Effect of Particle Shape on the Mixing of Powders

L. W. WONG AND N. PILPEL

University of London, King's College, Chelsea Department of Pharmacy, Manresa Road, London SW3 6LX, UK

Abstract—Mixtures were prepared containing 200 g of 600 μm lactose and 0·5 g of 3 μm calcium carbonate of different particle shapes using a Y cone mixer. Measurements were made of the time required to achieve the acceptable standard deviation of mixing σ_A and of the segregation that occurred on subsequently vibrating the mixtures. The time taken to achieve σ_A increased with the irregularity of the particles of both components and the mixtures containing irregular particles segregated less on vibration.

Ordered mixtures of powders comprising a microfine active ingredient adsorbed onto coarser particles of an excipient offer significant advantages in the manufacture of pharmaceutical solid drug delivery systems (Hersey 1975) and, in particular, those containing only a micro quantity of active ingredient.

The mixing of powders is influenced by the particle size, (Crooks & Ho 1976) size distribution (Thanomkiat et al 1979) and other variables like the design of the mixer (Hersey 1979), its method of operation and the proportions of the ingredients to be mixed. Little quantitative work has been done on the particular effect of particle shape on mixing. Particle shape is largely governed by the method used to prepare the powders, e.g. comminution, screening, spray drying, crystallization etc. The reason for the lack of quantitative results is the difficulty of obtaining samples which have the same narrow particle size distributions but different particle shapes, particularly when the size is less than 22 μm (Pang & Ridgway 1980; Nikolakakis & Pilpel 1985).

In the present study, granular lactose (≈ 600 μm diameter) has been used as a model excipient and was separated into four different shape fractions using a vibratory shape sorting table. Four different crystal forms of precipitated calcium carbonate (≈ 3.5 μm diameter) with different particle shapes were used as models for the active ingredients. Mixing was carried out in a small, specially constructed, Y cone mixer (Wong & Pilpel 1988) since only small amounts of samples were available for testing. Studies were made to see how the efficiency of mixing was affected by the shape of the calcium carbonate, by the shape of the lactose particles and by the total weight of the powder being mixed. These experiments were performed in a factorial design.

Materials and Methods

Lactose EPD10 from Forum Chemical Ltd, was sieved, and the fraction between 500 and 710 μm was sorted on a Jeffrey Galion shape sorting table (Ridgway & Rupp 1969) to obtain four different shape fractions denoted 1, 4, 8, 12 to signify the numbers of the pots into which they were shape sorted. The

Correspondence to: N. Pilpel, Chelsea Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX, UK.

calcium carbonates from Sturge Lifford Chemicals, codes CH, SL and SH were used as received. Another batch from BDH was comminuted in a fluid energy mill and then classified in a multiplex zig zag classifier to give sample BM. (These codes will identify the samples for other workers.) They all had particle diameters of 3–4 μm but were significantly varied in particle shape, which includes particle rugosity (equation 1), see plates 1, 2. The materials were dried at 60°C for 6 h under reduced pressure to ensure moisture contents below 1% w/v. Their particle densities ρ_s, g cm^{-3} were determined with a Beckman air comparison pycnometer (Beckman Instrument Model 930), their specific surface areas, S_w m^2 g^{-1} were measured with a sorptometer (Flowsorb II 2300, Micrometrics, Georgia). The shape coefficients of the sample were calculated from the expression

$$\alpha = S_w \rho_s d_e + N \qquad (1)$$

This is a modified form of Heywood's expression (Nikolakakis & Pilpel 1985) where N is the elongation ratio = (Length, L)/(Breadth, B) and d_e is the

$$\text{Heywood equivalent diameter} = \left(\frac{(4 \times 0.77 \times B \times L)}{\pi}\right)^{\frac{1}{2}} \mu\text{m}$$

Relevant properties of the materials are given in Table 1.

