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INFLUENCE OF MAGNESIUM STEARATE ON THE HOMOGENEITY OF A PREDNISONE-GRANULE ORDERED MIX

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ABSTRACT

The use of ordered systems has been advocated in the formulation of microdose delivery systems to improve and maintain drug homogeneity during mixing. This study considered the effect of a lubricant such as magnesium stearate on the degree of homogeneity and stability of a preformed prednisone-granule ordered mix. Micronized prednisone was mixed with starch-lactose granules to produce an ordered mix of satisfactory homogeneity. Magnesium stearate in concentrations above and below the theoretical surface saturation of the granule caused negligible change in the degree of homogeneity. Sieve analysis of the mix and subsequent analysis of size fractions for prednisone allowed the prednisone distribution within the mix to be determined. Prednisone was found to be associated with the granules in all the mixes; the magnesium stearate did not compete for the surface adsorption sites and did not dislodge the drug from the granule surface, during mixing and mild demixing conditions. However, a decrease in surface adsorbed prednisone occurred in all mixes (with and without magnesium stearate) under more severe segregating conditions.

Recent research in drug homogeneity studies in microdose tablets has highlighted serious problems in dosage variation[1] . Drugs are frequently micronized to improve their release from the solid dosage form. Micronization produces drug particles which are extremely cohesive and interactive. In practice, the adequate mixing of micronized powders with other excipients may be difficult to achieve since this cohesiveness produces aggregation of drug particles and interaction of the drug with the mixer surfaces. In recent years some research effort has been applied to using the interactive nature of drug particles to improve the homogeneity of mixes[2,3]. Controlled adsorption of a micronized drug particle onto a carrier particle to produce an "ordered unit" has been shown to minimize segregation within the mix[4,5]. Some of the factors affecting the degree of homogeneity of "ordered mixes" have been studied[6,7]. However, little research has been conducted on the influence of other excipients on the homogeneity and stability of preformed ordered mixes. A cautionary note on the use of magnesium stearate in ordered mixtures indicated that the lubricant may displace salicylic acid from a sucrose carrier under conditions of segregation[8]. The purpose of this study, therefore, was to evaluate the influence of a third component such as magnesium stearate on the degree of homogeneity and stability of a preformed prednisone-starch lactose granule ordered system during a mixing process.

MATERIALS AND METHODS

Materials

Prednisone U.S.P. (Upjohn) was micronized by fluid energy milling (Chrispro Jetmill model 75P, compressed air 5.8 atm at 12.7 l sec $^{-1}$).

The carrier was starch-lactose granules (lactose 2 parts, starch 1 part, prepared by moist granulation using starch paste as a binder). A 425-840μm fraction was obtained by sieve classification.

Magnesium stearate (Ajax Chemicals).

Absolute Alcohol AR (Ajax Chemicals).

Methods

Mixing was performed in an Erweka Cube Mixer (20 r.p.m.; load 100-500g). Twenty 100mg samples were withdrawn systematically for assay to evaluate homogeneity.

Prednisone was assayed by dissolving in absolute alcohol, adjusting to 100ml and centrifuging to remove the solids. The absorbance was measured at 240nm using a Hitachi-181 spectrophotometer. A Beer's Law calibration for prednisone over the concentration range 0.005-0.02mg ml^{-1} showed no significant non-linearity and prednisone concentrations were determined by inverse prediction[9]. Preliminary experiments showed complete recovery of the prednisone from the granules.

Particle size analysis of the granules was performed using Endecott test sieves (B.S.410, 20 min). The particle size analysis of prednisone and magnesium stearate were performed microscopically using a research microscope and appropriate stage and eyepiece micrometers.

All densities were obtained by liquid displacement.

RESULTS AND DISCUSSION

Particle Size Analysis

Particle size analysis of the granules revealed a log normal distribution with a weight geometric mean (d^1_g) of 670μm and a weight standard deviation (σ_g) of 1.29. The volume number diameter (d_{vn}= 608μm) was calculated from the Hatch-Choate Equation:

$$\log d_{vn} = \log d^1_g - 3.454 \log {}^2\sigma_g$$

Microscopic particle size analysis of the prednisone and magnesium stearate allowed the direct determination of their volume number diameter ($d_{vn} = (\Sigma nd^3/\Sigma n)^{1/3}$) which was 3.5μm and 4.0μm respectively.

