Experiments in Powder Blending and Unblending

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Abstract □ The effects of blending and segregation procedures on the uniformity of aspirin–lactose (1:99) blends were studied. The blending was conducted in a twin-shell blender with and without a high shear attrition bar and evaluated based on the mean and the coefficient of variation of 20 samples. In the mixing of the dry powders, the particle sizes were varied; preblending and the use of silica were also studied. The best blend was obtained with milled aspirin and powdered lactose when the liquid feed bar was used. Without the bar, a restriction often necessary for direct compression and heat-sensitive materials, the milled aspirin proved difficult to distribute. Segregation studies carried out in a two-dimensional segregation cell suggested that materials with good flow show unmixing tendencies, whereas blends with poor flow are less apt to separate. In the second part of the study, the drug was added as a solution in ethanol. This method yielded homogeneous blends when limited amounts of solvents were used. However, with a large quantity of solvent, drug migration occurred during drying. Subsequent milling of the dried material did produce good drug distribution, but the powder blend retained the potential to segregate.

Keyphrases □ Blending, powders—influence of attrition bar, particle size, preblending, solvents, and use of silica on uniformity of aspirin–lactose blends □ Segregation, powders—effects of processing variables on uniformity of aspirin–lactose blends □ Drugs, powder blends—effects of processing variables on uniformity of aspirin–lactose blends

One basic requirement in solid formulations is the preparation of a uniform blend prior to final tableting or encapsulation. The importance of uniform drug distribution in the final dosage form is recognized by the official compendia (1, 2) which require a content uniformity check on all dosage units containing 50 mg or less of active component. Recently, instances of excessive intertablet dose variation in commercial pharmaceutical products was brought to light (3, 4), and many drug recalls have occurred because of unsatisfactory drug distribution. Problems of excessive dose variation generally appear to be confined to high potency, low dose drugs where a substantial portion of the weight of the final product is due to excipients employed as fillers, lubricants, disintegrants, etc.

Several published reviews dealt with various aspects of mixing (including theories of mixing), methods of sampling, mixture and mixer evaluations, and related statistical techniques (5–7). Some articles also were published on mixing operations in V-type mixers (8–10). These studies focused their attention primarily on the rates of mixing, the operative mechanisms involved, and performance evaluations comparing V-mixers with other types of mixing equipment.

There is, however, a lack of information on methods to optimize the process, including the use of high speed attrition devices commonly available for pharmaceutical mixing operations. In addition, most published work involves the use of well-defined materials of narrow size distribution as opposed to actual industrial materials.

In pharmaceutical mixing operations where materials of different particle characteristics (size, shape, size distribution, density, etc.) are encountered, preparation of a uniform blend involves not only successful mixing but also the avoidance of segregation in any subsequent handling. It is generally felt that segregation is a potentially greater problem with free-flowing materials than with poor flowing blends. This is based on one criterion for mixing: powders must have independent motion or flow to mix or unmix (5).

In an attempt to understand the mechanism of segregation in idealized particulate systems, the various factors influencing the rate and extent of segregation were examined (11, 12) using steel and glass spheres. Williams (13) discussed different types of segregation which occur in the process of pouring, vibrating, and stirring and gave explanations of the properties that cause these phenomena. It was suggested that segregation resulting from small differences in physical properties of the components is better detected by a systematic sampling scheme, where samples are removed from selected sites, than from random or spot sampling schemes (14). One major drawback in this area is a lack of suitable procedures to assess the segregating tendencies of powders based on evaluations of small samples of materials.

The distribution of low dose drugs *via* solvent was suggested by previous workers (15). Colorants have commonly been added to tablet granulations in this manner. Migration of colors has long been recognized
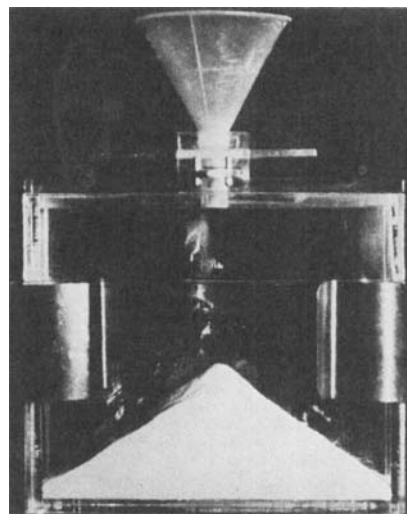

Figure 1—*Segregation cell during pile formation.*

as a problem and, more recently, drug migration (16) and binder migration (17) during drying of wet granulations were reported.

