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RESEARCH PAPER

The Effect of Particle Morphology on the Physical Stability of Pharmaceutical Powder Mixtures: The Effect of Surface Roughness of the Carrier on the Stability of Ordered Mixtures

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ABSTRACT

The effect of particle morphology of the components on the physical stability of ordered mixtures was determined for a model system comprised of a mixture of micronized aspirin and a monodisperse carrier. Spray-dried lactose, crystallized lactose, microcrystalline cellulose, and dextrate were used as carriers. The surface texture of the carriers was quantified in terms of the ratio of the perimeter of the particles to that of an idealized shape at a constant magnification. Mixtures containing highly textured carriers segregated to a lesser extent than those containing smoother textured carriers. This was postulated to be due to the presence of a higher concentration of surface asperities on the coarse carriers that can constitute potentially strong adhesion sites for the fine component because of their higher energy relative to adjacent areas on the surface. The effect of the addition of a ternary component, magnesium stearate, on the stability of the above mixtures was studied. The observed differences in the segregation response were attributed to electrostatic charge effects.

Key Words: *Mixture stability; Particle morphology; Roughness; Surface texture.*

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INTRODUCTION

Powder mixing is an important unit operation in the manufacture of solid dosage forms. The content uniformity of powder mixtures containing low doses of drug is a major area of concern. A widely followed practice in the industrial manufacture of solid dosage forms containing small amounts of potent drug is to reduce the particle size of the drug, resulting in the challenge of stabilizing a mixture that consists of a small concentration of a fine component and a large quantity of excipient (carrier). Such mixtures, in theory, can be stabilized by particulate interactions. Hersey proposed the concept of ''ordered mixing'' to explain the mixing of interacting powders (1). Ordered mixtures consist of a fine component adhering to a coarse carrier. The extent and strength of the interactions can logically be expected to be affected by the morphological characteristics of the component particles. Treatments cited in the literature do not include a quantitative surface roughness factor in the evaluation of this phenomenon. The objective of this study was to determine the effect of the surface texture of the carrier on the stability of ordered powder mixtures.

A narrow size range of carrier was used in the study so that the effects of morphological characteristics could be compared independent of particle size. Density effects were assumed to be negligible in this treatment. The surface texture of the micronized drug was assumed to be negligible relative to that of the carrier because of the smooth, round particles produced by the micronization process used to generate the fine component of the mixtures. A similar approximation has been made in the literature for microfine powders (2). The physical stability of the ordered mixtures was evaluated by determining the extent of segregation of the drug from the carrier under the following conditions: (*a*) vibration of the mixtures under controlled conditions for fixed periods of time and (*b*) vibration of the mixtures following the addition of a third component to the system. Magnesium stearate was used as the third component in the system because of its widespread use as a lubricant in the manufacture of tablets and capsules, for which it is usually added to a mixture of drug and diluent(s).

MATERIALS AND METHODS

The model system selected for the study was a binary mixture of micronized aspirin with various carriers. Micronized aspirin was obtained by milling the commercially available aspirin powder (aspirin USP, Miles Laboratories, Inc.) in a fluid energy mill (Trost Equipment Corp.). The carriers used were spray-dried lactose (NF Fast-flo lactose, α lactose monohydrate [spray-dried], Foremost, Wisconsin Dairies), crystallized lactose (crystalline, α lactose monohydrate, Foremost, Wisconsin Dairies), microcrystalline cellulose (MCC; Avicel PH-102 and PH-302, FMC Corp.), and dextrate (Emdex, Edward Mendell Co.). A narrow size fraction of the carriers (106–150 μm of lactose and MCC and 180–250 μm of dextrate) was obtained by sieving the bulk commercial powder. Magnesium stearate (Mallinckrodt, Inc.) was used as received. The powders were stored in a controlled environment (18°C–22°C and 25–30% relative humidity [RH]).

Characterization of the Components of the Mixtures

Particle Size Distribution

The mean particle size and size distribution were measured by light scattering using the Microtrac Full Range Particle Size Analyzer (Leeds and Northrup Corp.). Polysorbate 80 was used to aid in the dispersion of micronized aspirin and magnesium stearate in concentrations of 0.1% and 10% w/w, respectively.

Specific Surface Area

The specific surface area of the powders was determined by the BET method based on nitrogen adsorption (Quantasorb Surface Area Analyzer, Quantachrome Systems).