Evaluation of Homogeneity

The coefficient of variation (C.V.) was chosen in this study to describe the degree of homogeneity. The homogeneity standard was the coefficient of variation necessary to comply with a pharmacopoeial or manufacturing standard [5,10,11]. For example, the coefficient of

variation for 95% of samples falling within ± 10% of the mean is 5%; for 99.7% of samples within ± 15% of mean, C.V. = 7.8%. However, the coefficients of variation obtained in this study reflect not only the variance due to mixing (σ^2_M) but also the variances due to analytical method (σ^2_A), drug purity (σ^2_P) and sampling (σ^2_S), i.e. the total variance (σ^2_T) is $\sigma^2_M + \sigma^2_A + \sigma^2_S + \sigma^2_P$.

Mixing Studies

The micronized prednisone (1%) was mixed with the granules for 60 minutes. The mixing profile (Figure 1) revealed rapid mixing of the prednisone with the granules. A satisfactory degree of homogeneity occurred within the time of mixing (C.V. at 60 minutes = 5.8%). A microscopic examination (Figure 2) of samples of the mix validated that an ordered mix, with the prednisone particles adsorbed on the large granules, had been formed.

Samples of the preformed prednisone (1%) - granule ordered system were mixed with various concentrations of magnesium stearate for 30 minutes. Samples for analysis were withdrawn at 5, 10 and 30 minutes.

Concentrations of magnesium stearate were chosen both above and below the total theoretical monolayer surface saturation (Table 1). While the higher amounts of magnesium stearate were unrealistic lubricant concentrations, there was an obvious need to consider the competitive particle adsorption when all the surface sites were occupied.

Electron photomicrographs were obtained for all prednisone-granule-magnesium stearate mixes. One mix (10% magnesium stearate), shown in Figure 3, clearly illustrates a high proportion of particles adsorbed on the granule surface. The irregular appearance of the previous prednisone (1%) mix with the granules (Figure 2) is no longer seen; the particles adsorbed in the pores and crevices give a smooth, rounded appearance to the granule.

The effect of the added magnesium stearate on the prednisone homogeneity is illustrated in Figure 4, which shows that the presence of magnesium stearate in all concentrations, even those greatly in excess of the surface saturation, have little effect on the degree of