Mixtures were prepared containing 200 g of lactose and 0·25% w/w of calcium carbonate in a small Y cone mixer described previously (Wong & Pilpel 1988), its efficiency, however, being increased by replacing the 90° knife by a 60° knife. The mixer was rotated at 45 rev min^{-1} using the conditions shown in Table 2. During the mixing, ten 200 mg samples were removed at intervals of 1, 2, 5, 10, 15, 30 and 60 min using a sampling thief, taking five samples from the surface and another five samples from near the bottom of the mixer. The concentration of calcium carbonate in each sample was determined by atomic absorption spectroscopy (Instrumentation Laboratory Inc., USA, model 151). At the end of the mixing period the remaining powder was subjected to 60 min vibration on a Fritsch Laborette Vibrator, after which a further ten samples were taken as described above and the amount of calcium carbonate in each determined. The results were plotted in the form of graphs of the standard deviation of the samples' concentration of calcium carbonate σ, against the time of mixing. Typical graphs are shown in Fig. 1. The acceptable standard deviation σ_A with 95%
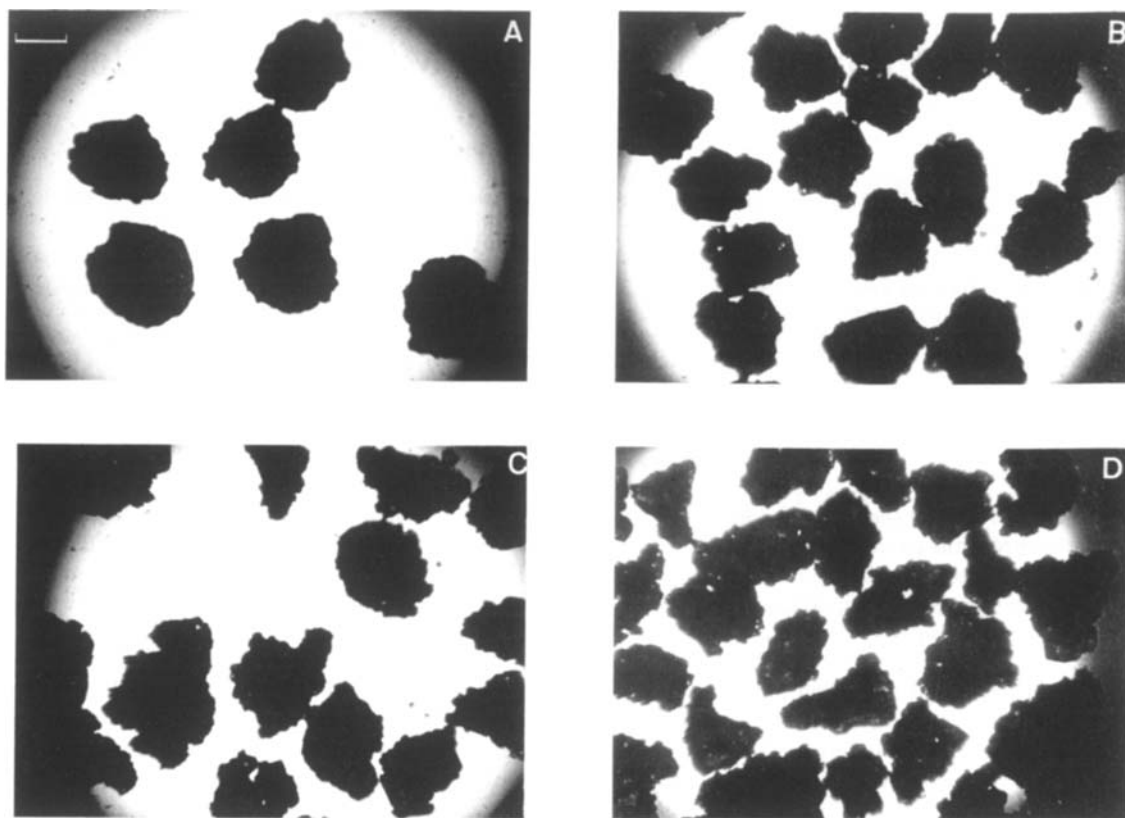
PLATE 1. Photo micrographs of lactose samples A, 1; B, 4; C, 8; D, 12. Scale 500 μm.

confidence within ±10% of the mean χ calculated using equation 2, is in all cases included in these graphs

$$1\cdot96\ \sigma_A = \pm0\cdot10\ \chi \qquad (2)$$

The points corresponding to 120 min on the abscissa, designated by V show the standard deviation σ_V after 60 min of vibration. As already mentioned, experiments were also carried out in a factorial design to determine the individual and combined effects of the shape of the calcium carbonate, the shape of the lactose and the total amount of powder to be mixed on the efficiency of mixing. Measurements were made of the tensile strengths of the calcium carbonates over a range of packing fraction from 0·2 to 0·4 using a split plate tensile tester (AJAX Ltd) and a standard procedure (Svarosky 1987).