Moisture Content

The moisture content of the samples was determined by Karl Fisher titration (Accumet® 150 Titration Controller, Fisher Scientific, using Hydranal® Coulomat as the reagent).

Morphological Characteristics

The surface roughness of the particles was computed from measurements obtained by image analysis of the two-dimensional projection of the particles. The image analysis system consisted of an optical microscope equipped with a charge-coupled camera to obtain the particle image as a pixel representation and a high-resolution monitor screen for display of the image (Nikon 7 optical microscope, Fryer Company, IL). The number of pixels in the image was counted to obtain the area of the particle profile, and the pixel count along the boundary of the

profile was used to estimate the perimeter. The software used to process the image and obtain the morphological parameters was Image Pro Plus (version 1.1, Media Cybernetics, Inc.). Particle profile data were collected from at least 100 particles of each powder sample.

Measurement of Electrostatic Charge

Charge measurements were made using a triboelectric charging apparatus (Air Pollution Laboratory, Civil Engineering Dept., Purdue University, West Lafayette, IN) in which the potential induced in a copper ring probe by a fixed amount of charged powder was measured. The powder was charged triboelectrically in its passage through a stainless steel tube in a stream of compressed air (50 ft/sec), and the resulting potential was recorded. The powders were equilibrated at 25% RH prior to the measurement. Five replicate measurements were made on each sample and averaged.

Preparation, Sampling, and Analysis of Mixtures

Mixtures (50 mg) of carrier and drug were prepared in a miniature V blender operated at 30 rpm. An optimum mixing time of 20 min (determined from preliminary experiments) was used. Samples of the mixture were analyzed for aspirin content by measuring the ultraviolet (UV) absorbance of a chloroform extract at 277.5 nm (Beckman DU-7 spectrophotometer).

Evaluation of Mixture Stability

Samples of 10 g of each mixture of aspirin and carrier were subjected to vibration on a screen of a mesh size 70 μm, which was large enough to allow passage of the detached aspirin, but too small for passage of the intact coarse carrier particles. Samples of the mixture were analyzed for their aspirin content prior to vibration and after 5 and 15 min of vibration. The results were expressed as percentage aspirin adhering to the carrier. Each carrier (10 g) was subjected to vibration under identical conditions and was examined for changes in its size distribution.

The effect of a ternary component on mixture stability was evaluated on mixtures of drug and carrier, which were blended with 0.5% magnesium stearate for 5 min. The mean aspirin content and its standard deviation were determined from 10 samples. On a nest of sieves, 10 g of each blend were subjected to vibration, and the amount of aspirin adhering to the carrier was determined from samples of the mixture after vibration for 5 and 15 min.

RESULTS AND DISCUSSION

The mean particle size (mean volume diameter) of micronized aspirin was 8 μm. The specific surface areas of the size fractions of carriers (0.34–0.48 m^2/g) were considered the same to a good approximation. There was no significant difference in the moisture content of the powders, which ranged from 4.8% to 5.6%. The moisture content of aspirin was less than 0.02%. Moisture can affect the adhesion of drug to carrier through capillary forces caused by the formation of liquid bridges between surfaces and through solid bridges resulting from solubility of the material in the liquid films between surfaces and subsequent recrystallization (3). Solid bridges are not likely to constitute a major stabilizing force for the mixtures studied given the moisture content of the powders and the relative humidity of the processing environment.

Morphological Characteristics

A distribution of morphological features of the powders is listed in Table 1. Roundness is a dimensionless number computed from the ratio $(\text{perimeter})^2/(4*\Pi*\text{area})$. Circular objects have a roundness of 1; values greater than 1 indicate greater deviation from the circular shape. The aspect is the ratio of the major axis to the minor axis of the ellipse equivalent to the object. It is a measure of the elongation of the particle and is always 1 or more. The more elongated the particle, the larger its aspect.

The smaller aspect ratio and the closer proximity to unity of the roundness of spray-dried lactose and dextrate particles indicate that they are more spherical than crystallized lactose and MCC particles. Differences in the shape of the carrier were assumed to have no effect on the stability of ordered mixtures of monodisperse carrier and micronized aspirin; that is, the extent of adhesion of micronized drug to the carrier surface is independent of the shape of the carrier. The feature of interest was the surface roughness.

The aspect ratio of micronized aspirin was about 1, while that of the commercial powder was 2.4. Micronization results in a change of shape of elongated needle-shaped particles (mean aspect 2.4) to almost spherical particles having an aspect of 1. This is not unusual since the particle is expected to break along its largest dimension.

The surface roughness was expressed in terms of the ratio $L_p/(L_{p,eq})$, a dimensionless quantity. The ratio of the perimeter of the particle profile being measured L_p with that of an ideal shape having the same area $L_{p,eq}$ was used

Table 1

Morphological Characteristics of Carriers

Carrier	Spray-Dried Lactose	Crystallized Lactose	MCC PH-302	Dextrate
Particle size range (μm)	90–106	90–106	90–106	180–250
Aspect	1.56 (0.42)	1.7 (0.35)	1.8 (0.58)	1.37 (0.31)
Roundness	1.3 (0.17)	1.6 (0.26)	1.84 (0.31)	1.20 (0.12)
Roughness ($L_p/L_{p,eq}$)	1.24 (0.08)	1.1 (0.07)[a]	1.32 (0.11)	1.28 (0.05)

Numbers in parentheses represent the standard deviation.
[a] Value represents the ratio of the perimeter of crystallized lactose particles to that of a square.

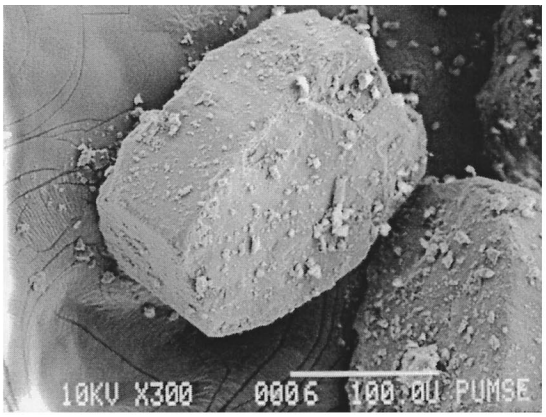
as a quantitative measure of the surface roughness (4). For spray-dried lactose, MCC, and dextrate, which are spherical, the reference ideal shape was a circle. For crystalline lactose, which is rectangular, the reference ideal shape was a square. The closer the measured perimeter was to that of the ideal shape, the smoother the texture. A valid comparison of the roughness of various carriers in terms of this factor requires constant magnification because the measured perimeter increases with an increase in the resolution used to characterize it. The surface roughness of spray-dried lactose is larger than that of its crystallized counterpart. Spray-dried lactose, MCC, and dextrate have mean roughness values in the range 1.24–1.32. These values suggest similar morphology and may be a consequence of the processing history of the excipients. The three excipients are produced by spray-drying, a process that confers a unique microstructure on the particle; the microstructure is quite distinct from that of crystallization. When the ratio of the perimeter of crystalline lactose particles to that of a square having the same area was computed, a value of 1.1 was obtained.

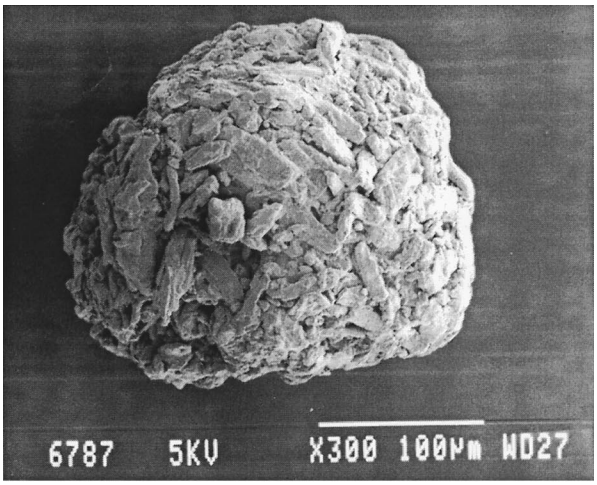
The surface details of crystallized and spray-dried lactose particles are clearly revealed in the scanning electron micrographs taken at a constant magnification of 300× (Fig. 1). The spray-dried product is highly textured compared to the crystallized lactose, which has a relatively smooth surface. MCC and dextrate also have highly textured surfaces, as evident from their scanning electron micrographs (Fig. 2). The proximity of the perimeter values to that of the idealized shape (circle or square) is a measure of surface roughness (rugosity). The perimeter of crystallized lactose was closer to the perimeter of its ideal shape (square) than were the perimeters of the spray-dried carriers to that of a circle. This was a clear indication of the greater rugosity of the spray-dried carriers relative to the crystallized lactose. In the case of dextrate particles, computation of the roughness at the same resolution yielded a roughness factor of 1.28, a value comparable to that of the other spray-dried carriers.

