Fluidized bed granulation of an ordered powder mixture

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The phenomenon of ordered unit segregation is of paramount importance in determining the homogeneity of an ordered mixture. This problem can be avoided by using a monodisperse carrier, but it is uneconomic. The fluidized bed granulation of a 0·1% ordered mixture has been studied as a method of reducing the effects of segregation. The ordered units were stable when fluidized and no significant loss of the microfine adsorbed material occurred during processing. The distribution of the minor component in the granules was significantly more uniform than in the original ordered mixtures. The demixing potential

$$DP\% = \frac{100}{\bar{p}}\sqrt{\Sigma \frac{w}{100}(p - \bar{p})^2}$$

(where p = proportion of cohesive minor component and w is the weight % of carrier material in a particular size range) was used to quantify the distribution of the minor component as a function of particle size. DP is a coefficient of variation and can be directly compared with the specification standard deviation σ_A. Batches of granules were compressed into 100 or 350 mg tablets, containing approximately 100 and 350 μg of model drug substance. The weight and content coefficients of variation (c.v.) were determined for 20 tablets. All batches had a weight c.v. ≤1·5% and a content c.v. ≤4·6%. Granulation of an ordered mixture greatly reduces the potential for segregation to decrease the mixture homogeneity. It also provides a solution to the problems which may be encountered when the mixing of small quantities of cohesive materials during conventional fluidized bed granulation is attempted.

The mixing of a cohesive powder and a coarse excipient to form a non segregating mixture was investigated by Travers & White (1971). Adsorption of microfine particles on the surface of the coarser carrier particles occurs. Hersey (1975) used the term ordered mixing to describe this phenomenon. The application of ordered mixing to the production of microdose pharmaceutical products has been discussed by Crooks & Ho (1976) and Johnson (1979).

However, there are two practical limitations to the homogeneity which can be achieved (Ryder 1979) caused by: (i) the tendency for ordered units to segregate causing a decrease in the mixture homogeneity, and (ii) the capacity of the carrier particles to adsorb the cohesive component. The effect of carrier particle size distribution on the homogeneity of ordered mixtures was investigated by Crooks & Ho (1976) who found monodisperse carrier particles formed more homogeneous mixtures than broad size range materials. This result can be explained on the basis of segregation of the ordered units (Yip & Hersey 1977; Thanomkiat & Stewart 1979). The capacity of various excipients to

adsorb drug and the strength of the adhesional forces was the subject of a recent investigation by Staniforth et al (1981). In mixtures containing up to 5% weight of cohesive component a significant amount of this material was found to be only weakly adsorbed. Hersey et al (1979) proposed the term *partially ordered random mixture* to describe a system in which some of the cohesive component was mixed in an ordered manner and the remainder existed as agglomerates which were free to random mix. The existence of partially ordered random mixtures has been noted by Bryan et al (1979) and Johnson (1979). Johnson (1979) concluded that the benefits of ordered mixing could only be realized if ordered unit segregation was avoided.

Stephenson & Thiel (1980) showed that an ordered powder mixture can be fluidized without loss of the adsorbed cohesive component. Fluidized bed granulation of an ordered mixture was suggested as a method of reducing the potential for ordered unit segregation, rather than the uneconomic alternative of using a monodisperse carrier material. This processing method would also eliminate the problem, reported by Crooks & Schade (1978), of insufficient input of energy to break down agglomerates of cohesive drug during mixing and granulation

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in the fluidized bed. However, the method proposed by Stephenson & Thiel (1980) does introduce an extra mixing operation into the manufacturing process. The objective of this investigation was to assess the effect of granulation of an ordered mixture in terms of: (a) reducing the potential for segregation to decrease the mixture homogeneity, and (b) content and weight uniformity of the tablets produced.

THEORETICAL CONSIDERATIONS
Mixing indices
A number of different indices have been used in powder mixing studies (see Fan & Wang 1975 for review). Many of the indices incorporate the variance of composition of samples drawn from a random mixture

$$\sigma_R^2 = \frac{xy}{n} \qquad (1)$$

where n is the number of particles in a sample and x and y are the proportions by weight of the two components. Thiel et al (1981) argued that the use of σ_R in relation to ordered mixing has no reasonable physical basis. In contrast, Egermann (1980) has proposed that ideal ordered and random mixtures both have a variance of σ_R^2. The specification index S/σ_A (Hersey 1967) is a measure which does not require the use of σ_R and is directly related to the ultimate use of the powder mixture in the final dosage form. The index S/σ_A takes a value less than, or equal to, unity once the degree of mixing is sufficient to meet the specification set. The value of σ_A is calculated using the method described by Hersey (1976).

$$3\sigma_A = 0 \cdot 15 \times (\text{mean}) \qquad (2)$$

For an ordered mixture containing a mean proportion of salicylic acid $\pi = 1 \times 10^{-3}$, the value of σ_A is 5×10^{-5}, or expressed as a coefficient of variation (σ_A/π), 5%.