Results and Discussion

The effect of the shape of the calcium carbonate

Fig. 1 A, B shows that with the particular batch of lactose 1, σ_A is achieved more slowly using calcium carbonates SL and SH (10 min) than using BM and CH (5 min). The mixtures containing calcium carbonates SL and SH were also found to be more stable towards segregation, as measured by the values of σ_V, than those of BM and CH. The explanation for this is that calcium carbonates SL and SH are more irregular than BM and CH. They are more cohesive and have more adhesive points of contact with the lactose particles. These

results are in agreement with those of Nikolakakis & Pilpel (1988) who studied the effect of particle shape on the tensile strengths of fine powders.

Fig. 2 shows the graphs of log tensile strength (N m^{-2}) against packing fraction for the different batches of calcium carbonate. Only four points are shown for simplicity, but in fact a full statistical analysis was carried out and the scatter was consistent with previous work with this instrument. They conform to the well-known relationship

$$\log T = A_1P_f + A_2 \qquad (3)$$

Where T is the tensile strength, P_f is the packing fraction and A_1, A_2 are constants for each sample. The slopes of the graphs increase as the shape coefficients α of the calcium carbonates increase and at any particular packing fraction, log T increases with α (Fig. 3).

It has already been found that the calcium carbonates with high values of α are more stable towards segregation than those with lower α and it has therefore been interesting to plot a graph of σ_V against α for the different shaped calcium carbonates. A straight line is obtained (Fig. 3); σ_V decreases linearly as α increases.

The practical significance of this finding is that by exercising control over the shapes of fine drug particles by appropriate milling, crystallization or precipitation, it should be possible to produce ordered mixtures with excipients which are stable towards demixing and segregation.
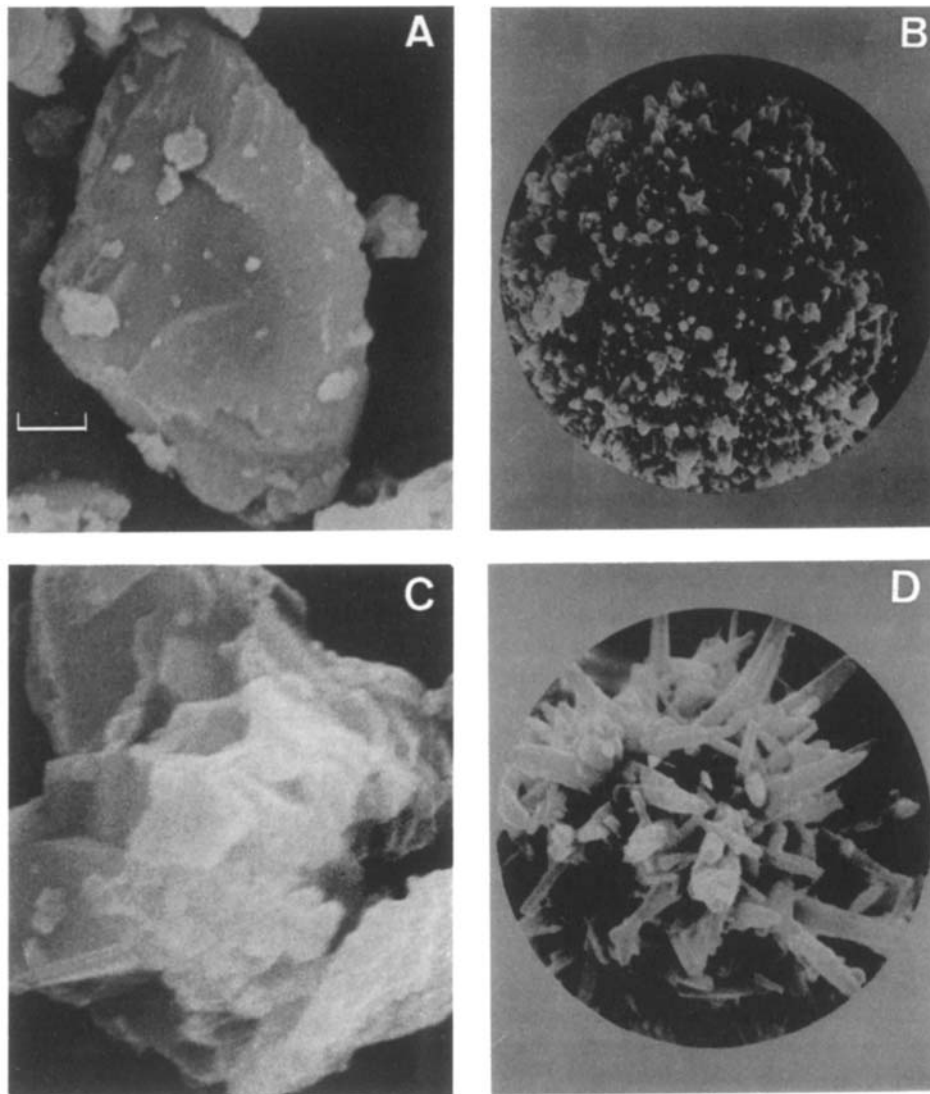
PLATE 2. Photomicrographs of calcium carbonates A) BM; B) CH; C) SL; D) SH scale 1 μm.

Table 1. Properties of materials.

	Calcium carbonate BM	Calcium carbonate CH	Calcium carbonate SL	Calcium carbonate SH	Lactose 1	Lactose 4	Lactose 8	Lactose 12
Particle density ρ_sg cm^{-3}	2·71	2·62	2·66	2·66	1·54	1·54	1·54	1·54
Mean Heywood diameter d_e μm	3·3	3·1	4·0	3·7	595	605	606	640
Elongation ratio N	1·50	1·50	1·30	1·40	1·01	1·04	1·06	1·08
Specific surface area S_w cm^{2}g^{-1}	2100	3800	3500	5000	325·4	342·4	368·7	410·8
Shape coefficient α	20·6	32·3	38·5	50·6	30·8	32·9	35·5	41·6

The effect of the shape of the lactose

Fig. 4 A, B shows that with the particular batch of calcium carbonate BM, σ_A is achieved more quickly when lactose 1 and 4 (5 min) are used than when lactose 8 and 12 (10 and 15 min, respectively) are used. However, the latter systems had lower values of σ_V and were therefore more stable to segregation.

Lactose 1 and 4 have lower values of α and flow more easily than lactose 8 and 12 in the mixer. They can therefore break up agglomerates of calcium carbonate and distribute it over

Table 2. Experimental conditions during mixing in the Y Cone Mixer (using 200 g lactose of 605 μm diameter, 0·25% w/w calcium carbonate and 45 rev min^{-1}).

Lactose	Calcium carbonate	Figures
1	BM	1A
1	CH	1A
1	SL	1B
1	SH	1B
1	BM	4A
4	BM	4A
8	BM	4B
12	BM	4B

their surfaces faster. However, the particles of calcium carbonate are not as firmly adsorbed on their relatively smooth surfaces (Fig. 5A) as on the rougher surfaces of lactose 8 and 12 (Fig. 5B) and this explains the different tendency to segregate on vibration.

Effects of and interactions between variables on mixing
In order to see how the particle shape coefficient of the calcium carbonate, α_1, of the lactose, α_2, and the total amount
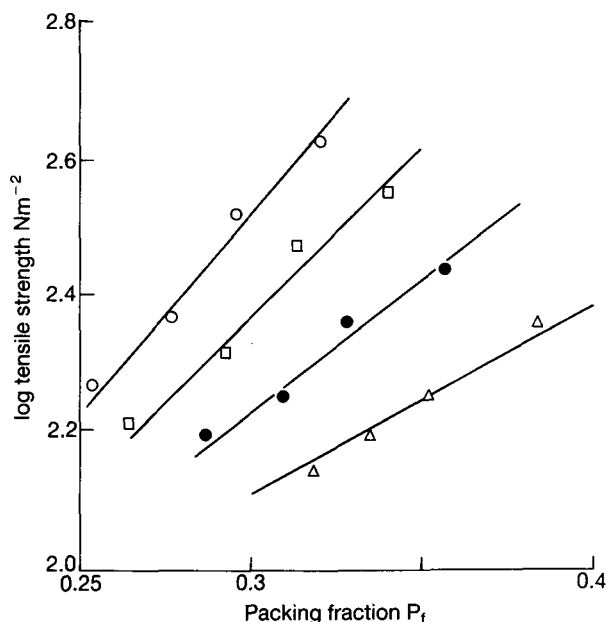

FIG. 2. Relationship between log tensile strength and packing fraction for the different batches of calcium carbonate ($\triangle$ BM, $\bullet$ CH, $\square$ SL, $\circ$ SH).
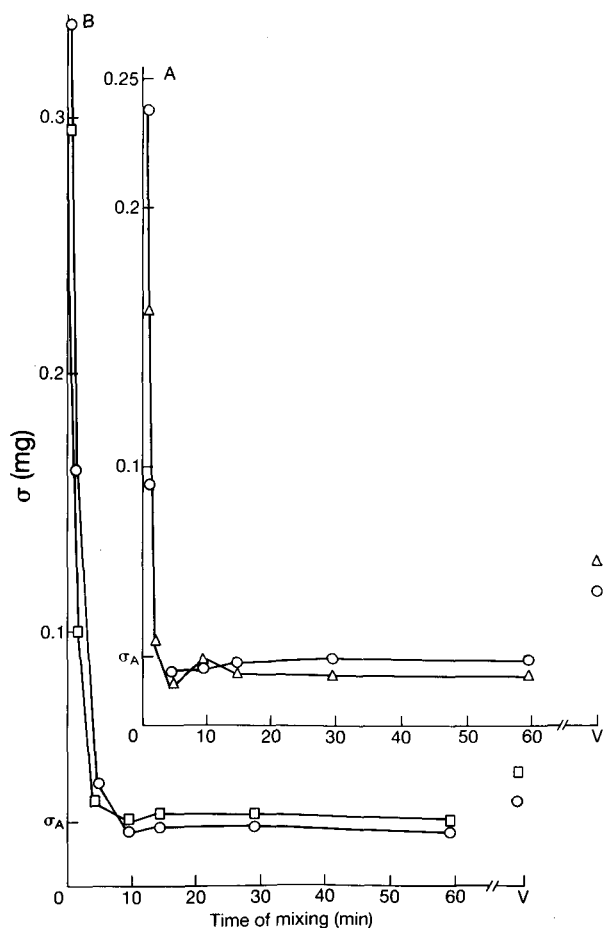

FIG. 1. Standard deviation versus mixing time for different shaped calcium carbonates (A: $\triangle$ BM, $\circ$ CH) (B: $\square$ SL, $\circ$ SH). V = 120.
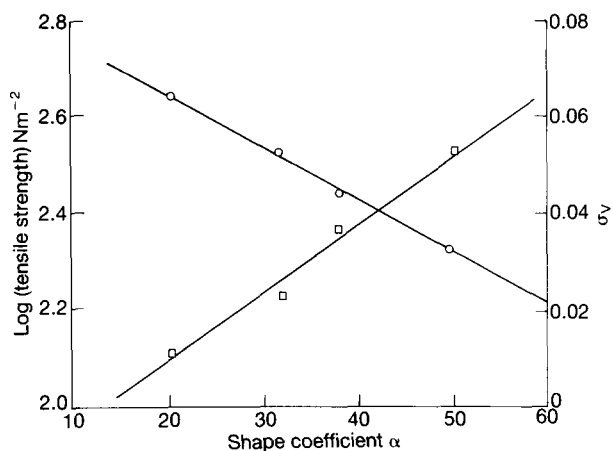

FIG. 3. Relationship between tensile strength at packing fraction of 0·3 $\square$——$\square$, σ_v $\circ$——$\circ$ and the shape coefficient of calcium carbonate.

of powder, A, affect the mixing efficiency parameters, i.e. time to achieve σ_A, and the value of σ_v, a standard method of analysis has been used (Woolfall 1964). The experiments done are shown in Table 3.

Each of the three variables was employed at a low level (subscript L) and high level (subscript H). By grouping the results into a number of sets, it is possible to assess the effect that each variable has separately on the mixing and also to determine the extent of interaction between them.

The effect of increasing, say A, from its low level to its high level on σ (with appropriate subscript) is found by summing
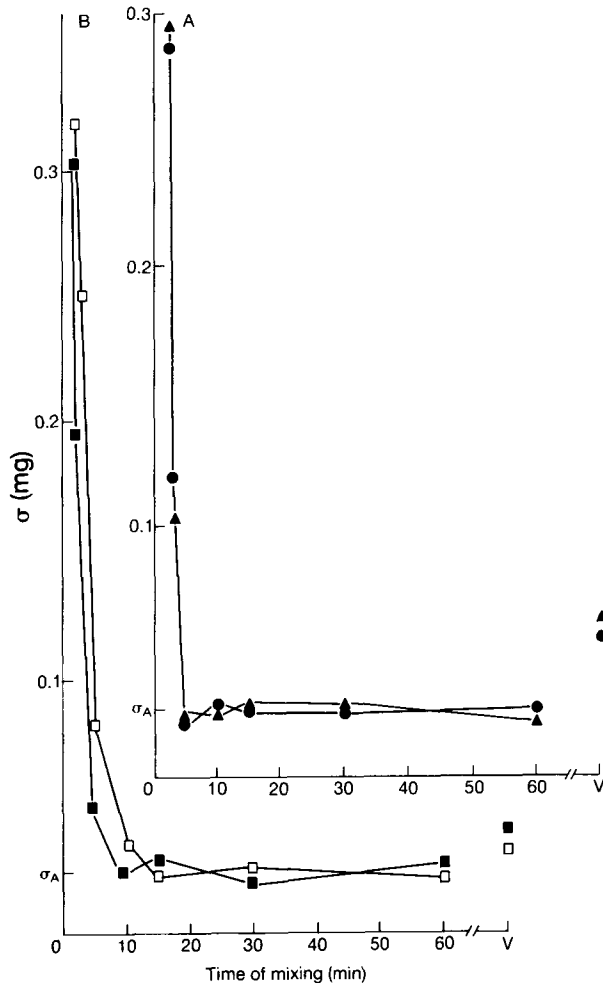
FIG. 4. Standard deviation versus mixing time for different shaped lactose (A: ▲ Lactose 1, ● Lactose 4) (B: ■ Lactose 8, □ Lactose 12).
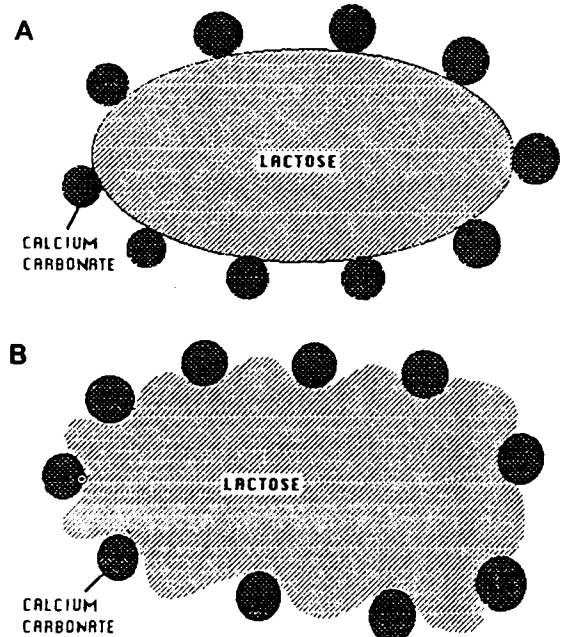

FIG. 5. A. Relatively smooth lactose 1 and 4 with loosely adsorbed calcium carbonate (schematic). B. Relatively rough lactose 8 and 12 with firmly adsorbed calcium carbonate.

Table 3. Levels of variables in factorial experiments.

Variables	Low level	High level
Shape of calcium carbonate α_1	20·6	50·6
Shape of lactose α_2	30·9	41·6
Total amount of powder A, g	100·3	200·5

all results from samples containing high levels of A and subtracting the sum of the σ results from samples containing low levels of A and then dividing by 4. That is

$$\tfrac{1}{4}[(\alpha_{1L}\alpha_{2L}A_H + \alpha_{1L}\alpha_{2H}A_H + \alpha_{1H}\alpha_{2L}A_H + \alpha_{1H}\alpha_{2H}A_H)$$
$$- (\alpha_{1H}\alpha_{2L}A_L + \alpha_{1H}\alpha_{2H}A_L + \alpha_{1L}\alpha_{2L}A_L + \alpha_{1L}\alpha_{2H}A_L)]$$

The amount by which the summation departs from zero is a quantitative measure of the effect of the particular variable. To find whether any two variables, say α_1 and α_2, are interacting, one sums

$$\tfrac{1}{4}[(\alpha_{1L}\alpha_{2L}A_H + \alpha_{1L}\alpha_{2L}A_L + \alpha_{1H}\alpha_{2H}A_L + \alpha_{1H}\alpha_{2H}A_H)$$
$$- (\alpha_{1L}\alpha_{2H}A_H + \alpha_{1H}\alpha_{2L}A_L + \alpha_{1H}\alpha_{2L}A_H + \alpha_{1L}\alpha_{2H}A_L)]$$

A result of zero indicates no interaction.

