Drug Development and Industrial Pharmacy, 28(1), 41–48 (2002)

RESEARCH PAPER

Polydisperse Powder Mixtures: Effect of Particle Size and Shape on Mixture Stability

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ABSTRACT

The effect of the shape and size of the components on the stability of mixtures was evaluated in binary mixtures of drug and carrier. Aspirin was used as model drug; spray-dried lactose and microcrystalline cellulose were used as carriers. The coefficient of variation (CV) of the drug in the mixture at various time intervals during mixing was used as a measure of homogeneity. The stability of mixtures was assessed under conditions that were conducive to segregation—in this case, prolonged mixing. The pattern of change in CV with time was analyzed in terms of convective, shear, and diffusive mixing stages. The variation resulting from a change in the shape of the carriers was smaller than that resulting from size differences. The segregation rate constant, calculated on the assumption of a first-order mixing process, was found to be larger in mixtures having components of different shape than in mixtures having components of similar shape. In mixtures of micronized drug and carrier, the pattern of change in the CV of drug with mixing time was attributed to the distribution of agglomerates of micronized drug during convective mixing, followed by shearing of agglomerates and, finally, the distribution of the primary particles during diffusive mixing. Mixtures of non-cohesive powders of similar size and shape behaved like random mixtures of non-interacting components.

Key Words: *Particle morphology; Particle shape; Surface roughness; Mixtures of micronized drug and carrier; Polydisperse power mixtures; Segregation*

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INTRODUCTION

Solids mixing is an important unit operation in the manufacture of pharmaceutical solid dosage forms. The importance of producing stable mixtures to ensure the uniformity of dosage units with respect to the active ingredient, particularly low-dose potent active ingredients, cannot be overstated. Whereas the uniformity of a blend does not in itself guarantee uniformity of the drug in a final dosage form, producing a stable mixture still remains the first important step in solid dosage form manufacture. Each post-mixing handling step is a potential segregating influence. Segregation is caused by differences in the physical properties—particle size, density, and morphology—of the constituent particles. There is a considerable body of work in the literature on the effects of size (1,2) and density (3). Density differences have been shown to be relatively unimportant (3). The term "morphology" refers to the overall shape and surface texture. Although it has been listed as a potential cause of powder segregation, particle morphology has received experimental attention only recently (4). Particle shape has been reported to affect the flow and packing properties of noncohesive granular materials (5–7). The earliest quantitative information on the effects of particle shape on mixing and segregation in ideal systems of regularly shaped particles—chrome steel balls and rods—was obtained by Rippie et al., who reported substantial differences in bulk behavior resulting from minor changes in particle shape (8).

The current study was aimed at determining the effect of the morphology of the components of non-random mixtures on mixture stability. The objective was to determine the effect of the shape of the components of a binary system of carrier (major component) and drug (minor component) on the mixing profile and on the stability of the resultant powder mixtures.

The experimental approach consisted of preparing mixtures of each of the carriers with a constant concentration (1%) of minor component (aspirin) of various size and aspect ratio and measuring the coefficient of variation (CV) of the minor component in the mixtures at various times during mixing and segregation. The mean size (diameter) and aspect ratio of the minor component of the mixtures were as follows:

- micronized aspirin of 8 μm size and aspect ratio ~1;
- polydisperse aspirin powder, having a mean size of 100 μm and an average aspect ratio of 2.4, and;
- coarse monodisperse aspirin in the size range of 100–150 μm, having an aspect ratio of 2.9.

MATERIALS AND METHODS

Commercially available excipients—spray-dried lactose (Foremost, Wisconsin Dairies) of three grades of 103 μm, 60 μm and 36 μm mean size (mean volume diameter) and microcrystalline cellulose (MCC: Avicel PH302 and PH102, FMC Corp.) of 100 μm mean size—were used as carriers. The carriers were polydisperse. Commercial aspirin was obtained from Miles Laboratories. The coarse material in the size range of 100–150 μm was obtained by sieving the commercial powder. Micronized aspirin was obtained by milling the commercial powder in a fluid energy mill (GemT Model, Trost Equipment Corp.).

The components were mixed in a tumbling stainless steel V blender that was loaded to a constant volume equal to 60% of its total capacity of 3 L. The order of loading in the mixer was one-half the quantity of carrier, minor component, followed by the rest of the carrier. Mixing was carried out in a controlled environment [20 ± 2°C and 30 ± 2% RH (relative humidity)]. The mixtures were sampled at various time intervals, ranging from 2.5 to 120 min, using a thief sampler that was selected to remove a volume of powder corresponding to 200 mg. The samples were discharged into pre-weighed vials, which were subsequently weighed to compensate for the variation in sample amount in thief sampling. The actual amount of sample was obtained by the difference of the two weights. Ten samples were removed at each time interval from five locations in the mixer. The aspirin content was determined from the absorbance of chloroform extracts of the samples at 277.5 nm. The CV of aspirin (relative standard deviation expressed as a percent of the mean) was calculated at each time point.

Inducing Segregation In Situ

Mixing was continued for an extended period of time—120 min— to study segregation in situ, i.e.,

to evaluate the propensity of the system to segregate under conditions that were potentially conducive to segregation in the blender itself. While we recognize that in practice mixing is never carried out for such prolonged times, this served as a means for inducing controlled segregation, obviating the necessity of subjecting the mixture to an uncontrolled process such as discharge from the blender. From preliminary experiments we determined that there was no significant change in the mean particle size of the carriers after they had been tumbled in the V-blender for 120 min (Student's t test at a significance level of 0.05). The particle size distribution of the major component of the mixtures remained essentially unchanged during the mixing process.

Determination of Particle Size and Shape

The particle size distribution of the powders was measured using a Microtrac Full Range particle size analyzer (Leeds & Northrup Corp.). The morphological characteristics were computed from image analysis of the two-dimensional projection of the particles. The image analysis system (Fryer Company, IL) consisted of an optical microscope fitted with a CCD (charge-coupled device) camera for obtaining the particle image as a pixel representation and a high-resolution monitor screen for display of the image. The software used to obtain the morphological parameters was Image Pro Plus (Media Cybernetics Inc.). Particle profile data were collected from at least 100 particles of each powder sample. The number of pixels in the image was counted to obtain the area of the particle, and the pixel count along the boundary of the profile was used to estimate the perimeter of the particle. The shapes of the particles were characterized in terms of the aspect ratio, which is the ratio of the major to the minor axis of the ellipse equivalent to the object. The more elongated the object, the larger the aspect ratio.

The surface roughness values of the carrier particles were computed from a parameter based on the excess of perimeter length over that of a circle of the same area. The quantity $L_P/L_{p,eq}$ is a ratio of the perimeter of the particle profile being measured L_p, with that of a circle having the same area, $L_{p,eq}$ (9). The measurements were made at the same magnification for comparison of the roughness of various carriers in terms of this factor.

Measurement of Flow Characteristics of Powders

The Micron Powder Characteristics Tester (Model PT-N, Hosakawa Micron Corp.) was used to measure the flow properties of powders based on the Carr indices. The measurements included the angle of repose, aerated and packed bulk densities, compressiblity, cohesiveness, and dispersibility. The compressibility and the overall flowability were obtained from these parameters (10). The flow rates of powders were determined from the time recorded for the flow of 100 g of powder from a hopper having an orifice of 15 mm diameter. The hopper was vibrated at 60 Hz to aid flow of powders that did not flow freely.

RESULTS AND DISCUSSION

Generally, three processes—convection, shear and diffusion—are involved in the mixing of powders. The extent of mixing is affected by the operating conditions and powder properties (11,12). The former were maintained constant in our experiments. The changes in the mixing curve, therefore, principally reflect differences in powder properties.

Effect of Shape of the Carrier on Mixture Stability

The physical characteristics of the carriers are listed in Table 1. Spray-dried lactose (SD lactose) and MCC (Avicel PH302 and PH102 grades) have comparable mean particle size and size distribution but differ considerably in their shape (aspect ratio). The aspect ratio of SD lactose, Avicel PH302, and PH102—1.36, 1.61, and 3.7, respectively—represents a change from spherical to fiber-like morphology. The aspect ratio of PH302 is intermediate between that of a sphere and a fiber. The surface roughness values of the carriers are comparable and this is likely to be due to similarity in processing history.