Evaluation of the Physical Stability of Mixtures

Testing the physical stability of mixtures involved subjecting them to vibration for a fixed period of time. For the data to be valid, there must be no change in the size of the components. From fracture mechanics, it can be shown that small particles are less easily ruptured than coarser particles. The ''fine'' component of the mixture consists of micronized material that is not easily comminuted further. The logical approach was to determine whether attrition of the coarse component (carrier) of the mixture occurred under the conditions of vibration. Any change in the size and size distribution of the carrier would confound the results since a change, if any, in the extent of drug adhering to the carrier surface might then be attributed to the rupture of existing surfaces and creation of new surfaces.

The response of mixtures of micronized aspirin with spray-dried and crystallized lactose carriers to vibration is shown in Fig. 3. The mean and the standard deviation of the aspirin content of the mixtures before (0 min) and following vibration for 5 and 15 min are plotted. The micronized aspirin was retained entirely on the carrier surface, as indicated from the assay of the carrier particles. Mixtures of spray-dried and crystallized lactose with micronized aspirin were comparable in their initial aspirin content. The standard deviation of aspirin was 6.5% in the mixture containing crystallized lactose and 2.1% in the mixture with spray-dried lactose. After 5 min





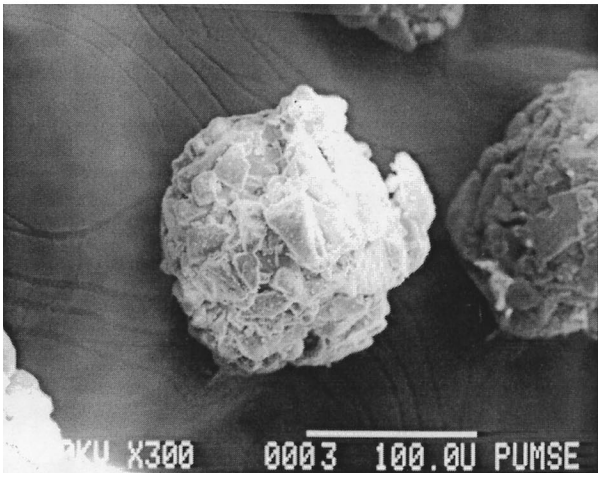


Figure 1. Scanning electron micrographs of crystallized lactose and spray-dried lactose.

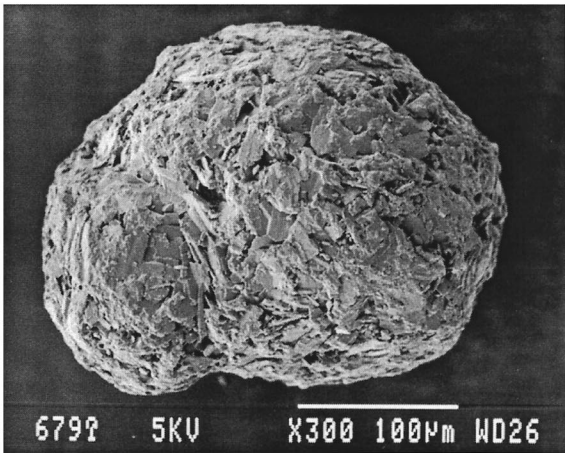


Figure 2. Scanning electron micrographs of MCC (Avicel PH-302) and dextrate (Emdex).

of vibration, the average retention on the spray-dried lactose was over 90% of the initial drug content, while that on the crystallized lactose carrier was about 60%. After 15 min vibration, spray-dried lactose particles retained 86% ($\pm$10%) of their initial drug content, whereas crystallized lactose particles retained only 40% ($\pm$15%) of their initial drug load.

The carriers did not significantly differ in particle size, specific surface, area and moisture content nor did they undergo attrition (particle size change) under the conditions of vibration. The principal difference in the (measured) characteristics that is likely to account for the difference in the observed vibrational stability is the surface texture.

Figure 4 includes the stability data for mixtures of micronized aspirin with MCC and dextrate. From the behavior of the mixtures, a significantly greater proportion of the initial drug content was retained on more highly textured carriers than on the smoother textured crystallized lactose when the ordered mixtures were subjected to vibration (Tukey-Kramer multiple comparison of means, $\alpha = .05$). The observations appear to support the concept of greater physical stability of ordered mixtures with an increase in the roughness of the carrier. While MCC particles had similar equivalent size and surface roughness values as spray-dried lactose, there were differences observed in the stability of the two mixtures. About 15% of the initial drug was displaced from the MCC carriers

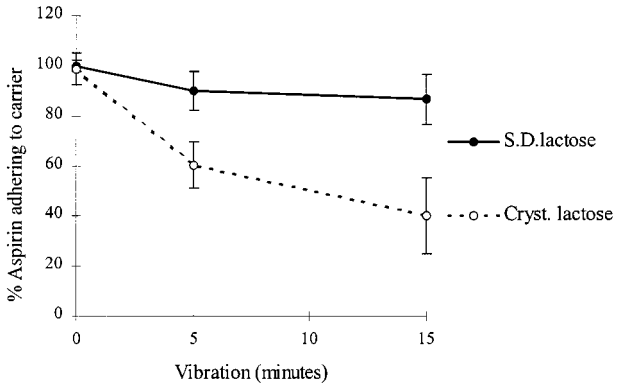


Figure 3. Segregation of mixtures of micronized aspirin with spray-dried and crystallized lactose carriers when subjected to vibration.

after 5 min vibration and nearly 25% after 15 min vibration. Thus, a larger extent of aspirin was dislodged from MCC particles than from spray-dried lactose.

For dextrate, an interesting observation was the greater extent of segregation of aspirin after 5 min vibration compared to that from spray-dried lactose and MCC; 20% of the drug was dislodged from the carrier surface, and there was no further segregation. Dextrate has a notably larger particle size, which might argue for enhanced stability of the mixture.

However, since most surfaces are not homogeneous, adhesion of drug is not likely to occur uniformly over the entire carrier surface. The observation that carriers, although apparently similar in surface roughness, differ in the kinetics of segregation of the drug from their surface following vibration suggests a difference in the strength of adhesion of the drug to the various carrier sites. This is likely to be due to differences in the chemical nature of the carrier and/or the relative occurrence of higher energy sites (asperities) on the carrier surface. The magnitude of a drug-carrier interaction will then affect mixing outcome.

Effect of Magnesium Stearate on Mixture Stability

The mean particle size of magnesium stearate was comparable to that of aspirin. The effect of magnesium stearate on the segregation of drug from a mixture of spray-dried lactose and aspirin is shown in Fig. 5. The mean aspirin content of the mixture prior to vibration was the same as that of the control (without magnesium stearate). The mixture containing magnesium stearate, however, showed a larger standard deviation, indicating greater variability in the distribution of drug in the mixture. After 5 min vibration, the mixture containing magnesium stearate retained 76% (±13.2%) of its initial aspirin content compared to 90% (±7.8%) by the control; the amount of aspirin retained on the carrier surface remained unaltered even after 15 min vibration. It was inferred that a fraction of the aspirin was dislodged from the carrier during the mixing process, thus adversely affecting the homogeneity of the system. The segregation that occurred on vibration appeared to be largely a consequence of the free or weakly adhering aspirin.

The effect was even more pronounced in the mixture of MCC, aspirin, and magnesium stearate (Fig. 6). The

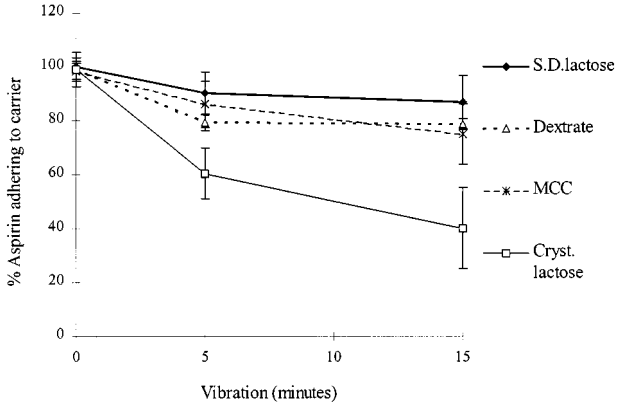


Figure 4. Segregation of mixtures of micronized aspirin with carriers of different surface roughness when subjected to vibration.

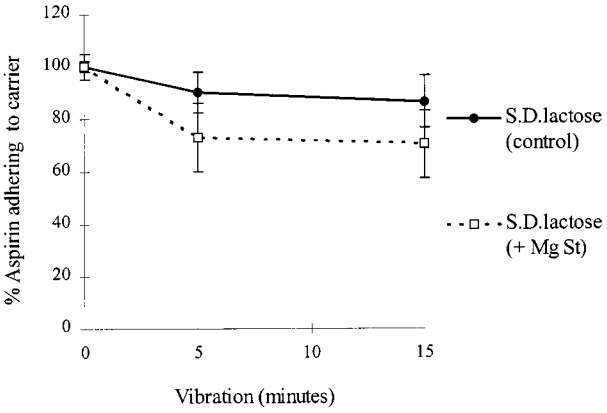


Figure 5. Effect of magnesium stearate (0.5%) on the segregation of micronized aspirin from spray-dried lactose carrier.

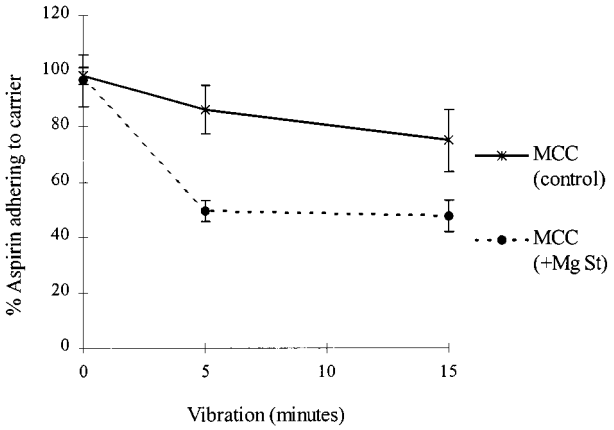


Figure 6. Effect of magnesium stearate (0.5%) on the segregation of micronized aspirin from MCC carrier.

standard deviation of the mixture prior to vibration was nearly three times larger than that of the control, and only 50% of the initial drug content was retained by the carrier after 5 min vibration—a significantly lower retention relative to the 86% retention in the control. Again, the amount of aspirin adhering to the carrier surface remained constant after 15 min vibration.

The effect of magnesium stearate on the segregation of aspirin from dextrate is shown in Fig. 7. There was no significant difference in the mean aspirin content and the standard deviation of the two mixtures both before and after vibration. Magnesium stearate did not appear to have an effect on the stability of the dextrate-aspirin mixture. The observation was surprising because the surface texture of dextrate was comparable to that of spray-

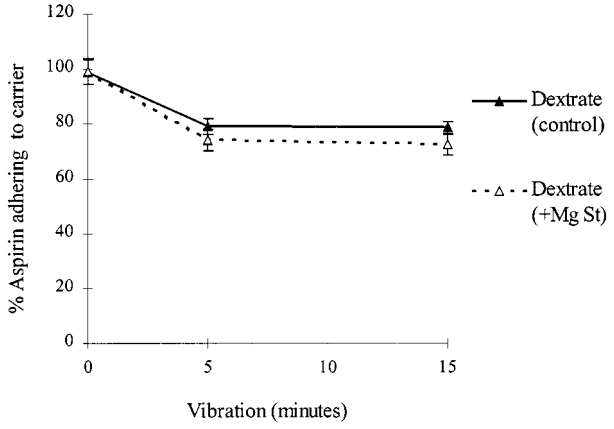


Figure 7. Effect of magnesium stearate (0.5%) on the segregation of micronized aspirin from dextrate carrier.

dried lactose and MCC. A similar observation has been reported on the effect of magnesium stearate on the homogeneity of an ordered mixture of micronized prednisone and dextrate; magnesium stearate had no effect on the homogeneity of the mixture at concentrations both below and above the theoretical surface saturation of the carrier (5). This implied that the effect of magnesium stearate was not because of the differences in the surface area of the carrier. It was inferred that there was an additional factor pertaining to the surface that influenced the stability of the mixture.

All the studies described previously were conducted in an environment of low relative humidity (<30% RH), which is conducive to the operation of electrostatic charge effects. Further, magnesium stearate has been reported to have the ability to disperse electrostatic charge (6,7). The electrostatic charge on the powders is listed in Table 2. The numbers listed represent the potential corresponding to the maximum charge developed. It must be noted that the values are not absolute, but are very specific to the conditions of measurement. They do, however, permit comparison of the systems being studied. Under the conditions of measurement, spray-dried lactose and MCC acquired a net positive charge, while dextrate and aspirin acquired a net negative charge.

The behavior of the mixtures following the addition of magnesium stearate can be explained with reference to their electrostatic charge characteristics. The addition of magnesium stearate resulted in segregation of mixtures (i.e., lactose-aspirin and MCC-aspirin mixtures) that are stabilized by electrostatic charge. It is likely that, while the addition of magnesium stearate had no effect on a mixture of dextrate and aspirin, the mixture itself was not stabilized by electrostatic attraction between the carrier and drug as was the mixture of spray-dried lactose and aspirin. This is likely to be a reason for the larger amount of aspirin displaced from the surface of dextrate than from spray-dried lactose when the mixture was vibrated. A point of interest is that there is no significant difference in the charge on the bulk spray-dried and crystallized lactose carriers.

To determine whether the decrease in the stability of aspirin-carrier mixtures following the addition of magnesium stearate to the mixture was due to the displacement of aspirin from the carrier sites by magnesium stearate, the order of addition of magnesium stearate to a mixture of carrier and aspirin was reversed; that is, spray-dried lactose was blended with 0.5% magnesium stearate, and aspirin was added as a third component to this mixture. Based on earlier observations, it was expected that the adhesion of aspirin to some of the potential adherence

Table 2

Electrostatic Charge[a] of Mixture Components

	Mean Particle Size (μm)	Potential (Volts) Mean	Potential (Volts) Standard Deviation
Spray-dried lactose	103	0.083	0.019
Crystallized lactose	100	0.086	0.022
MCC	102	0.100	0.003
Dextrate	200	−0.079	0.007
Aspirin	8	−0.028	0.007

[a] Triboelectric charge developed during flow through a stainless steel tube.

sites on the carrier must be reduced in the presence of magnesium stearate, leading to large deviations in the aspirin content and its rapid segregation on vibration. The observations supported this hypothesis (Fig. 8). The standard deviation of the initial aspirin content was over twice as large as that of the mixture that had been lubricated in the normal sequence. This was a clear indication of nonhomogeneous distribution of aspirin in the mixture.

The destabilizing effect of magnesium stearate may be attributed to the reduction in the sites available for the adhesion of aspirin and to the reduction in the affinity of the available sites due to dissipation/neutralization of the electrostatic charge on the surface. The free aspirin and the fraction of aspirin at the weaker adherence sites were rapidly dislodged on vibration, causing the observed behavior.

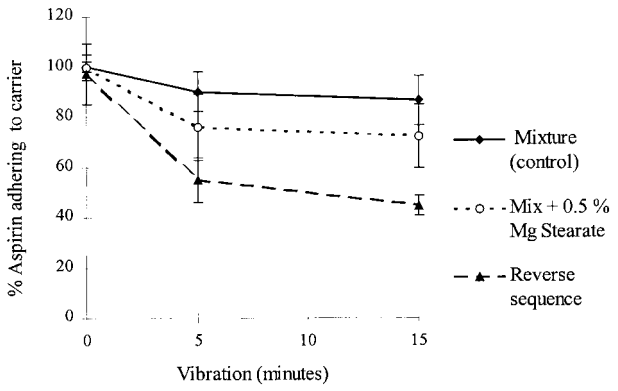


Figure 8. Effect of reversal of lubrication sequence of magnesium stearate on the segregation of micronized aspirin from spray-dried lactose carrier.

SUMMARY AND CONCLUSIONS

The stability of mixtures based on particle interactions was found to be affected by the surface roughness of the components. Ordered mixtures containing carriers that had high surface roughness were observed to be more stable than those with smoother textured carriers when subjected to potentially segregating conditions; this was in support of our initial hypothesis. The mechanism is likely to be a combination of surface texture and electrostatic charge. It must be pointed out that the two effects may be linked (8). Electrostatic forces generally operate only at extremely low relative humidity. In ambient conditions (>60% RH), electrostatic charge effects may be negligible. However, even if the charge is dissipated rapidly, the particles brought into close proximity by the long-range electrostatic forces can be held by dispersion forces. This effect can only hold true up to a point since roughness results in a reduction in the true area of contact over which van der Waals forces can act (9). Image analysis using optical microscopy is not sensitive to details of surface texture for detection of this limit. Techniques such as atomic force microscopy, which can map the surface at extremely high resolution, may make it possible to detect this region.

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