The current investigation was designed to study several different methods of producing a good blend using a twin-shell blender. The twin-shell blender was selected because of its widespread use in the pharmaceutical industry. Powdered or spray-dried lactose at a 99% level was used as the excipient; 1% aspirin, powdered or milled, was used as the active ingredient. The choice of aspirin was partly based on the relatively simple assay procedure for this drug, an important consideration in view of the large number of samples to be analyzed. In addition, unblending was also investigated. First attempts at unblending involved vibration of the powder beds. This invariably led to bed consolidation and no segregation. A segregation cell was devised which permitted segregation to occur in an "open bed" system. The cell, the method of segregation, the sampling procedure, and data are presented.

Finally, in addition to dry blending, blends were produced through the use of a solvent. The uniformity of the resultant blends before and after drying was evaluated. The volume of solvent was shown to affect the potential drug migration markedly during the drying operation. The segregation of these blends was also investigated.

EXPERIMENTAL

Materials—Lactose USP powder[1], lactose USP spray dried[2], aspirin USP powder[3], and silica[4] were used as received. Milled aspirin was obtained by milling aspirin through a hammer mill[5] using a 0.15-cm (0.062-in.) diameter perforated screen.

Equipment and Methods—The blending operations were carried out in 4.7-liter (5-qt)[6] and 15-liter (16-qt)[7] working capacity twin-shell blenders, equipped with liquid feed bars. Sieve analyses of the different materials were carried out in an oscillating air column particle-size analysis instrument[8]. Chemical assays of the mixtures were performed using a spectrophotometer[9].

In the mixing studies, 7 kg of blend [equal to the recommended working capacity of the 15-liter (16-qt) blender] was used for each run. Depending on the type of experiment, the blender was run with or without a liquid feed bar. At the specified time intervals, the blender was stopped and each leg of the blender was sampled with plunges of the sample thief parallel to the shell walls. The sample thief was a modification of a reported design (18). It consisted of a brass rod, 1.57 cm (0.62 in.) o.d. and 38.1 cm (15 in.) long, and contained six capsule-shaped cavities, each with a capacity of 200–250 mg drilled at regular intervals. This rod was fitted inside an outer brass sleeve. Rotation of the two members would either cover or expose the cavities. In actual practice, the sample thief was introduced into the powder mixture with the cavities covered; then the brass rod was rotated, and the powder was taken into the exposed cavities. The rod was rotated again to cover the cavities and then withdrawn from the blend. These samples were deposited on a sheet of paper for direct weighing or
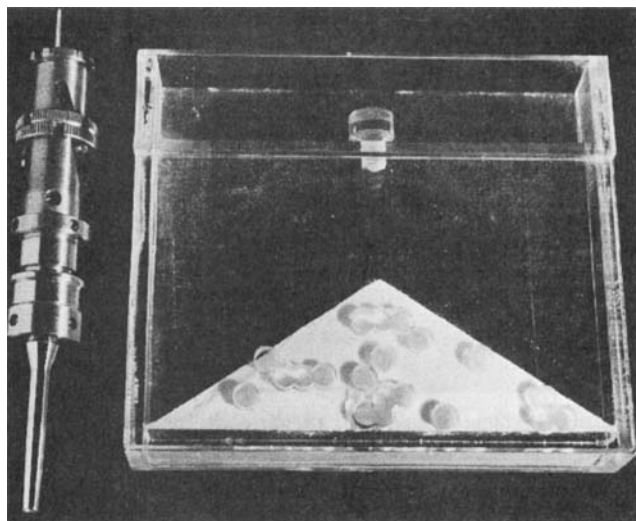

Figure 2—*Segregation cell at the sampling stage along with the dosator.*

stored in capsules. The sample size in all experiments was 100 mg.

The fabrication of the two-dimensional segregation cell was based on the concept originally proposed by Williams (19) to demonstrate visually the segregation of colored materials. The unit designed here was reduced in size, so that a suitable powder pile could be formed with about 70 g of blend. The dimensions of the box are 15.2 × 13.3 × 2.54 cm (6 × 5.25 × 1 in.). A portion of the front face of the unit is removable for sampling. Fitted to the top of the unit is a slide assembly patterned after that suggested previously (20). Variable orifice openings are available as well as a slide plate to initiate and stop powder flow. The fully assembled unit is shown in Fig. 1 during powder pile formation.