Experimentally the variance S^2 is usually determined using a sample size of twenty. The confidence interval for S^2 can be calculated using the χ^2 distribution (Harnby 1971/72). However, the lower critical limit is of no practical interest; in terms of setting the standard deviation required for a batch to be acceptable it is the upper confidence limit which is significant. The χ^2 distribution is used to set the upper limit as follows:

$$\text{Probability } (10 \cdot 1 \leqslant \chi^2) = 0 \cdot 95 \qquad (3)$$

implies

$$\text{Probability } (\sigma^2 \leqslant \frac{(n-1)S^2}{10 \cdot 1}) = 0 \cdot 95 \qquad (4)$$

so the value $\frac{(n-1)S^2}{10 \cdot 1}$ is the upper limit below which σ^2 falls with a probability of 0·95. The limit $U_{0.95}$ for the content standard deviation is

$$U_{0 \cdot 95} = S \sqrt{\frac{19}{10 \cdot 1}} \qquad (5)$$

This value should be used for both the specification index and coefficient of variation. Thus a 0·1% ordered mixture has a probability of 0·95 of being within specification if

$$\frac{U_{0 \cdot 95}}{\sigma_A} \leqslant 1 \qquad (6)$$

and substituting for $U_{0.95}$ gives

$$\frac{S}{\sigma_A} \leqslant 0 \cdot 73 \qquad (7)$$

The coefficient of variation

$$\frac{U_{0 \cdot 95}}{\pi} \leqslant \frac{\sigma_A}{\pi} = 0 \cdot 05 \qquad (8)$$

gives

$$\frac{S}{\pi} \leqslant 0 \cdot 036 \qquad (9)$$

where π is the population mean proportion of minor component. The above relations can be used for other sample sizes by changing the values of $n - 1$ and χ^2.

Demixing potential
Ordered unit segregation decreases the homogeneity of an ordered mixture because the finer carrier particles are associated on a weight basis with a higher proportion of the cohesive second component. If w is the weight % of carrier material in a particular size range and p is the proportion of cohesive minor component, the mean content of the mixture is

$$\bar{p} = \frac{\Sigma pw}{\Sigma w} \qquad (10)$$

The potential for the homogeneity of the ordered mixture to decrease if segregation occurs is dependent on the distribution of the cohesive minor component as a function of particle size. This can be measured by the demixing potential

$$DP\% = \frac{100}{\bar{p}} \sqrt{\Sigma \frac{w}{100}(p - \bar{p})^2} \qquad (11)$$

which is the coefficient of variation of the minor cohesive component in the different size fractions of carrier material. The larger the value of DP%, the more susceptible is the mixture to a reduction in

homogeneity if ordered unit segregation occurs. If the ordered units could be randomly mixed and granulated so the value of p in each size fraction equalled p̄, the demixing potential would then be zero. Segregation in this ideal granulation cannot decrease the homogeneity; in terms of the final dosage form, segregation could only affect the weight uniformity.

MATERIALS AND METHODS

Ordered mixtures, containing 0·1% microfine salicylic acid and spray dried lactose excipient, were produced in a Revolvo cube mixer fitted with an internal agitator (load 3·3 kg, cube 17 rev min⁻¹, agitator 35 rev min⁻¹, 120 min mixing). Two different grades of spray dried lactose were used, a fine material containing 95% weight in the size range 0–150 μm and a coarser grade with 95% falling between 75 and 350 μm. The particle size distributions are shown in the first two columns of Tables 1 and 2. The cohesive salicylic acid had a mean particle size of 3·5 μm, measured by air permeability.