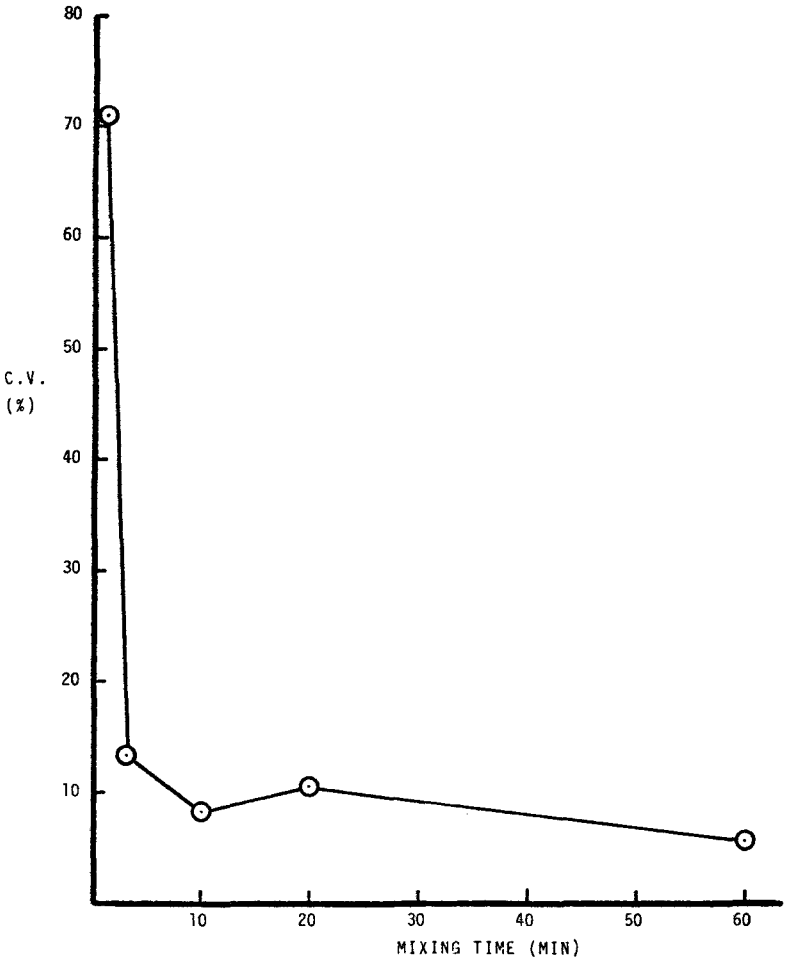


FIGURE 1
Mixing profile for the ordered mixing of prednisone (1%) and starch lactose granules.

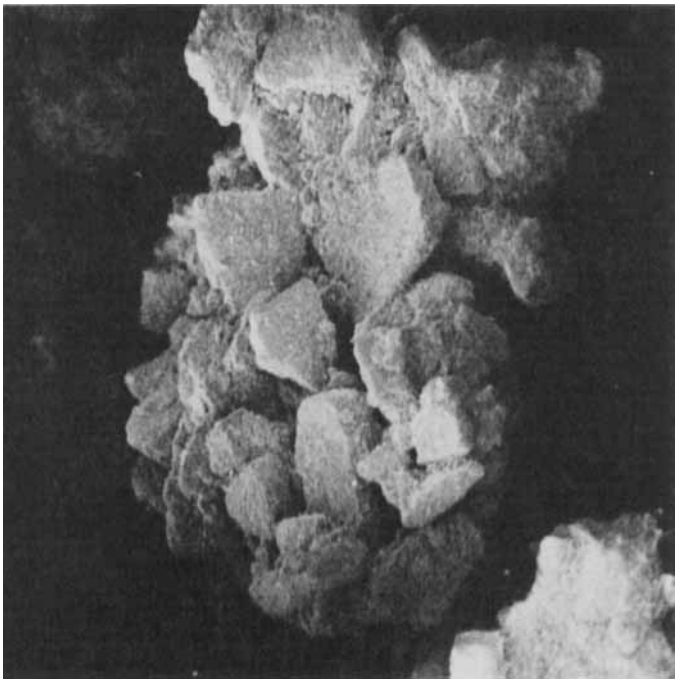


FIGURE 2 (a)
Electron photomicrograph of the prednisone-granule mix. (magnification x 100).

homogeneity of prednisone. These results indicate that prednisone is probably not dislodged from the granule surface since the presence of free prednisone would result in increased variability due to the difficulties associated with random mixing of small amounts of a micronized drug with a large particle size carrier. In addition, dislodge prednisone would be highly interactive and any aggregation of the drug particles that occurred within the ordered system would cause decreased homogeneity[5].

Distribution of Prednisone

In order to validate that the prednisone was associated with the granule after mixing of the magnesium stearate, a sieve classification

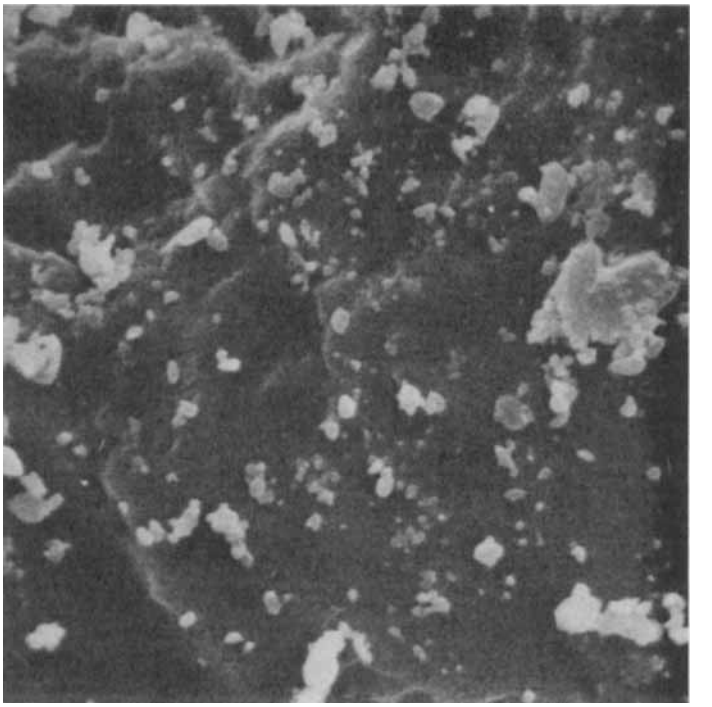


FIGURE 2 (b)
Electron photomicrograph of the prednisone-granule mix. (magnification x 5000).