The effect of shape of the carrier on the CV of aspirin in a binary mixture of carrier and 1% micronized aspirin is shown in Fig. 1. As the aspect ratio of the carrier increased, large variations in CV were observed in the initial and intermediate stages

Table 1

Physical Characteristics of Carriers

	Spray-dried Lactose	MCC PH302	MCC PH102
Mean size (μm)	103	99	102
Aspect ratio	1.36	1.61	3.7
Surface roughness	1.27	1.31	1.28
Angle of repose (deg)	32.2	38.0	41.6
Compressibility (%)	13.4	19.4	24.9
Cohesiveness (%)	23.0	23.5	[a]
Flow rate (kg/min)	0.9	0.8[b]	0.43[b]

[a]Could not be determined by this technique due to tangential passage of material through sieve apertures.
[b]Aided by 60 Hz vibration.

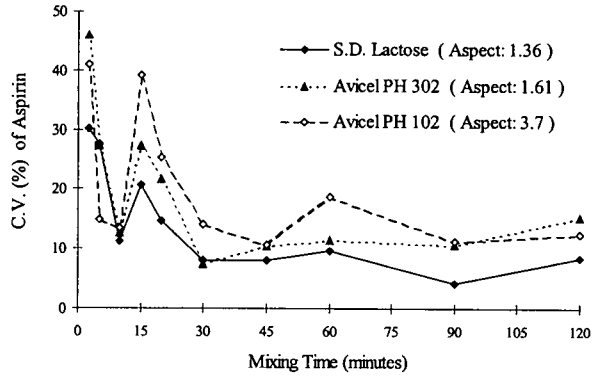

Figure 1. Effect of shape of carrier on the coefficient of variation (CV) of the drug in a binary mixture of carrier and drug. The aspect ratios are in parentheses in the figure.

of mixing. Once a homogeneous mixture as indicated by a low CV was formed, there was no further change in the CV, even upon prolonged mixing. This indicated the formation of stable mixtures that were resistant to segregation.

The variation in CV during the initial stages suggests the influence of factors that affect convective mixing: specifically, differences in the flow properties of the carriers. The flow properties of the carriers are listed in Table 1. The angle of repose increased from 32°, through 38°, to 42°, as the elongation of the carrier increased. There was no significant difference in the cohesiveness of the carriers and this is expected, given their similar size. The principal effect of shape of the carriers on mixing is likely to be by its effect on flow. The fibers of MCC do not flow as freely as the spherical lactose particles.

This was supported by the rate of flow of the powders through a 15 mm orifice. The flow rate of Avicel PH102 was 0.43 kg/min, aided by 60 Hz vibration, whereas that of spray-dried lactose was 0.9 kg/min (free flow). Avicel PH302 flowed at an intermediate rate of 0.8 kg/min aided by 60 Hz vibration. A point of interest is that in the mixing of aspirin with carriers having similar size and surface roughness, but different aspect ratio (Fig. 1), variations in CV were observed mainly during the convective mixing stage; subsequently, there was little in the CV even under conditions that could induce segregation.

Effect of Size of the Carrier on the Stability of Mixtures of Carrier and 1% Micronized Aspirin

Lactose grades of 103 μm, 60 μm and 36 μm mean size were used as carriers. From the plot of the CV vs. mixing time (Fig. 2), it is evident that the effect of particle size on mixture homogeneity is greater than that of particle shape. As the mean particle size of the carrier decreased, large variations were measured in the distribution of drug in the mixture. Agglomerates of the micronized drug were visually evident in the mixture containing lactose of 36 μm size as carrier even after it was mixed for 120 min. With decreasing particle size, the specific surface of the carrier increases, and with it, cohesive interactions among the particles.