Table 1. Ordered mixture containing 75–350 μm carrier particles. Salicylic acid distribution in the bulk sample and mean content and standard deviation for 20 × 350 mg samples.

| Particle size μm | Bulk Sample | |
	Weight % (w)	Content by proportion (p) × 10⁻³
>300	16·7	0·52
212–300	43·0	0·65
180–212	11·9	0·85
150–180	6·7	1·01
106–150	10·2	1·23
75–106	7·2	1·65
<75	4·3	3·47
$\bar{p} = \frac{\Sigma pw}{\Sigma w}$	0·93 × 10⁻³	
p̄ theoretical	1·00 × 10⁻³	
DP%	67·0%	
	20 × 350 mg samples	
p̄ (±95% CI)	1·03 (±0·02) × 10⁻³	
S	4·1 × 10⁻⁵	
Content c.v.%	4·0	

After production of the mixture, each batch was split into two portions by removing the material from the mixer single scoop at a time alternately into two containers. One portion was sampled to permit the ordered mixture to be characterized, the second portion was granulated, sampled and then tableted.

Table 2. Ordered mixture containing 0–150 μm carrier particles. Salicylic acid distribution in the bulk sample and mean content and standard deviation for 20 × 350 mg samples.

| Particle size μm | Bulk Sample | |
	Weight % (w)	Content by proportion (p) × 10⁻³
>150	3·4	0·15
106–150	15·0	0·33
90–106	14·5	0·40
75–90	14·3	0·48
53–75	23·1	0·70
<53	29·7	2·09
$\bar{p} = \frac{\Sigma pw}{\Sigma w}$	0·96 × 10⁻³	
p̄ theoretical	1·00 × 10⁻³	
DP%	77·3%	
	20 × 350 mg samples	
p̄ (±95% CI)	1·01 (±0·02) × 10⁻³	
S	3·3 × 10⁻⁵	
Content c.v.%	3·3	

Sampling the ordered mixture

To enable the mixture content and variance to be determined, twenty 350 mg samples were taken using a concentric cylindrical sampling thief. These were taken from three different levels in the mixture and from six or seven different positions at each level. An 80 g bulk sample was also removed for subsequent sieve analysis. This sample was taken by allowing the mixture to discharge from a tablet machine hopper, a sample container was passed into the stream of material at set time intervals. A similar method was used by Johnson (1979) to obtain representative samples.

Production and sampling of the granules

The second portion of mixture (1·65 kg) was transferred into the Aeromatic fluidized bed (capacity 1–2 kg) and granulated using a 5% aqueous solution of polyvinylpyrolidone (BASF Kollidon 30). Typical granulation conditions were; inlet air temperature 70 °C, 40–80 min granulation, solution rate of 800–1200 cm³ h⁻¹, atomizing air pressure 200 kN m⁻² and an air flow rate of 60–75 m³ h⁻¹. The granules were dried for 20 min with air at 50 °C and then passed through a 800 μm sieve to break up any oversize material. An 80 g bulk sample of the granules was taken for sieve analysis using the hopper flow method.

Tableting

After sampling, each batch of granules was mixed with 1% weight of magnesium stearate (5 min

mixing in a tumbling mixer) and tableted using a single punch Manesty F3 machine. Approximately 4500 tablets (mass 350 mg) were produced from each batch of granules.

Analysis

The 350 mg samples were assayed individually for salicylic acid spectrophotometrically at 300 nm in 50% aqueous ethanol. The same method was used for 350 mg tablets with the additional step of filtration through a 0·8 μm microporous filter before measuring the absorbance.

Determining the distribution of salicylic acid

The 80 g bulk samples of ordered mixture and granules were split into different size fractions by sieving (20 min Endecotts test sieves, B.S. 410). An A.C. Cheers sieve shaker was used run at 50V. Lai & Hersey (1981) used the same sieve shaker to investigate the segregation of fine particles in ordered mixtures. Running the shaker at 50V corresponded to the lowest level of vibrational energy input. After sieving each fraction was weighed, dissolved in 50% aqueous ethanol and assayed. The proportion of salicylic acid in each size fraction was then calculated. Johnson (1979) and Stewart (1981) have used similar methods, based on sieving, to determine the distribution of minor component in ordered mixtures.

Production of 100 mg tablets

As a final test of the processing method, three batches of granules were made from 0·1% ordered mixtures produced from the 0–150 μm carrier. An 80 g bulk sample was taken to permit DP to be determined for the granules, which were then compressed to produce 100 mg tablets (containing 95–96 μg of salicylic acid). A sample of 20 tablets was taken, one tablet being taken at 15 min intervals during compression of the batch. The tablets were individually assayed using u.v. spectrophotometry.

Experimental errors

The total variance (S^2) determined experimentally includes the analytical (S_a^2) and sampling variance (S_s^2), in addition to the content variance of the mixture (S_m^2). The variances are independent and are related by

$$S^2 = S_a^2 + S_s^2 + S_m^2 \tag{12}$$

Orr (1979) showed that the analytical and sampling variances can mask the content variance in samples withdrawn from very homogeneous ordered mixtures. The value of $S_a^2 + S_s^2$ is not easily measured

but most likely lies in the range $4–9 \times 10^{-10}$. For a perfect 0·1% mixture, where $S_m^2 = 0$, the experimentally determined variance (S^2) may lead to a content c.v. in the range 2–3%.

Assessment of the sampling techniques

The technique used to remove the mixture from the mixer and split into two 1·65 kg portions, and the hopper flow method used to remove 80 g samples for sieve analysis were assessed to ensure that representative samples were taken. Thiel & Stephenson (1982) showed the effect of ordered unit segregation on the mean content of minor component in ordered mixtures. Representative sampling is characterized by the sample mean ($\bar{p}$) being an unbiased estimator of the population proportion (π).

The sample dividing methods were tested by taking seven 80 g bulk samples from one of the two portions removed from the mixer. The total salicylic acid content was determined for each sample. The average content ($\pm95\%$ CI) was $0·999$ ($\pm0·011$) $\times 10^{-3}$ and established that the methods used removed representative samples from the 75–350 μm lactose ordered mixture.

The ability of the sampling thief to remove 20×350 mg representative samples is shown in the results presented in Tables 1 and 2. The value of $\bar{p}$ ($\pm95\%$ CI) is very close to the value calculated from the weights of material loaded into the mixer ($\bar{p}$ theoretical).

RESULTS AND DISCUSSION

The distributions of salicylic acid on the 0–150 and 75–350 μm carrier particles are given in Tables 1 and 2. The proportion of salicylic acid varies from 0·52 to $3·47 \times 10^{-3}$ in the 75–350 μm mixture, increasing with decreasing carrier particle size, and from 0·15 to $2·09 \times 10^{-3}$ with the 0–150 μm lactose. The value $\bar{p}$ theoretical is the proportion of salicylic acid which should be present, determined by the masses of material initially loaded into the cube mixer. From the assay of 20×350 mg samples taken with the thief, the value of $\bar{p}$, sample standard deviation (S) and content coefficient of variation (c.v.%) were calculated. The value of $\bar{p}$ ($\pm95\%$ CI) for the samples is close to the value of $\bar{p}$ theoretical. The results from the sieve analysis of the bulk sample also permit $\bar{p}$ to be calculated from $\Sigma pw/\Sigma w$. The value in Table 1 shows a 7% loss of salicylic acid for the 75–350 μm lactose and a 4% loss for the 0–150 μm material (Table 2). The loss of salicylic acid is believed to be due to constituent segregation and abrasion of the surface of the carrier particles during sieving. As a

result, a layer of fine dust was left adhering to the sieves after removal of the sized carrier particles. The fine adhering dust was rich in salicylic acid; washing of each sieve in 50% aqueous ethanol and assaying the solution gave total recovery of salicylic acid for the 80 g sample. The demixing potential values (DP%, equation 11) presented in Tables 1 and 2 have been calculated using only the tabulated values of p and w. An alternative method is to assign the salicylic acid lost to the smallest size range in Tables 1 and 2 (i.e. as unbound salicylic acid). The values of DP% increase to 80·0% for the 0–150 μm carrier and to 92·4% for the 75–350 μm material. The distribution of salicylic acid in the ordered mixture has been determined under conditions which may promote some constituent segregation. This is not an unrealistic approach as pharmaceutical mixtures must ideally be able to totally resist segregation under the demixing conditions met during processing.

Tables 3–6 show the values obtained for the granules under the same sieving conditions and the twenty 350 mg tablets sampled from the batch after compression. The values in Tables 3 and 4 are for granulated 75–350 μm ordered mixtures and Tables 5 and 6 for 0–150 μm material. The proportion of salicylic acid in the different size fractions of the granules is significantly more uniform than in the original ordered mixtures and is reflected in the lower DP% values. In Tables 3–6 the values of $\bar{p}$ theoretical have been calculated taking into account the amount of PVP added during granulation. The

Table 3. