets were uniform. Eventual individual tablet analysis revealed a high content variability. Soon, the problems with content uniformity were recognized with other high potency drugs such as digoxin, reserpine, nitroglycerin, chlorpromazine hydrochloride, ethinyl estradiol, and adrenocorticosteroids tablets. Subsequent detailed investigations (1-3) indicated many possible causes for the content variation in tablet dosage forms. Among them, variations associated with manufacturing procedures were primary.

This work documents the effect of four granulating methods, wet granulation, microgranulation, slugging and direct compression on the content uniformity of dexamethasone and sulfadiazine tablet formulations. Their physical properties were also compared.

EXPERIMENTAL

Materials - All materials used in these tablet formulations were USP grade as reported earlier (4)

Preparation of Tablets - Dexamethasone 0.25 mg per tablet and sulfadiazine 130 mg per tablet were prepared by using four different

granulating methods (4).

Testing Procedure - Loss-on-drying moisture in the granules was determined with a moisture balance[1]. The percent compressibility was calculated using Equation 1.

$$\text{percent compressibility} = \frac{T - B}{T} \times 100 \qquad \text{(Eq. 1)}$$

where T is tapped density, and B is bulk density. Densities were determined using a graduated cylinder and a motorized tapping device[2] set to operate for 200 cycles. True density of the mixture consisting of a fine blend of all the tablet ingredients in correct proportion was measured with a pycnometer using benzene as the immersion fluid. Porosity was calculated by dividing bulk density by the true density.

The angle of repose was measured for each of lubricated granules by the method of Nelson (5), where the angle of repose α is defined by:

$$\alpha = \tan^{-1} \frac{h}{r} \qquad \text{(Eq. 2)}$$

in which h is the height and r is the radius[3] of the base of the cone formed by the granules. Flow time was measured by the flow of 50 g of material through a flow-tester[4].

The tablet properties measured included individual weights determined by using a semimicro analytical balance[5], and hardness measurements determined with a Stokes hardness tester[6]. The disintegration time of tablets was measured by the USP XIX method.

Sample Collection - Tablet and granule samples were collected according to the sampling plan as described by Lachman and Sylwestrowicz (6). Systematic tablet sampling of six tablets each were collected from the machine at fixed time intervals. Ten tablet samples were collected from the finished batch following a random procedure. The tablets were weighed and assayed individually. Ten

granule samples, each equivalent to one tablet were collected and analyzed as described below.

Assay Procedure - A dexamethasone tablet or granules equivalent to one tablet was placed in a 25 ml volumetric flask, 20 ml of 0.1 N HCl was added, and the tablet or granule was allowed to disintegrate by gentle shaking. The volume was adjusted to 25 ml with 0.1 N HCl, the suspension was mixed well, filtered through a Whatman No. 1 filter paper, and the first 10 ml. of the filtrate was discarded. The absorbance of the filtrate was determined at 242 nm against a blank solution obtained from a placebo tablet.

Sulfadiazine tablets were also assayed by ultra violet spectrophotometry as described above, at 244 nm. The validity of the methods was checked by verification of Beer's law. The coefficient of variation for the dexamethasone assay method was found to be 0.69%.

Control Charts - The control charts using range, R as a measure of spread, were drawn by the use of the following relationships[7].

$$\text{Upper limit for average} = \bar{\bar{X}} + A_2\bar{R}$$

$$\text{Lower limit for average} = \bar{\bar{X}} - A_2\bar{R}$$

RESULTS AND DISCUSSION

Properties of Granules and Tablets - The properties of granulations (Tables I and II) prepared by the various methods showed some differences.

The three factors of compressibility, repose angle and flow time, which would give some information on flow properties, generally predict that the granulations prepared by wet granulating

TABLE I

Properties of Dexamethasone Granules and Tablets Prepared by Four Different Methods

	Wet Granulation	Micro Granulation	Direct Compression	Slugging
Loss on drying, %*	2.0	1.60	1.70	1.90
Density, g/ml *				
Tapped	0.754	0.798	0.872	0.961
Bulk	0.691	0.646	0.683	0.820
True	1.511	1.511	1.562	1.511
Compressibility, %	8.35	19.04	21.67	14.67
Porosity, %	54.27	57.25	56.28	45.74
Angle of repose *	27.4°	37.2°	44.5°	39.2°
Flow, sec *	2.53	8.91	20.18	2.66
Flow, rotary press	very good	very good	good	very good
Mean granule diameter, micron*	315	100	120	400
Average weight, mg	152.5	152.3	153.5	154.6
Hardness, kg	3.6	3.9	3.4	3.9
Disintegration, min	2.5 to 3.8	1.1 to 1.5	3.7 to 4.7	1.4 to 1.7

* Average of four observations

method will flow better. The lower the compressibility factor (7) and the lower the angle of repose (5), the better is the predicted flow.

The microgranulating method was found to produce a blend which had a high porosity, indicating bridging due to the cohesive forces (8). The porosity values of the granulations prepared by slugging were found to be minimal, indicating little intraparticular void volume in the granules.

The disintegration rates of dexamethasone tablets (Table I) prepared by the four granulating methods were all satisfactory. The disintegration times of sulfadiazine tablets (Table II) prepared by three different methods were significantly different

TABLE II

Properties of Sulfadiazine Granules and Tablets Prepared by Three Different Methods

	Wet granulation	Micro granulation	Slugging
Loss on drying, % *	1.90	1.50	2.00
Density, g/ml *			
Tapped	0.621	0.613	0.819
Bulk	0.550	0.480	0.640
True	1.568	1.568	1.568
Compressibility, %	11.43	21.69	21.85
Porosity, %	64.93	69.39	59.19
Angle of repose *	30.6°	35.1°	42.8°
Flow, sec *	3.53	6.36	3.33
Flow, rotary press	very good	very good	very good
Mean granule diameter, micron*	390	200	435
Average weight, mg	151.8	152.8	159.6
Hardness, kg	5.8	5.5	5.4
Disintegration, min	12 to 26	2 to 4	21 to 36

* Average of four observations.

from each other. The sulfadiazine tablets prepared by slugging did not meet the USP XIX limit. The rapid disintegration of the tablets prepared by the microgranulating method is believed due to the hydrophilic and readily dispersible nature of the micro-granulate (4).

Content Uniformity - The achievement of homogeneity of dexamethasone in granules prepared by four different granulation techniques is shown in Table III. The microgranulating method produced the best dispersion of dexamethasone in powdered lactose at the high dilution of 1 in 600. The fine granule size could account for the homogeneity of drug distribution in the microgranulate. On the other hand, wet granulation showed the poorest homogeneity. This was due to the larger particle size and wider distributions. The slugging method

TABLE III

Homogeneity of Dexamethasone Distribution in Granules Prepared by Four Different Methods

Granulating Method	Average[a] Content mg	Maximum Content mg	Minimum Content mg	Coefficient of Variation %
Wet granulation	0.240	0.265	0.222	5.97
Microgranulation	0.251	0.253	0.247	0.99
Direct compression	0.249	0.267	0.239	3.90
Slugging	0.247	0.252	0.243	1.43

[a]Average of 10 individual assay

TABLE IV

Average Range, $\bar{R}$ Against Average Granule Size Obtained by Different Granulating Methods

Granulating Method	Dexamethasone Avg. Range $\bar{R}$, mg	Dexamethasone Avg. Particle Size, microns	Sulfadiazine Avg. Range $\bar{R}$, mg	Sulfadiazine Avg. Particle Size microns
Wet granulation	5.35	315	3.6	390
Microgranulation	3.85	100	2.0	200
Slugging	6.60	400	4.6	435
Direct compression	3.90	120	-	-

TABLE V

Coefficient of Content[a] Variation for Dexamethasone Tablets

	No. of Assay	Average Absorbance	Standard Deviation	Coeff. of Variation,%
Wet granulation	50	0.430	0.0248	5.767
Microgranulation	50	0.452	0.0092	2.039
Direct compression	50	0.450	0.0182	4.044
Slugging	50	0.455	0.0129	2.835

[a]Contents are expressed in term of absorbance.

was found to be the second best granulating method for producing homogeneous granules. In the slugging method dexamethasone was dispersed in powdered lactose in a suitable blender. The homogeneous blend was lubricated and slugged under high pressure. Unlike wet granulation, the slugging method did not call for so many processing steps, such as wetting, wet screening, drying, dry-screening. Moreover, bonding of drug-excipient had occured during the slugging operation under high compressional force. Subsequent breaking into larger particle sized granules did not result in segregation of drugs. Thus, the homogeneity of drug distribution in granules are not only dependent on the granule size distributions and or particle sizes, but also dependent on the granulating method.

The coefficient of variation is also high for the directly compressible method. This is explained, by the two dissimilar size distributions i.e., the drug was in micronized form and the directly compressible excipient was in coarser form.

The control chart, a useful tool for process control, is based on standard deviation or range. The control charts for the weight variation of dexamethasone (Figures 1 to 4) and sulfadiazine tablets (Figures 5 to 7) prepared by different granulation techniques show that the microgranulating procedure yielded the best weight uniformity (Figures 1 and 5). This was evident since it gave the lowest values for $\bar{R}$, where $\bar{R}$ was the measure of spread. In Table IV. the average range $\bar{R}$ values, that are obtained from the control charts, are tabulated against the average particle size of the respective granules. A correlation was found that lower the average particle size, the less is the value of $\bar{R}$. Hence, it could be said that the weight

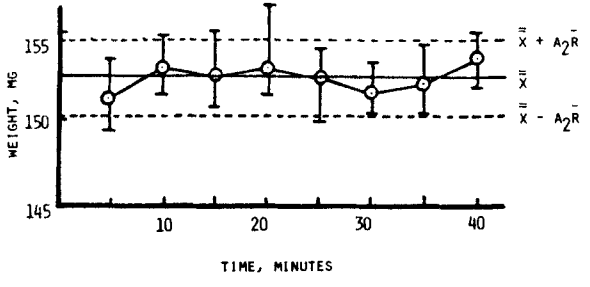

FIGURE 1

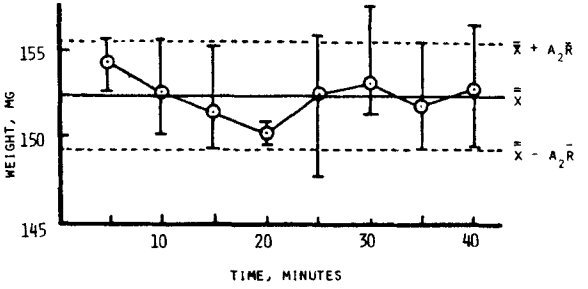

FIGURE 3

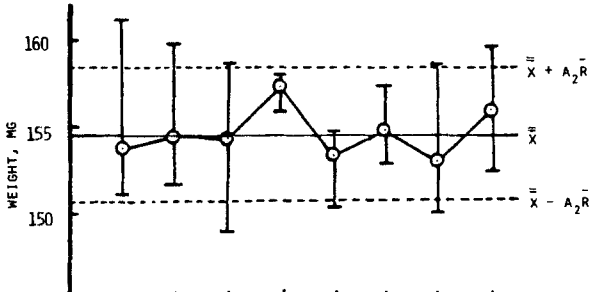

FIGURE 2

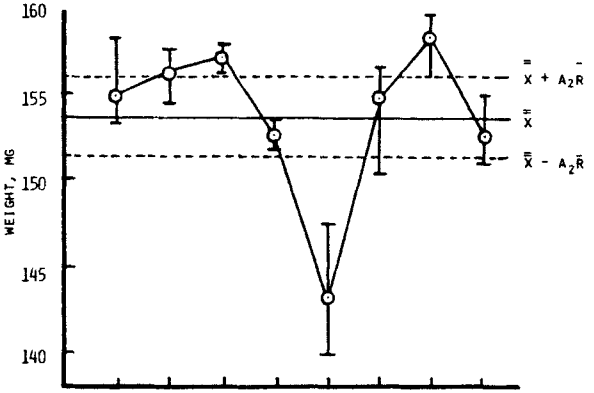

FIGURE 4

Control charts for the Weight Variation of Dexamethasone Tablets. Figure 1- Prepared by the Microgranulating Method; Figure 2 - Prepared by the Slugging Method; Figure 3 - Prepared by the Wet Granulating Method; Figure 4 - Prepared by the Direct Compression Method.

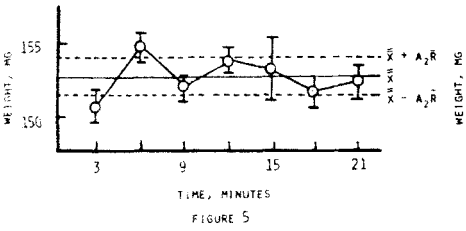

FIGURE 5

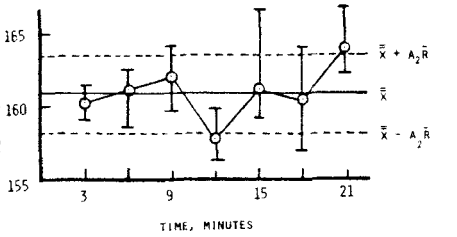

FIGURE 6

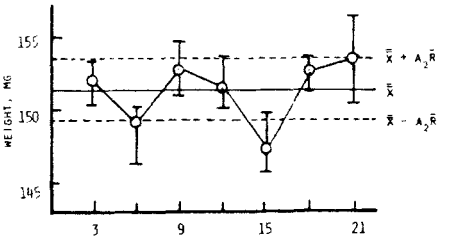

FIGURE 7

Control Charts for the Weight Variation of Sulfadiazine Tablets. Figure 5 - Prepared by the Microgranulating Method; Figure 6 - Prepared by the Slugging Method; Figure 7 - Prepared by the Wet Granulating Method.

variation is a function of the average particle size obtained by the granulating process.