Following pile formation, the upper slide assembly is removed, and a solid Plexiglas wedge cut with an inverted "V" (45°) is inserted into the box to immobilize the powder pile. The wedge fits snugly to the inside dimensions of the two-dimensional box. A slight distortion in the actual pile occurs when the wedge is inserted, but it does not materially change the segregation accomplished by the flow onto the pile.

With the wedge in place, the box is placed flat on a tabletop and the solid front panel of the box is removed. A templet drilled with randomly positioned holes is placed over the open face of the box. The positions of the drilled holes were selected by numbering all of the possible positions available for a vertical sampling (approximately 70 samples) and selecting 20 consecutive numbers from a random number table.

The unit at this stage is shown in Fig. 2 along with a No. 1 dosator from a capsule filler[10] which was used to sample the powder bed. The dosator consists of a filling or dosing chamber which collects and discharges the desired quantity of powder and a piston which slides into the filling head and controls the depth of the dosing chamber. Samples of about 110 mg were removed at each of the 20 random positions, and 100 mg of powder was weighed and assayed as before.

In actual operation of the segregation cell, a freely flowing material such as spray-dried lactose will easily flow from the funnel through the various orifices selected. For nonflowing materials such as powdered lactose, the funnel must be hand fed with the powder to form the pile satisfactorily. The inability to compare segregation at the same flow rates is a serious limitation of the apparatus. However, the data obtainable are still viewed to be useful in a comparative manner.

No attempt was made to control the humidity in the segregation experiments, except the area was air conditioned and the relative humidity was in the 40–70% range. Extremes in humidity have been shown to affect segregation.

In the liquid addition experiments, a drying cell is employed to

[1] McKesson Chemicals, Detroit, Mich.

[2] McKesson & Robbins, Highland Park, Mich.

[3] Mallinckrodt Chemical Works, St. Louis, Mo.

[4] Cab-O-Sil, G. L. Cabot Corp., Boston, Mass.

[5] Raymond Laboratory Mill, Combustion Engineering, Inc., Chicago, Ill.

[6] Change-shell lab blender, Patterson Industries, Inc., East Liverpool, Ohio.

[7] Patterson-Kelley twin-shell liquid-solids blender, Patterson-Kelley Co., East Stroudsburg, Pa.

[8] Allen-Bradley sonic shifter, model L3P, Allen-Bradley Co., Milwaukee, Wis.

[9] Beckman model DU spectrophotometer, Beckman Instruments, Fullerton, Calif.

[10] Automatic capsule-filling machine, model LZ/64, Fratelli Zanasi S.p.A., Ozano Emilia-Bologna, Italy.

Figure 3—*Drying cell used in the study of drug migration shown after the top ring has been sampled and removed. The second level is now exposed and ready to be sampled.*

facilitate the study of drug migration. This Plexiglas unit consists of three concentric, interlocking rings, 13.9 cm (5.5 in.) i.d., 0.45 cm (0.18 in.) wall thickness, and a total assembled height of 5.08 cm (2 in.). The wetted powder is filled into the cell in a manner similar to that employed in loading trays for oven drying. After drying, the top layer of the dried bed is sampled in the four quadrants. At this point, the top ring is removed and the powder above the next ring is scalped off with a spatula. The exposed bed of powder is again sampled at this level in the four quadrants. This operation is repeated for the next layer. These samples are worked up in the same manner as previous samples. The partially assembled cell during sampling is shown in Fig. 3.

The assay of aspirin was carried out as follows. One hundred milligrams of blend, accurately weighed to the nearest 0.5 mg, was dissolved in 0.1 M H_2SO_4 and brought to volume in a 10-ml volumetric flask. Absorbance readings were made at 275 nm, 0.3-mm slit width, against 0.1 M H_2SO_4, with additional dilution if necessary.

RESULTS AND DISCUSSION

The degree of mixing achieved was evaluated based on the mean assay value ($\bar{X}$) and percentage coefficient of variation (% CV), calculated from the experimental data. The theoretical maximum degree of mixedness is based on the relationship developed by Stange (21) as modified by Poole *et al.* (22). For binary mixtures where each component has a size range, the standard deviation for a completely random mixture is given by the expression (23):

$$\sigma_R = \left[(xy) \bigg/ \left(\frac{M}{y(\Sigma fw)_x + x(\Sigma fw)_y} \right) \right]^{1/2} \qquad \text{(Eq. 1)}$$

where:

x = proportion of one component
y = proportion of second component
M = sample size in grams
f = weight fraction of each component within a given particle-
    size range
w = mean particle weight of the given size fraction
Σfw = effective mean particle weight of a component

As an example, the calculated standard deviation for a completely random mixture for 1% powdered aspirin in powdered lactose with a sample size of 100 mg would proceed as follows. The mean particle weights, $(\Sigma fw)_x$ and $(\Sigma fw)_y$, are calculated based on the particle-size data in Table I for these materials; $(\Sigma fw)_x$ is shown in Table II for powdered aspirin.

The mean particle sizes calculated are 118 μm [$(\Sigma fw)_x = 1.18 \times 10^{-6}$ g] for aspirin powder and 87 μm [$(\Sigma fw)_y = 0.53 \times 10^{-6}$ g] for lactose powder. From these values, the theoretical standard deviation and coefficient of variation are calculated to be 3.4×10^{-4} and 3.4%, respectively.

Finally, because of the limited sampling (20 samples in this study), the measured variability (% CV) is only an estimate of the true variability of the population. The chi-square distribution

Table I—Particle-Size Analysis by Sieving

Sieve Number	Size, μm	Cumulative Percent Retained			
		Powered Aspirin[a]	Milled Aspirin[b]	Powdered Lactose[b]	Spray-Dried Lactose[b]
60	250	1.0	0.2	0.5	0.8
100	149	10.0	4.8	3.1	22.7
120	125	24.9	7.2	6.9	35.4
170	88	62.1	19.0	18.9	67.2
270	53	88.8	44.5	43.0	89.7
325	44	96.0	61.1	53.7	95.6

[a] Mean of three determinations. [b] Mean of two determinations.

may be used with the experimentally determined values to establish a range in which the theoretical value should fall. Alternatively, the range around the theoretical value can be calculated in which experimental values would be expected. The latter procedure was carried out. The theoretical percentage coefficient of variation and range values based on 20 samples with a 95% confidence interval are shown in Table III for the four possible blends.

As shown in Table III, the theoretical variation attainable is dependent on the particle size of the aspirin and essentially independent of the size of the lactose. This is to be expected in view of the fact that the standard deviation of a random mixture is primarily dependent on the mean particle size of the minor component.

Since the calculated variance from a group of sample assays contains the contribution due to weighing and analytical errors, the magnitude of the latter was independently determined and subtracted in arriving at the data presented in the tables. The analytical and weighing error makes a significant contribution to the measured variance only when the latter is relatively small (CV <2.0%), *i.e.*, as the blend approaches a random state.

The results obtained are shown in Tables IV–XII. In Table IV, the data are presented for the blending of powdered aspirin and powdered lactose in the twin-shell blender with and without the use of the high speed bar. The $\bar{X}$ (expressed as percent of theory) is at the theoretical value for all sampling times. The coefficient of variation is within the theoretical range for 20 samples throughout both blending trials. The changes in $\bar{X}$ or coefficient of variation appear random with time in these two studies. The blend approaches a random state within 10 min of mixing without the bar and within 5 min of mixing with the bar. These findings are in accord with what was reported previously by others—*viz.*, with this equipment, long blending times are not needed (10). Moreover, no segregation occurred on prolonged blending. The use of the bar did not result in a better blend. As shown later, however, the bar does have an effect where agglomerates are present.

Table V shows the data for the blending of powdered aspirin and spray-dried lactose in the 15-liter (16-qt) twin-shell blender without the use of the high speed bar. The use of the bar in this case is counter-indicated due to the friable nature of the spray-dried lactose. Experimental values for $\bar{X}$ and coefficient of varia-

Table II—Calculation of Mean Particle Weights $(\Sigma fw)_x$ for Powdered Aspirin[a]

Average Sieve Opening, μm	Mean Particle Weight, μg	Fraction (f) of Sample in Each Range	Mean Particle Weight in Each Range (fw), μg
274	14.55	0.001	0.01455
200	5.66	0.090	0.5091
137	1.82	0.129	0.2352
107	0.867	0.391	0.3390
71	0.254	0.268	0.0681
49	0.0834	0.072	0.0060
25	0.0111	0.040	0.0044

$$(\Sigma fw)_x = \overline{1.18} \text{ μg}$$
$$\text{or } 1.18 \times 10^{-6} \text{ g}$$

[a] Based on data in Table I, density = 1.35 g/cm³.

Table III—Theoretical Coefficients of Variation and Range Intervals[a]

Blends $(x:y):(1:99)$	CV, %	Range
Powdered aspirin– powdered lactose	3.4	2.6–5.0
Powdered aspirin– spray-dried lactose	3.4	2.6–5.0
Milled aspirin– powdered lactose	2.3	1.6–3.2
Milled aspirin– spray-dried lactose	2.3	1.6–3.2

[a] Calculated from equation of Poole *et al.* (22). Based on 20 samples with 95% confidence.

tion approximate calculated values at all sampling times without the use of a bar.

Table VI shows the segregation data on the two blends prepared without a bar (described in Tables IV and V). These data indicate the increase in variability resulting from the segregation of the powder as it is allowed to flow through an orifice and form a pile. Difficulties with the flow of the powdered lactose are indicated, particularly with the 0.32-cm (0.125-in.) orifice. The relative segregating tendency of these two blends is probably best compared at an equal flow rate. Although sufficient data are not available to do this with great accuracy, comparison of the 0.63-cm (0.25-in.) orifice data for the powdered lactose with the 0.32-cm (0.125-in.) orifice spray-dried lactose data indicates the greater tendency for the spray-dried preparation to segregate. At the same flow rates, it is reasonable to presume that the difference would be still greater.

The $\bar{X}$'s obtained for the most segregated samples are seen to depart significantly from theory. This is not too unexpected when one considers that the population being evaluated with only 20 samples is no longer normally distributed. These data and other data on nonuniform blends suggest that the departure of the average value from theory may possibly be related to the formation of a bimodal or multimodal distribution. In such situations, the possibility exists that high concentrations of drug are localized in a relatively small proportion of the total blend. To obtain powder from such areas with only 20 samples would appear to be a difficult task.

The next set of experiments describes the mixing behavior of 1% milled aspirin with powdered lactose (Table VII). The theoretical $\bar{X}$ is still, of course, 100%, but the theoretical coefficient of variation for a random mixture has decreased to 2.3% because of the fine size of the milled aspirin. With 20 samples, the 95% confidence interval for the theoretical coefficient of variation is 1.6–3.2%.

The blends produced in the twin-shell blender without the bar are poor, as demonstrated by a low experimental mean value and a high coefficient of variation. The data are clearly poorer than those reported earlier for the unmilled aspirin blended with the powdered lactose. Therefore, under these mixing conditions, the fundamentally finer particle size of the milled aspirin does not aid blending because of the agglomeration present in this powder.

The use of the high speed bar produces totally different data. The $\bar{X}$ and coefficient of variation values in the theoretical range are obtained within 5 min of mixing. Further blending with the bar, up through 15 min, produces no further noticeable changes.

Table IV—Results of Blending of 1% Aspirin Powder with Powdered Lactose with and without Use of Liquid Feed Bar

Time of Mixing, min	Without Bar $\bar{X}$, % Theory	Without Bar CV, %	With Bar $\bar{X}$, % Theory	With Bar CV, %
5	—	—	99.2	3.4
10	100.5	3.4	100.0	4.2
15	—	—	99.1	3.9
20	100.0	4.3	—	—
30	101.4	4.0	—	—
60	100.2	3.5	—	—

Table V—Results of Blending of 1% Aspirin Powder with Spray-Dried Lactose and without Use of Liquid Feed Bar

Time of Mixing, min	$\bar{X}$, % Theory	CV, %
10	99.4	3.4
20	99.4	3.1
30	99.1	3.6
60	100.2	3.5

Table VI—Segregation of 1% Aspirin Powder in Powdered and Spray-Dried Lactose

Orifice Diameter, cm (in.)	Flow Time for 70 g	$\bar{X}$, % Theory	CV, %
Powdered Lactose			
0.63 (0.25)	190 sec[a]	99.1	5.4
0.31 (0.125)	26 min[a]	93.4	8.4
Spray-Dried Lactose			
0.63 (0.25)	23 sec.	99.2	5.4
0.31 (0.125)	120 sec	93.7	7.8

[a] Hand feeding, with interruption; particularly difficult with 0.31-cm (0.125-in.) orifice.

