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Effect of Magnesium Stearate on the Content Uniformity of Active Ingredient in Pharmaceutical Powder Mixtures

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ABSTRACT The objective of this study was to determine the effect of magnesium stearate on the physical stability of polydisperse powder mixtures. The effects of concentration of magnesium stearate and the time of lubrication of mixtures with magnesium stearate on the content uniformity of the active ingredient in the mixtures were evaluated in a model mixture of lactose and aspirin. These effects were compared in a random mixture of non-interacting components and a mixture based on particle interaction. A statistical model that adequately described the relationship between the factors examined and the response was generated. The model indicated the presence of an interaction between magnesium stearate concentration and lubrication time. At a given concentration of magnesium stearate, there was a significant reduction in the content uniformity of aspirin as the time of lubrication of the mixture with magnesium stearate was increased. This effect was larger in mixtures based on particle interaction than in random mixtures of non-interacting components.

KEYWORDS: magnesium stearate, content uniformity, powder mixtures.

INTRODUCTION Magnesium stearate is widely used as a lubricant in the manufacture of pharmaceutical solid dosage forms. While the effect of magnesium stearate on the disintegration and dissolution of tablets and capsules has been extensively studied and documented, its effect on the physical stability of mixtures has received little attention to date. It has been shown that magnesium stearate can displace "fine" active ingredient from coarse monodisperse carriers in mixtures based on particle interactions [1,2]. In practice, most mixtures are polydisperse. The objective of this study was to determine the effect of magnesium stearate on the physical stability of polydisperse powder mixtures. Specifically, the effects of concentration of magnesium stearate and the time of lubrication of mixtures comprising a drug and inert carrier with magnesium stearate on the content uniformity of the active ingredient were determined in a model mixture of lactose and aspirin. The coefficient of variation (CV) of aspirin in the mixture was used as a measure of content uniformity. These effects were compared in two types of mixtures - a random mixture of non-interacting components and a mixture based on particle interaction.

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MATERIALS AND METHODS

Materials

Spray-dried lactose of 100-µm median volume diameter was obtained from Foremost Wisconsin Dairies (Foremost Farms, Baraboo, WI). Commercial aspirin powder having a median volume diameter of 100 µm was obtained from Miles Laboratories, Elkhart, IN. Micronized aspirin of 8 µm median volume diameter was obtained by milling the commercial powder in a fluid-energy mill (Gem-T Model, Trost Equipment Corporation, Newton, PA). The temperature of the processing environment was 20 ± 5°C, and the relative humidity was 40% ± 5%.

Measurement of particle size of powders

The size distribution of powders was measured by laser diffraction using the Microtrac particle size analyzer (Leeds & Northrup, Clearwater, FL). Absolute ethanol (High performance liquid chromatography [HPLC] grade) was used as the dispersion medium for lactose; micronized aspirin and magnesium stearate were dispersed in double-distilled water with the aid of 2% wt/vol polysorbate 80.

General procedure for preparation of mixtures

A premix of aspirin and lactose, prepared by sieving aspirin and ten parts of lactose on a 250µm mesh screen, was mixed with bulk lactose in a stainless steel tumbling V-mixer for 20 minutes. The optimum mixing time was determined from preliminary experiments. Each mixture was lubricated with magnesium stearate; the concentration of magnesium stearate and time of lubrication in each series of experiments are listed in the following section. Fifteen samples (200 mg each) were removed from each mixture with a stainless steel thief sampler prior to and following lubrication with magnesium stearate. The samples were assayed for aspirin by measuring the UV

Table 1. Effect Tests of Magnesium Stearate Concentration and Lubrication Time on the Coefficient of Variation of Aspirin in Ordered Mixtures of Aspirin and Lactose

Source	*df*	Sum of Squares	F Ratio	*P* >F
Magnesium stearate concentration	2	63.1025	36.7786	<.0001
Lubrication time	2	13.4611	7.8456	.0035
Interaction between magnesium stearate concentration and lubrication time	4	13.0607	3.8061	.0206

absorbance of chloroform extracts at 277.5 nm (Beckman spectrophotometer, Beckman Instruments, Schaumburg, IL).The CV was calculated from the mean and standard deviation of the aspirin content in the samples.