The tablets prepared by the microgranulating method were found to have the best content uniformity (Figure 8) and those prepared by the slugging method were next (Figure 9). The tablets manufactured by wet granulation (Figure 10) and direct compression methods (Figure 11) showed the poorest content uniformity. This is also confirmed from the coefficients of variation shown in Table V which were calculated from 50 individual assay results on random and systematic samples.

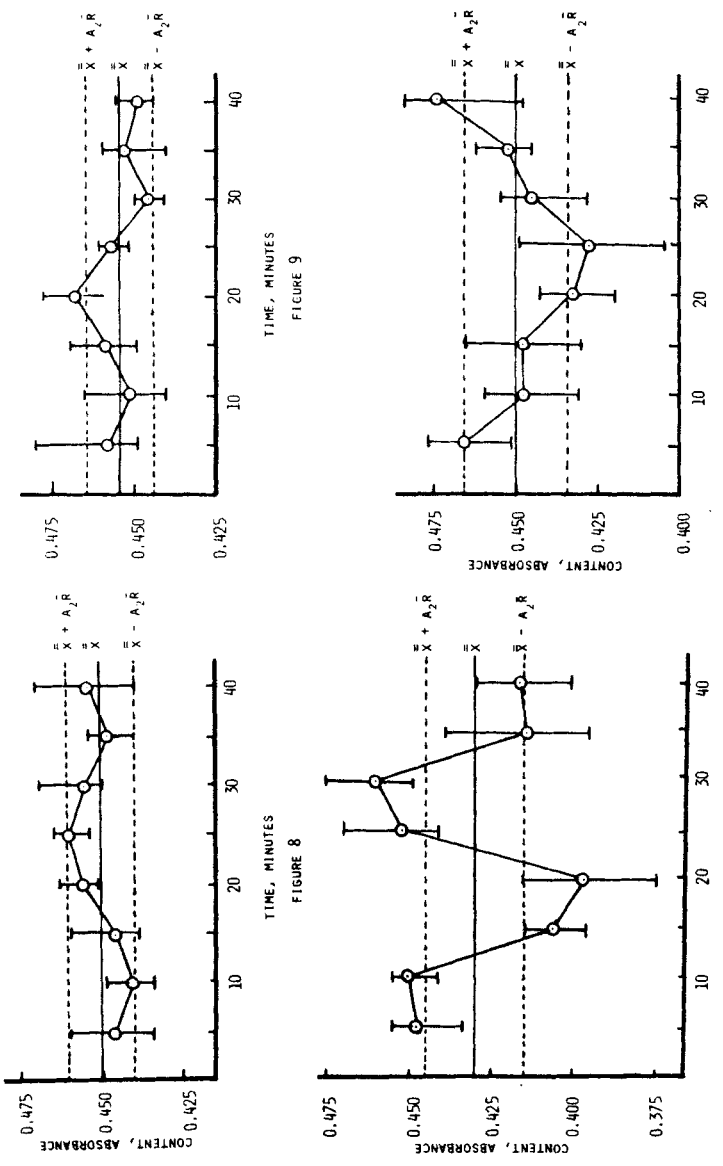

FIGURE 8

FIGURE 9

FIGURE 10

FIGURE 11

Control Charts for the Content Variation of Dexamethasone Tablets. Figure 8 - Prepared by the Microgranulating Method; Figure 9 - Prepared by the Slugging Method; Figure 10 - Prepared by the Wet Granulating Method; Figure 11 - Prepared by the Direct Compression Method.

FOOTNOTES

[1] Model 6000, Ohaus Scale Corp., Florham Park, N.J.

[2] Organon Inc., West Orange, N.J.

[3] The value of r was 2.70 cm.

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

[5] Model H 20 T, Mettler Instrument Corp., Princeton, N.J.

[6] Stokes Company, Philadelphia, Pa.

[7] The value for the factor A_2 is 0.577, when n is equal to 5.

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