of particles less that 425µm was performed. The granules, prednisone (1%) - granule mix, and the prednisone (1%) - granule magnesium stearate (1%, 4%, 10%) mixes were sieved for 30 minutes. Particle size distributions were determined at 5 and 30 minutes (Table 2). Samples for prednisone analysis were taken from each of the sieve fractions enabling the prednisone content associated with each particle size fraction to be determined (Table 3).

The particle size distribution (Table 2) showed that some communition of the granules occurred during the mixing and sieving processes. After 5 minutes sieving, about 6 - 7% of the granules were less than the 425µm lower particle size range specification. The prednisone content in fractions less than 425µm should therefore be

TABLE 1

Degree of surface saturation of the carrier for the prednisone-granule ordered mixes.

Material adsorbed	Degree of surface saturation[a] (%)	
	Alone	Added to prednisone (1%)-granule mix
prednisone (1%)	39.5	-
magnesium stearate (1%)	32.9	72.4
magnesium stearate (4%)	135.8	175.3
magnesium stearate (10%)	362.4	401.9

[a] Calculated from a knowledge of the particle number ($6/\pi d^3_{vn}\rho$) of each component in the mix and the theoretical number of particles per granule for each material to cause surface saturation [$4\ d_g^2/d_p^2$, where d_g = granule diameter and d_p = adsorbed particle diameter^2].

interpreted carefully since it could represent both free prednisone and prednisone associated with the comminuted granules.

A study of the prednisone distribution after sieving for 5 minutes (Table 3) clearly shows that over 90% of the drug is associated with granules greater than 425μm in all the mixes. In addition, there is little difference between the particle fraction distribution of prednisone in all the mixes. Therefore, under normal mixing conditions and gentle demixing conditions (5 minutes sieving), the prednisone is not being dislodged from the granule by the magnesium stearate.

After more severe demixing conditions (30 minutes sieving), the results indicate some loss of prednisone from the granules. Dislodged prednisone particles were found at the lower rim of the 425 and 355μm sieves and were removed between the particle size distribution determinations. These losses are not shown in Table 3. There was little trend or difference in the prednisone distribution for all mixes after 30 minutes sieving indicating that the magnesium stearate did not accelerate the demixing of the prednisone.

TABLE 2

Particle size distribution of the granules and ordered mixes

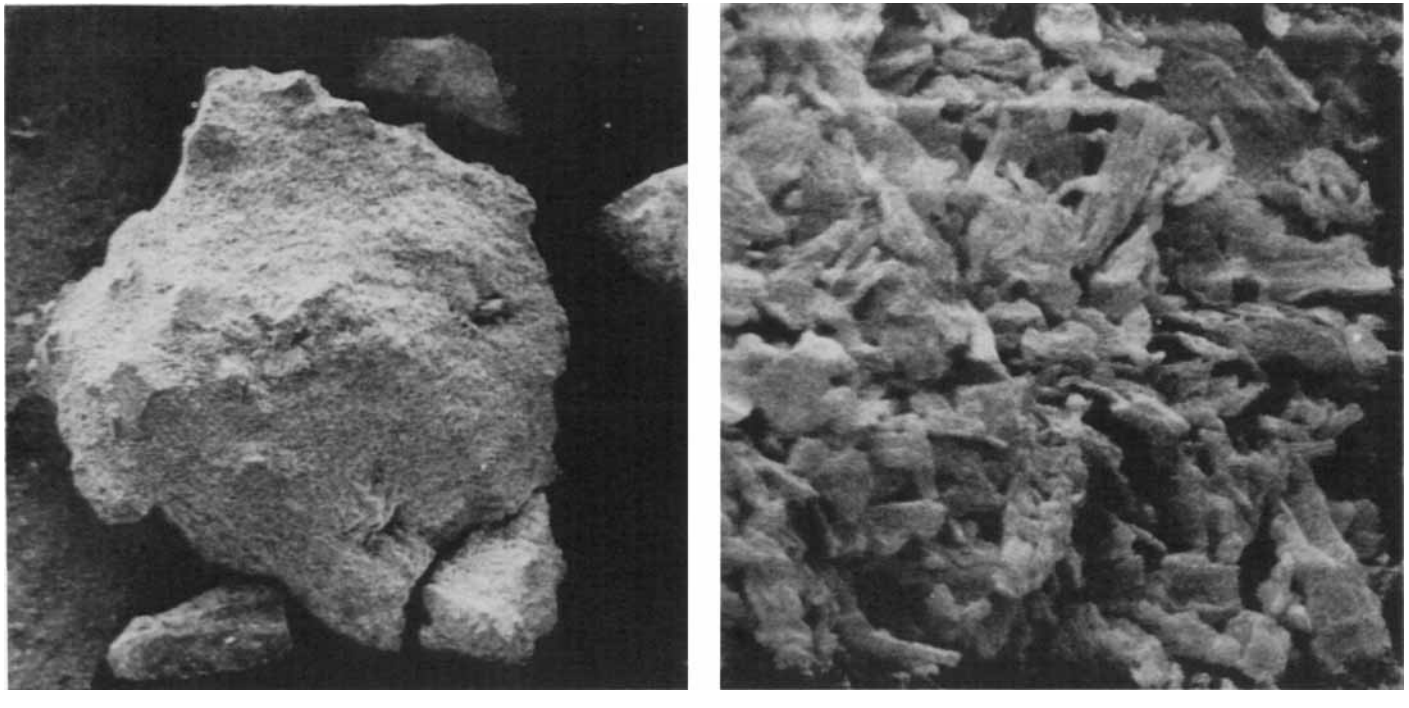
Sieve size (μm)	Percent of particles retained on each sieve									
	granules		prednisone 1% -granule mix		prednisone (1%)-granule-magnesium stearate mix					
					1%		4%		10%	
	5min	30min	5min	30min	5min	30min	5min	30min	5min	30min
425	93.4	89.4	93.8	89.6	92.7	88.8	93.5	90.1	94.1	90.4
355	5.3	8.0	5.1	7.6	5.2	7.6	5.2	7.3	4.2	6.8
250	0.6	1.3	0.7	1.3	1.1	1.6	0.7	1.2	0.6	0.8
150	0.3	0.7	0.2	0.7	0.6	1.1	0.3	0.6	0.4	0.8
<150	0.3	0.8	0.2	0.8	0.4	0.9	0.2	0.8	0.8	1.3

TABLE 3

Distribution of prednisone within mix

Size Fraction (μm)	prednisone (1%) granule		prednisone (1%)granule - magnesium stearate					
			1%		4%		10%	
	5min	30min[a]	5min	30min	5min	30min	5min	30min
425	91.3	73.9	90.0	67.2	90.9	80.7	91.2	78.3
355	6.9	8.4	6.8	9.1	7.0	10.1	6.2	7.9
250	1.0	1.6	1.5	2.1	1.1	1.8	0.8	1.4
150	0.3	0.9	1.0	1.2	0.5	1.1	0.5	1.3
<150	0.5	1.3	0.7	1.9	0.5	1.8	1.3	2.5

[a]The figures shown in the 30 min sieving columns represent the percentage of the total prednisone in all size fractions after 5 minutes sieving. Losses are not included in the table.



A B

FIGURE 3

A) Electron photomicrograph of the prednisone-granule-magnesium stearate (10%) mix. (magnification x 100) B) Electron photomicrograph of the prednisone-magnesium stearate (10%) mix. (magnification x 5000).

CONCLUSIONS

Stable prednisone - granule ordered mixes were prepared with satisfactory degrees of homogeneity. The addition of magnesium stearate in amounts below and above the theoretical surface saturation did not cause dislodgement of the presnisone particles under normal mixing conditions and had negligible effect on the degree of homogeneity of such ordered systems.

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