Experiment 1: Effect of magnesium stearate concentration and lubrication time on the CV of aspirin in mixtures of micronized aspirin and lactose

The effects of magnesium stearate concentration and lubrication time on the CV of aspirin in mixtures of 1% micronized aspirin and lactose were evaluated in a full factorial design. We used 0.25%, 0.5%, and 2% of magnesium stearate and lubrication times of 2, 5, and 15 minutes—corresponding to low, intermediate, and high levels of the factors. The experimental runs were fully randomized. JMP Statistical Analysis Software (SAS Institute, Version 3.1, Research Triangle Park, NC) was used in experimental design and data analysis.

Experiment 2: Comparison of the effect of magnesium stearate on the CV of aspirin in random mixtures and mixtures based on particle interactio

For this study, a mixture of lactose and 1% micronized aspirin was used as a model mixture of interacting components, and that of lactose and polydisperse aspirin (20% wt/wt) was assumed to represent a random mixture of noninteracting components [3]. The effect of magnesium stearate concentration on the content uniformity of aspirin in these mixtures was evaluated at a fixed lubrication time in a mixed-level factorial design. Mixtures were prepared as described previously and lubricated with magnesium stearate (in concentrations of 0%, 0.5%, and 1%) for 5 minutes. The CV of aspirin in the mixture was calculated from the mean and standard deviation of the aspirin content in the samples. The experimental runs were randomized.

RESULTS AND DISCUSSION

Effects of magnesium stearate concentration and lubrication time on the CV of aspirin in mixtures of lactose and 1% micronized aspirin

The whole model and effect tests are listed in **Table 1**. The parameters, the degrees of freedom associated with the effect, the sum of squares for the hypothesis that the listed effect is zero, the F statistic for testing that the effect is zero, and the significance probability for the F ratio for each effect are listed. The least squares means (LSM) were compared in testing the effects. The measured response was adequately accounted for by the factors in the statistical model, as indicated by the whole model test. The leverage plot for the whole model test shown in **Figure 1** is a display of how the fit carries the data. The confidence curve crosses the sample mean (represented by the horizontal line) if the F test is significant at some alpha level, 0.05 in this instance. The P>F value of <.0001 (**Table 1**) indicates that the line of fit carries the points significantly better than the sample mean of a partially constrained model.

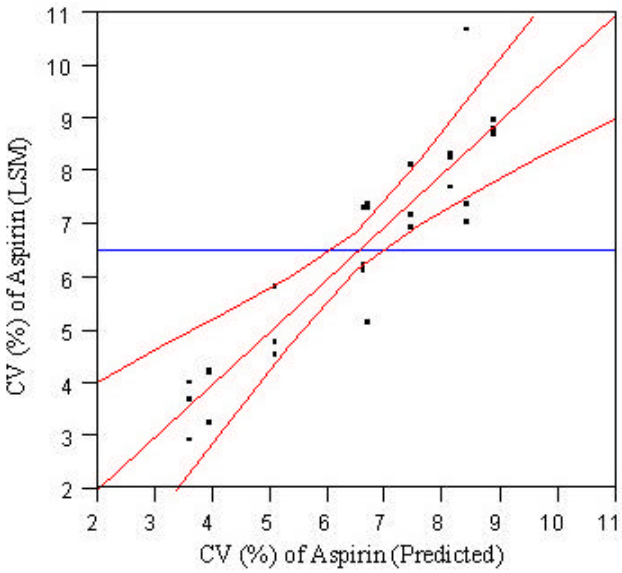

Figure 1. Whole model leverage plot of the effects of magnesium stearate concentration and lubrication time on the coefficient of variation of aspirin in ordered mixtures of aspirin and lactose (R^2 = 0.84). The horizontal line in the center represents the sample mean.

The difference in response among magnesium stearate concentrations at the various lubrication times indicated the presence of an interaction between the factors. The interaction is represented by the non-parallel lines in the plots of the response among the three levels of magnesium stearate concentration at different lubrication times (**Figure 2**). To draw inferences about main effects in the presence of the interaction, the concentration of

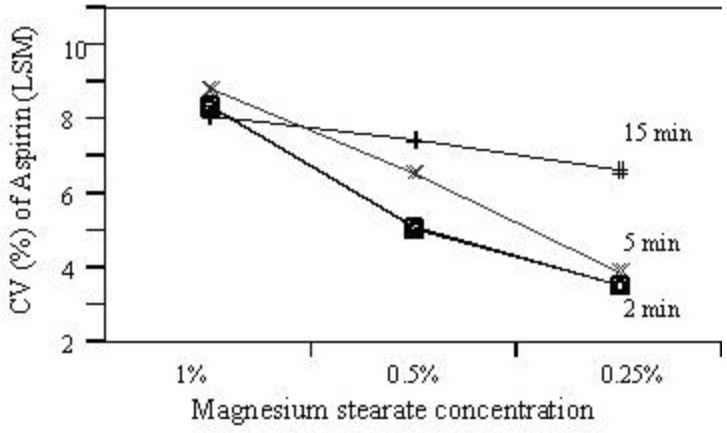

Figure 2. Profile plot of the interaction between magnesium stearate concentration and lubrication time on the coefficient of variation of aspirin in ordered mixtures of aspirin and lactose.

magnesium stearate was fixed at 0.5% and the effect of varying the lubrication time on the CV of aspirin content was determined [4]. The mean response was compared using the Tukey-Kramer test for multiple comparisons of the means at a significance level of 5%. **Figure 3** is a plot of the effect of lubrication time on the CV of aspirin in the mixtures. Data at zero time represent the CV of aspirin in samples removed from the mixture before it was blended with magnesium stearate. There was an increase in the CV of aspirin in the mixture as lubrication time was increased, indicating a decrease in the homogeneity of the mixture. The CV of aspirin in mixtures that were blended with magnesium stearate for over 5 minutes was significantly larger than that measured at lubrication times of 5 minutes or less (P>F: .0001). Further increase in the lubrication time resulted in only a small increase in the CV of aspirin in the mixture. Since lubrication times of over 5 minutes are rarely exceeded in practice, data corresponding to the time period of 0 to 5 minutes were compared by the same test. The difference in the CV of aspirin between the control (ie, mixture sampled prior to blending with magnesium stearate) and the mixture blended with magnesium stearate for 2.5 minutes was not significant. The CV of aspirin in mixtures lubricated for 2.5 and 5 minutes was significantly larger than that measured in mixtures lubricated for 2.5 minutes. The practical implication of this observation is that lubrication time can have a significant effect on the content uniformity of drug in low-dose mixtures. The extent of its impact on mixture homogeneity is dependent upon the composition of the mixture and the concentration of magnesium stearate.

Comparison of the effect of magnesium stearate on the CV of aspirin in random mixtures and mixtures based on particle interaction

Mixtures comprising a coarse carrier and a small concentration of a "fine" component, such as microfine drug, are widely held to be stabilized by interactions between the components. Such mixtures have been referred to as ordered mixtures in the literature [3]. It has previously been shown that under

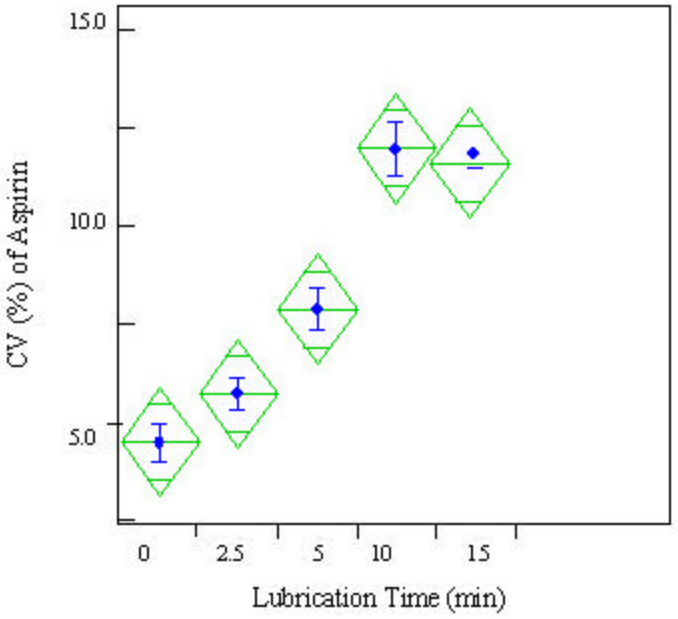

Figure 3. Effect of lubrication time on the coefficient of variation of aspirin in ordered mixtures of aspirin and lactose lubricated with 0.5% of magnesium stearate. Diamonds represent the 95% confidence interval, and error bars represent the standard error.

similar processing conditions, when the size distribution of the minor component and inert carrier are similar and the powders are largely non-cohesive (ie, having a median particle size larger than 70 µm), the resulting mixtures generally behave like random mixtures of noninteracting components, assuming the absence of other surface effects [5]. Mixtures of (1) lactose and micronized aspirin of 8-µm volume median diameter and (2) lactose and polydisperse aspirin of 100-µm volume median diameter were assumed to represent ordered and random mixtures respectively in this study, and the effect of magnesium stearate on the content uniformity of these mixtures was compared.

The whole model and effect tests are given in **Figure 4** and **Table 2**. The model adequately described the response at various levels of the factors. The concentration of magnesium stearate and type of mixture (ordered vs random) were main effects for the CV of aspirin content. There was no significant interaction between the 2 main effects (P>F = .1028). The overall effect of the addition of magnesium stearate to the mixture was a decrease in homogeneity of the mixture, as indicated by the large CV of aspirin content. The CV of aspirin was larger in mixtures lubricated with magnesium stearate than in the control (mixture prior to addition of magnesium stearate). The addition of magnesium stearate to a mixture of micronized aspirin and lactose resulted in a larger CV (9%) than that measured in a mixture of lactose and polydisperse aspirin (5.4%). In the latter, the CV of aspirin in mixtures lubricated with 0.5% and 1% magnesium stearate was comparable (**Figure 5**).

Table 2. Effect Tests of Magnesium Stearate Concentration and Type of Mixture on the Coefficient of Variation of Aspirin in Aspirin-Lactose Mixtures

Source	*df*	Sum of Squares	F Ratio	*P* >F
Mixture type (ordered vs random)	1	11.8167	19.6401	0.0044
Magnesium stearate concentration	2	13.4579	11.1840	0.0095
Interaction between magnesium stearate concentration and type of mixture	2	4.0951	3.4032	0.1028

The mixture of polydisperse lactose and aspirin of 100-µm median diameter can be considered (roughly) to be a system of noninteracting components. Adhesion of the fine fraction of the components is expected to be minimal, given the size distribution of the minor component. The effect of magnesium stearate on the content uniformity of such a mixture appears to be significantly smaller than that in a mixture of coarse lactose and micronized aspirin, where there is considerable adhesion of the fine component to the carrier [2,3].

It has been shown that magnesium stearate can displace drug from the surface of the carrier [1,2]. A likely mechanism for this has been postulated to be due to dissipation of electrostatic charge of the components of the mixture by magnesium stearate [6,7]. The dry process environment (20°C, 40% relative humidity) is conducive to electrostatic charge effects. The tendency of magnesium stearate particles to delaminate under shear can result in its rapid dispersion in the mixture at mixing times that are a fraction of those used in dispersing active ingredient in the bulk. While no direct evidence of adhesion of magnesium stearate to the surface of the carrier was obtained in this study, the large dispersion component of the surface energy of magnesium stearate relative to that of aspirin [8] can facilitate its adhesion on the carrier surface.

CONCLUSION The concentration of magnesium stearate and time of lubrication of mixtures with magnesium stearate can affect the content uniformity of active ingredient in mixtures that are based on particle interactions, as determined in model mixtures of lactose and micronized aspirin in this study. By comparison, this effect was significantly smaller in mixtures of noninteracting components. Translated into practical terms, the effect of magnesium stearate on the content uniformity of active ingredient in coarse powder mixtures such as granules for encapsulation or compaction into tablets, is not likely to be as significant as that in ordered mixtures containing low-dose active ingredient and diluent. In the latter, lubrication time can have a significant effect on the content uniformity of active

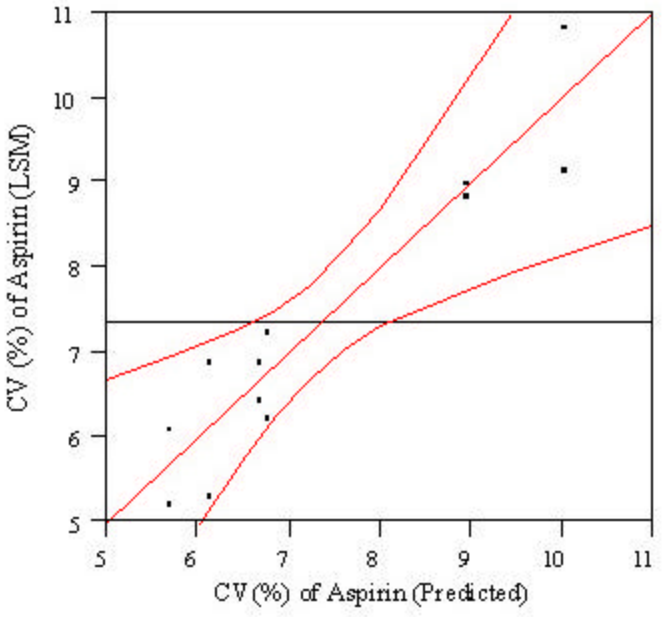

Figure 4. Whole model leverage plot of the effects of magnesium stearate concentration and type of mixture (ordered vs random) on coefficient of variation of aspirin in aspirin-lactose mixtures (R^2 = 0.89).

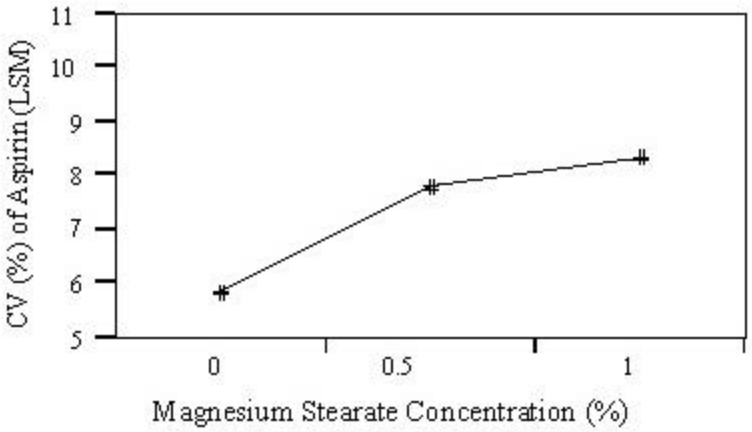

Figure 5. Profile plot of the effect of magnesium stearate concentration on the coefficient of variation of aspirin in aspirin-lactose mixtures at a fixed lubrication time.

ingredient. The extent of the impact of lubrication time depends on the composition of the mixture and on the concentration of magnesium stearate in the mixture.

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