Examining the bulk properties of the powders (Table 2), the cohesiveness was 23% for the free-flowing lactose of 103 μm size, 34% for the 60 μm lactose, and ~35% for the 36 μm lactose. Comparing these with the values of 23–24% that were measured in carriers of the same equivalent size and different aspect ratio, it is evident that the impact of particle size on cohesiveness is considerably greater than that of shape. It must be noted that the moisture content of the lactose grades was between 4 and 6% and did not vary much among the grades. Since the mixtures were prepared in an environment of constant and comparable temperature and RH, the contribution of moisture to cohesiveness was considered to be constant in the mixtures examined. The large value of CV in the mixture containing 36 μm lactose was attributed to large cohesive interactions among the carrier parti-

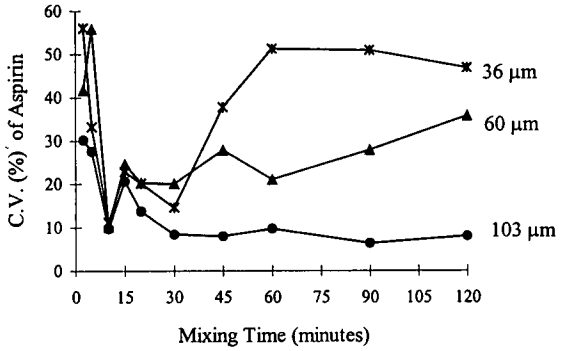

Figure 2. Effect of the size of the carrier on the coefficient of variation (CV) of the drug in the mixing of 1% micronized drug with lactose carrier.

Table 2

Physical Characteristics of Lactose Carriers

	Spray-dried Lactose	Crystallized Lactose	Crystallized Lactose
Mean size (μm)	103	60	36
Aspect ratio	1.36	1.61	3.7
Angle of repose (deg)	32.2	47.9	53.2
Compressibility (%)	13.4	38.4	52.1
Cohesiveness (%)	23.0	34.0	34.7

cles, which are not conducive to effective mixing. The critical particle size at which cohesive forces are dominant varies for each material. For lactose, this is around 60 μm; above this size, diminished cohesive forces have little effect on flow properties.

Whereas the principal difference in the lactose grades used was the particle size distribution, variation in surface roughness was a confounding factor. However, no significant difference in surface roughness between the 60 μm and 36 μm grades was observed at a magnification of 1000. The variation in CV with time appears to be mainly due to particle size.

Effect of Morphology of the Minor Component on CV of Mixtures

The practical difficulty of obtaining aspirin of several shapes in the same equivalent size posed a problem in evaluating the effect of morphology of the drug on mixture stability. Commercial aspirin powder consists of needle-shaped crystalline particles with a mean size of 100 μm and an aspect ratio of 2.4. The coarsest fraction (100–150 μm size fraction) has an aspect ratio of 2.9. Material of ~8–10 μm size that was obtained by micronization had comparatively negligible surface roughness. Sieving was not an effective technique for separating the various size fractions, since the needle-shaped particles passed through sieve apertures tangentially. However, by comparing the mixing (and segregation) of systems in which the drug and carrier had similar shapes to those containing components of different shapes, information on the effect of the morphology of the minor component could be obtained. Accordingly, the following combinations were examined for a comparison of the profile of the CV of the drug in the mixture with mixing time:

- mixtures of micronized aspirin (1%) having an aspect ratio of ~1 with spherical (SD lactose) and elongated (Avicel PH102) carriers, respectively;
- mixtures of aspirin (1%) having an aspect ratio of 2.9 with spherical and elongated carriers.

A plot of the CV of aspirin during the mixing of micronized aspirin with the various carriers (Fig. 3) was characterized by an initial rapid drop in the CV, followed by a slight increase and a subsequent decrease to a constant value. The pattern of initial decrease in the CV followed by an increase, before a constant value was reached, was initially attributed to variations in sampling. However, its repeated occurrence in each mixing experiment involving micronized aspirin at about the same time interval suggested that it was not an artifact entirely due to sampling. Visual examination of the mixture provided a pointer to the cause. Whereas the primary size of micronized aspirin particles was ~8 μm, the bulk material exists as agglomerates. The mean size of the agglomerates was ~150 μm (i.e., approximately the same as the mean particle size of the carrier) and they flowed freely. The distribution of agglomerates in the mixture during the continuous division and recombination of the powder bed during the initial (convective) stage of mixing may account for the initial decrease in CV. Following the distribution of agglomerates, the measured increase in the CV was attributed to the breakdown of the agglomerates during shear mixing, which resulted in high local concentrations of the drug. As the distribution of the primary particles in the

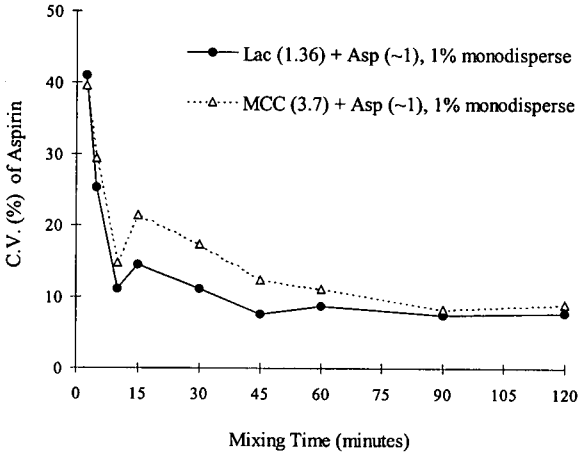

Figure 3. Effect of the aspect ratio of the carrier on the segregation of mixtures of carrier and micronized drug. Numbers in parentheses represent the aspect ratio of the component.

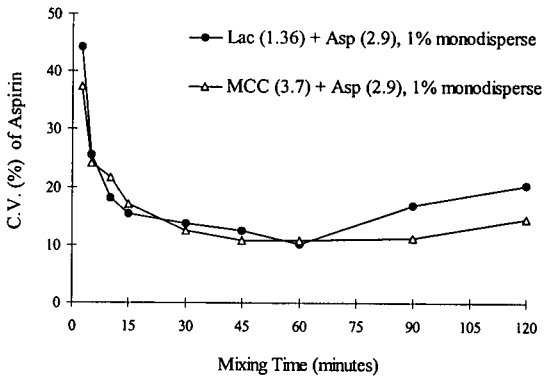

Figure 4. The effect of aspect ratio of the carrier on the segregation of mixtures. Numbers in parentheses represent the aspect ratio of the component.

mixture proceeded, the CV once again decreased and assumed a constant value. No segregation was observed after 120 min of mixing.

Effect of Increasing the Aspect Ratio of the Minor Component on Mixture Segregation

An increase in the aspect ratio of aspirin from ~1 to 2.9 was accompanied by an inevitable increase in particle size. A plot of CV vs. mixing time in mixtures of needle-shaped aspirin particles with lactose and MCC carriers, respectively, is shown in Fig. 4. It was evident that segregation occurred upon prolonged mixing, as indicated by the increase in the CV. This is characteristic of random mixtures in which the components segregate due to differences in size and shape. The pattern of change in CV (i.e., initial decrease followed by an increase) that was observed in mixtures containing micronized drug was absent in this case. Essentially, by increasing the size and aspect ratio of the minor component to match that of the carrier, the nature of the mixture was altered from a system based on particulate interaction to one approaching a random mixture of non-interacting components.

The difference in segregation rate between mixtures of needle-shaped aspirin with the spherical lactose and fibrous MCC is a measure of the contribution of shape to segregation. Aspirin and MCC have similar shapes, whereas mixtures of aspirin with lactose represent systems having components of different shapes.

Rate Constants of Mixing and Segregation

The rate constants of mixing and segregation were computed for mixtures containing aspirin of different aspect ratio, assuming a first-order mixing process. The slope of the first part of the mixing curve (2.5–10 min) represents the convective mixing rate during which particles of drug (agglomerates in the case of micronized drug, and primary particles in mixtures containing 100 μm aspirin) are distributed in the mixture. The rate constants are listed in Table 3. The rate constant of mixing of lactose with micronized aspirin was nearly 10 times as large as that in the subsequent period of time during which shear mixing was dominant. The rate constant during the steady-state period was smaller by a factor of 100 than that during convective mixing. For the mixture of MCC and micronized aspirin, the rate constant of convective mixing was 0.057 min^{-1} with almost similar rates of mixing thereafter. The difference in the convective rate constants of mixtures containing carriers of different shape was attributed to differences in flow characteristics of the carriers.

In random mixtures of drug and carrier, the convective rate constants were smaller than those in mixtures containing micronized drug, regardless of the shape of the carrier. This was attributed to the slower distribution of the elongated, needle-shaped

Table 3

Rate Constants of Mixing of Carrier and Drug

Mixtures	Rate Constants (min^{-1}) During Mixing		
	0–10 min	10–45 min	45–120 min
Lactose (1.36) + Aspirin (~1)	0.075	0.01	0.0003
MCC (3.7) + Aspirin (~1)	0.057	0.008	0.0014
Lactose (1.36) + Aspirin (2.9)	0.048	0.004	−0.0049[a]
MCC (3.7) + Aspirin (2.9)	0.029	0.006	−0.0021[a]

Numbers in parentheses represent the aspect ratio of the component.
[a]Segregation rate constant.

aspirin particles with either carrier relative to that of spherical agglomerates of micronized aspirin. The rate constant in the mixture containing MCC was smaller than that in the mixture containing lactose and this was due to the poorer flow characteristics of the former. The rate constant in the 15–45 min period was comparable in mixtures containing carriers of different shapes. The CV reached a constant value during this time. After this period, there was an increase in the CV that was indicative of segregation (change in the sign of the slope). It is interesting to note that the segregation rate constant is higher for the mixture of lactose and aspirin, in which the components have different shapes, than for the MCC–aspirin mixture, in which the components have the same shape.

The mixtures examined thus far consisted of polydisperse carrier and monodisperse drug. The effect of varying the aspect ratio of the drug on the segregation of mixtures in which both carrier and drug were polydisperse is shown in Fig. 5. The pattern of mixing and segregation was very similar to that of the systems containing aspirin of aspect ratio 2.9. The extent of segregation was greater in lactose–aspirin mixture than in the MCC–aspirin mixture.

Effect of Concentration of Minor Component on Segregation of Polydisperse Mixtures

When the concentration of drug in the mixture was increased to 10% (Fig. 6), the extent of segregation was greater in mixtures of components of different shape (spherical lactose and elongated aspirin) than in mixtures having components of similar shapes. An observation of interest was the

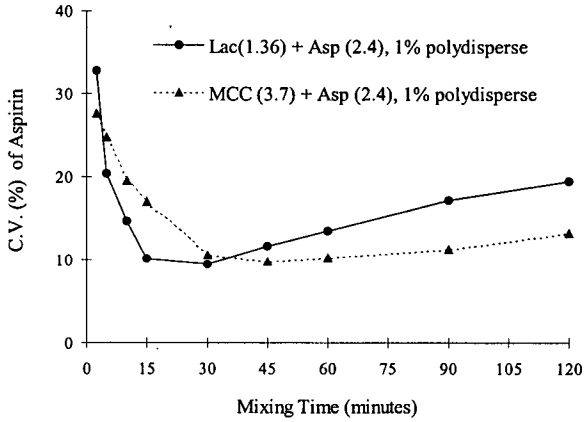

Figure 5. Effect of the aspect ratio of the components on the segregation of mixtures of polydisperse carrier and drug. Numbers in parentheses represent the aspect ratio of the component.

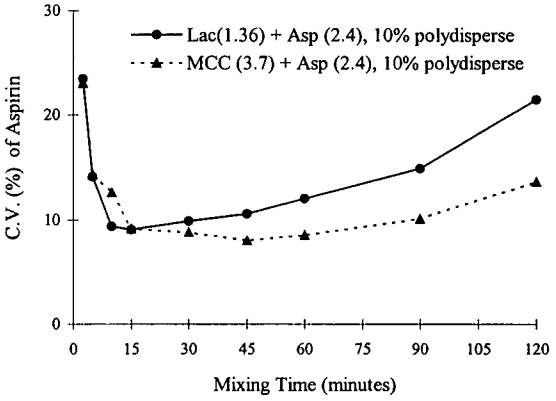

Figure 6. Effect of the aspect ratio of the components on the segregation of mixtures of polydisperse carrier and 10% polydisperse drug. Numbers in parentheses represent the aspect ratio of the component.

smaller CV after 2.5 minutes mixing in mixtures of polydisperse carrier and drug. The CV was 40–44% in mixtures of micronized aspirin with either carrier; 28–32% in mixtures with 1% polydisperse drug; and 23–24% in mixtures containing 10% drug. As the proportion of minor component in the mixture was increased, homogeneity (as indicated by a low CV) was more rapidly achieved.

Effect of De-agglomeration of Micronized Drug on Its CV in Mixtures

The rate-limiting step in obtaining a uniform mixture with micronized drug has been postulated to be the breakdown of agglomerates of the micronized drug. To test this hypothesis, agglomerates of the micronized aspirin were broken down by sieving the drug with 10 parts of lactose and mixing this with the remainder of the lactose for 20 min. The resulting CV values are listed in Table 4. CV values of less than 5% were obtained in mixtures containing de-agglomerated drug, whereas the CV in the control (without de-agglomeration) was around 10%. The smaller CV values measured as a result of the sieving process were attributed to a reduction in cohesive interactions among the drug particles and an increase in adhesive interactions between the drug particles and carrier.

Table 4

Comparison of the CV of Aspirin in Mixtures Made with De-agglomerated Drug and That of the Control

Experiment #	CV of Aspirin in Mixtures in Which Micronized Drug Was Sieved with Carrier	CV of Aspirin in Control
1	4.1%	10.5%
2	3.2%	11.2%
3	5.0%	8.4%

CONCLUSION

The effect of varying the aspect ratio of the carrier and drug on the segregation of polydisperse mixtures was determined from the CV of the drug in the mixture as a function of mixing time. The variation resulting from a change in the shape of the carriers was smaller than that resulting from size differences. The shape of the components was found to affect the magnitude of the segregation rate constants—these were larger in mixtures having components of different shape than in mixtures of components of similar shape. In mixtures of micronized drug and carrier, the pattern of change in the CV with mixing time was attributed to the following sequence—distribution of agglomerates of micronized drug during convective mixing; breakdown of agglomerates during shear mixing; and the distribution of the primary particles during the diffusive mixing stage. Such mixtures did not segregate when they were subjected to conditions that were conducive to segregation. Mixtures in which the size and aspect ratio of the minor component and carrier were similar and the powders were largely non-cohesive (with mean particle size of around 100 μm) behaved like random mixtures of non-interacting components.

ACKNOWLEDGMENT

The authors acknowledge the financial support provided by the Purdue Research Foundation and the NSF Industry-University Co-operative Center for Pharmaceutical Processing Research at Purdue University.

REFERENCES

1. Lawrence, L.R.; Beddow, J.K. Powder Technol. **1968**, *2*, 253.
2. Williams, J.C. Powder Technol. **1976**, *15*, 245–251.
3. Nienow, A.W.; Rowe, P.N.; Cheung, L.Y.L. Powder Technol **1978**, *20*, 89–97.
4. Swaminathan, V.; Kildsig, D.O. Drug Dev. Ind. Pharm. **2000**, *26*(4), 365–373.
5. Ridgway, K.; Scotton, J.B. J. Pharm. Pharmacol. **1970**, *22*(Suppl.), 24s–28s.
6. Ridgway, K.; Rupp, R. J. Pharm. Pharmacol. **1969**, *21*(Suppl.), 30s–39s.
7. Aoki, R.; Suzuki, M. Powder Technol. **1970–71**, *4*, 102–104.
8. Rippie, E.G.; Faiman, M.D.; Pramoda, M.K. J. Pharm. Sci. **1967**, *56*(11), 1523–1525.
9. Beddow, J.K.; Meloy, T. *Testing and Characterization of Powders and Fine Particles*, Heyden & Son Ltd.: 1980, 88–90.
10. Carr, R.L., Jr. Chem. Eng. **1965**, *January 18*, 163–168.
11. Schofield, C. Trans. Inst. Chem. Eng. **1970**, *48*, T28.
12. Lacey, P.M.C. J. Appl. Chem. **1954**, *4*, 257.