The results are divided into two categories according to the index of mixing performance used.

Time taken to achieve σ_A

Table 4 shows that increasing both α_1 and α_2 causes an increase in the time taken to achieve σ_A, the effect of the latter being greater than that of the former. This agrees with the earlier findings on the increased time taken to achieve σ_A by the more irregular calcium carbonate and lactose. Table 4 also shows that an increase in A causes a reduction in the time taken to achieve σ_A. This, as found previously, is because using more powder produces more intense shearing in the mixer.

The ranking order of the interaction is $\alpha_1 \times \alpha_2 >> \alpha_1 \times A$

Table 4. Summarized results for the effect of increasing variables.

Increase	Effect on time for σ_A, min	Effect on $\sigma_v \times 10^2$ mg
$\alpha_{1L} \rightarrow \alpha_{1H}$	5	−7·6
$\alpha_{2L} \rightarrow \alpha_{2H}$	10	−8·3
$A_L \rightarrow A_H$	−5	−2·6

Interaction coefficients	α_1 and α_2	α_1 and A	α_2 and A
Time for σ_A min	2·5	−2·5	−2·5
$\sigma_v \times 10^2$ mg	−0·9	−1·6	−1·1

and $\alpha_2 \times A$. This is expected since the individual effect of A is very much less than that of α_1 and α_2.

Values of σ_V

Table 4 also shows that increases in α_1, α_2 and A cause reductions in the values of σ_V. The effects are in the order of $\alpha_2 > \alpha_1 > A$. This again agrees with the previous finding that increases in the shape coefficient of the lactose and in the amount of powder produce more stable mixtures. The interactions are in the order $\alpha_1 \times \alpha_2 > \alpha_2 \times A > \alpha_1 \times A$. Therefore the shape coefficients of both the calcium carbonate and the lactose are important factors in determining the stability of the mixtures towards segregation.

Conclusions

The conclusions of this work are:

1. The time taken to achieve σ_A increases when more irregular calcium carbonates and lactose are used.
2. By increasing the shape coefficient of the calcium carbonate, the shape coefficient of the lactose and the amount of powder, more stable mixtures are produced.

Acknowledgement

We thank Dr K. Ridgway for the use of his shape sorting equipment and Sturge Lifford Chemicals for the gift of materials.

References

Crooks, M. J., Ho, R. (1976) Ordered mixing in direct compression of tablets. Powder Technology 14: 161–167

Hersey, J. A. (1975) Ordered mixing: A new concept in powder mixing practice. Ibid. 11: 41–44

Hersey, J. A. (1979) Development and applicability of powder mixing theory. Int. J. Pharm. Technology and Prod. Mnfr. 1: 6–13

Nikolakakis, I., Pilpel, N. (1985) Effect of particle shape on the tensile strengths of powders. Powder Technology 42: 279–283

Nikolakakis, I., Pilpel, N. (1988) Effect of particle shape and size on the tensile strengths of powders. Ibid. 56: 95–103

Pang, H. M., Ridgway, K. (1980) The extension of the vibratory shape sorting technique to smaller particle size. J. Pharm. Pharmacol. 32: Suppl. 19P–20P

Ridgway, K., Rupp, P. (1969) The effect of particle shape on powder properties. Ibid. 21: 30S–39S

Svarosky, L. (1987) Split Cell Testers. In: Svarosky, L. (ed) Powder Testing Guide. 1st edn., Elvesier Applied Science, London. pp 63–66

Thanomkiat, P., Stewart, P. J., Grovers, P. S. (1979) Influence of carrier particle size on prednisolone—direct compression vehicle ordered mixes. Powder Technology 24: 97–98

Wong, L. W., Pilpel, N. (1988) The performance of a small Y cone mixer. Drug Dev. and Ind. Pharm 14(5): 609–616

Woolfall, R. C. (1964) An approach to product formulation. Soap. Perfum. Cosmet. 37: 965–970