The blending of the milled aspirin with the spray-dried lactose presents a particular difficulty. The use of the high speed bar is known to alter the flow and compressing characteristics of a direct-compression material such as spray-dried lactose. In the earlier experiment in which powdered aspirin was blended with spray-dried lactose (Table V), a good blend was obtainable without a bar. However, the milled aspirin with powdered lactose experiment failed to produce a good blend until the bar was employed. The blending of the milled aspirin with spray-dried lactose was, therefore, attempted in three ways, each designed to avoid or minimize high shear attrition of the spray-dried lactose. The data for the blending without a bar, with and without pretreatment of the milled aspirin with silica (1% of the aspirin level), are shown in Table VIII. A poor blend, low $\bar{X}$ and high coefficient of variation, was obtained without the bar and without pretreatment with silica. The blend is quite comparable to that obtained when the milled aspirin was blended with powdered lactose without a bar.

Pretreatment of the milled aspirin appears to have a definite beneficial effect on the blending of these materials. However, the 3.0–3.5% coefficients of variation are at, or above, the calculated upper limit. The use of a bar with milled aspirin–powdered lactose produced approximately a coefficient of variation of 2%.

A further attempt was made to accomplish the blending of the milled aspirin and spray-dried lactose by first preparing a preblend. The preblend used about one-third of the total spray-dried lactose and was carried out in a 4.7-liter (5-qt) blender fitted with a high speed bar. This preblend was then transferred to the larger blender, the remaining two-thirds of spray-dried lactose was added, and the blending was continued without the bar. The data are shown in Table IX.

A good preblend was obtained in 3–5 min with the use of the

Table VII—Blending of 1% Milled Aspirin with Powdered Lactose with and without Use of Liquid Feed Bar

Time of Mixing, min	Without Bar $\bar{X}$, % Theory	Without Bar CV, %	With Bar $\bar{X}$, % Theory	With Bar CV, %
5	—	—	100.1	2.0
10	—	—	100.3	1.6
15	—	—	101.2	2.2
20	95.4	6.5	—	—
30	96.3	5.8	—	—
60	95.4	6.2	—	—

Table VIII—Blending of 1% Milled Aspirin with Spray-Dried Lactose without Use of Liquid Feed Bar

Time of Mixing, min	Without Additive		With Aspirin Pretreated with Silica	
	$\bar{X}$, % Theory	CV, %	$\bar{X}$, % Theory	CV, %
10	—	—	102.7	3.4
20	96.5	5.3	101.7	3.5
30	96.2	5.5	102.4	3.0
60	95.4	6.1	100.8	3.1

Table IX—Preblend with High Speed Bar and Final Blend without Bar for 1% Milled Aspirin in Spray-Dried Lactose

Time of Blending, min	Preblend with Bar		Final Blend without Bar	
	$\bar{X}$, % Theory	CV, %	$\bar{X}$, % Theory	CV, %
1	88.9	6.0	—	—
3	98.6	2.3	—	—
5	99.5	2.6	—	—
30	—	—	92.2	5.4
60	—	—	94.8	5.1

high speed bar. Dilution of this blend with additional spray-dried lactose failed to produce a satisfactory blend without a bar, as measured by the $\bar{X}$ and percentage coefficient of variation. It would appear that a carefully restricted use of the high speed bar on the total blend would have provided a good blend, if changes in the structure of the spray-dried lactose did not result in this time interval. Recently, capping and low hardness were experienced by the authors for tablets compressed from spray-dried lactose subjected to 5 min with a bar. A control material compressed satisfactorily at the same time.

The segregating tendencies of the milled aspirin from the powdered lactose prepared with a bar and the spray-dried lactose prepared without a bar (aspirin pretreated with silica) are shown by the data in Table X. These data illustrate the ready segregation of the spray-dried lactose blend and the nonsegregating nature of the powdered lactose blend, even under extremely slow hand feeding of the latter powder. The segregation of the milled aspirin (pretreated with silica) was also greater than the powdered aspirin from the spray-dried excipient (Table VI). The increased difference in particle masses due to the milling could account for part of this effect. The use of the silica, which aided blending to some extent, may also facilitate segregation. The blend of the milled aspirin, without silica, accomplished with the liquid feed bar showed no tendency to segregation. This could in part be due to the cohesive/adhesive nature of the milled aspirin.

The distribution of low concentrations of active ingredients can be, and often is, carried out by dissolving the drug in a liquid and mixing with the excipient, usually with the use of high shear. This is conveniently accomplished with the twin-shell blender

Table X—Segregation of 1% Milled Aspirin in a Powdered Lactose Blend (Prepared with Bar) and Spray-Dried Lactose (without Bar) with Aspirin Pretreated with Silica

Orifice Diameter, cm (in.)	Flow Time for 70 g	$\bar{X}$, % Theory	CV, %
Powdered Lactose			
0.63 (0.25)	180 sec	99.9	1.2
0.31 (0.125)	30 min[a]	99.8	1.1
Spray-Dried Lactose			
0.63 (0.25)	23 sec	99.8	8.3
0.31 (0.125)	110 sec	89.9	15.7

[a] Hand feeding, interrupted flow.

Table XI—Blending by Liquid Addition, 1% Aspirin in Powdered Lactose[a]

State of Processing	$\bar{X}$, % Theory	CV, %
Wet blend	99.9	2.2
Dried cake		
Individual $\bar{X}$ Values, % Theory		
Top layer	146, 167, 263, 177	
Second layer	56, 81, 77, 42	
Third layer	37, 35, 39, 45	
Bottom layer	55, 81, 51, 31	
Dried cake		
Screened-minimal Blending	101.2	11.7
Total blend		
After screening and blending	99.8	0.9
Segregated blend		
0.63-cm (0.25-in.) orifice, 55 sec	99.7	2.2
0.31-cm (0.125-in.) orifice, 6 min	101.5	5.6

[a] Seventy grams aspirin, 6.93 kg lactose, and 1500 ml ethanol.

equipped with the high speed liquid addition bar. On some occasions, where a wet granulating procedure is employed in the work-up of the blend for tableting, it appears logical to use this liquid to distribute the drug as well as the binder throughout the excipient. The first liquid addition experiment described employed 1500 ml of absolute ethanol to distribute 70 g of aspirin on the 6.93 kg of powdered lactose. This volume of solvent, greater than necessary to dissolve the drug, was selected since it approaches the quantity that would be used if wet granulation was being accomplished. Experimentally, the aspirin was added in 500 ml ethanol followed by the remaining liter of ethanol, which served as wash and would normally contain the binder. The total liquid addition time was 5 min. Five additional minutes of blending with the bar then followed. The blend was sampled wet for content uniformity at this stage of processing. A portion of the wetted powder was placed in the drying cell described previously and was then dried at 48° (120°F). The remainder of the material was also dried at the same time in open trays. The dried cake in the Plexiglas frame was sampled in each of four quadrants at the top level, with one section removed, with two sections removed, and at the bottom of the bed. A portion of the dried cake was carefully size reduced through a No. 40 screen, avoiding as much blending as possible. This material was also sampled. Finally, the bulk of the dried material was handled in a more normal way by screening through a No. 40 screen with no attempt to minimize blending at this point. The results of this work are shown in Table XI.

The wet blend is shown to be well blended. However, the drying operation caused extensive migration and, therefore, un-

Table XII—Liquid Addition, 1% Aspirin in Powdered Lactose[a]

State of Processing	$\bar{X}$, % Theory	CV, %
Wet blend:		
1 min to add liquid	99.6	2.6
5 min added use of bar	99.8	0.9
10 min added use of bar	100.1	1.1
Dried cake		
Individual $\bar{X}$ Values, % Theory		
Top layer	99.7, 101.1, 101.4, 101.5	
Second layer	102.3, 98.8, 99.7, 99.4	
Third layer	100.4, 97.1, 97.4, 97.0	
Bottom layer	101.5, 100.3, 97.8, 97.2	
Final blend[b]	98.8	1.5
Segregated blend, 0.31-cm (0.125-in.) orifice, 5 min	101.3	1.1

[a] Seventy grams aspirin, 6930 g lactose, and 450 ml ethanol. [b] After screening and blending.

blending of the sample. This is shown by the data for the various layers of the undisturbed dried powder bed as well as for the screened material where mixing was avoided. The total blend, following screening and blending, is seen to be quite uniform. Finally, this blend was shown to have a slight segregating tendency, more than was observed for the milled aspirin–powdered lactose blend in Table X. This tendency to segregate is understandable in light of the migration data on the intact dried cake.

The last experiment repeated the above work but restricted the total solvent used for the liquid addition to that needed to dissolve the drug (350 ml) and wash the feed system (100 ml). The wet mix is seen to be quite uniform with 5 min of shear using the bar. The dried cake was sampled at various locations, and no evidence of migration was found.

The final powder blend after drying and mixing was not sampled, since there was no evidence of migration during drying. In addition, the subsequent attempt to segregate the blend also showed no tendency for migration to occur.

Similar data were obtained in the authors' laboratories in mixing studies involving salicylic acid and lactose (1:499). A good blend was obtained with a limited amount of solvent; drug migration occurred with a large amount of solvent.

In the two liquid addition experiments, 450- and 1500-ml total alcohol volumes, both gave good blends at the wet stage and the final dry stage (screened and remixed). However, significant unblending due to migration occurred with the use of a large amount of solvent. In addition, one sample did show a tendency to segregate. The restricted use of solvent provided a good wet and dry blend with no evidence of migration or segregation.

SUMMARY

The blending of 1% aspirin with lactose was experimentally studied. Changes in particle size of the active component as well as the excipient were included. The best dry mix was obtained with milled aspirin and powdered lactose with the use of a high speed bar. There was no segregating tendency for this mix. The blends with spray-dried lactose were more difficult to accomplish and more readily separated by flow.

Distribution of the aspirin *via* solution could produce excellent blends. However, problems of drug migration in the drying operation were observed. Segregation was again a problem for samples where migration had occurred.

REFERENCES

(1) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 930.

(2) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 790.

(3) J. G. Wagner, M. Christensen, E. Sakmar, D. Blair, J. D. Yates, P. W. Willis, A. J. Sedman, and R. G. Stoll, *J. Amer. Med. Ass.*, 224, 199(1973).

(4) S. A. Fusari, *J. Pharm. Sci.*, 62, 122(1973).

(5) D. Train, *J. Amer. Pharm. Ass., Sci. Ed.*, 49, 265(1960).

(6) S. S. Weidenbaum, in "Advances in Chemical Engineering," vol. 2, T. B. Drew and J. W. Hooper, Jr., Eds., Academic, New York, N.Y., 1958, pp. 209–324.

(7) L. T. Fan, S. J. Chen, and C. A. Watson, *Ind. Eng. Chem.*, 62, 53(1970).

(8) N. Harnby, *Powder Technol.*, 1, 94(1967).

(9) J. Okada, Y. Matsuda, and Y. Matsuda, *J. Pharm. Soc. Jap.*, 89, 1562(1969).

(10) A. Kaufman, *Ind. Eng. Chem.*, 1, 104(1962).

(11) J. L. Olsen and E. G. Rippie, *J. Pharm. Sci.*, 53, 147(1964).

(12) E. G. Rippie, J. L. Olsen, and M. D. Faiman, *ibid.*, 53, 1360(1964).

(13) J. C. Williams, *Univ. Sheffield Fuel Soc. J.*, 14, 29(1963).

(14) A. R. Rogers and J. R. Clements, *Powder Technol.*, 5, 167(1971).

(15) D. Train, *Pharm. J.*, 186, 129(1960).

(16) I. A. Chaudry and R. E. King, *J. Pharm. Sci.*, 61, 1121(1972).

(17) K. Ridgway and M. H. Rubenstein, *J. Pharm. Pharmacol.*, 23, 115(1971).

(18) N. K. Maitra and J. M. Cowlson, *J. Imp. Coll. Chem. Eng. Soc.*, 4, 135(1948).

(19) J. C. Williams, *Powder Technol.*, 2, 12(1968).

(20) T. M. Jones and N. Pilpel, *J. Pharm. Pharmacol.*, 18, 81(1966).

(21) K. Stange, *Chem. Ing. Tech.*, 26, 331(1954).

(22) K. R. Poole, R. F. Taylor, and G. P. Wall, *Trans. Inst. Chem. Eng.*, 42, T305(1964).

(23) F. H. H. Valentin, *Chem. Eng.*, 45, CE99(1967).

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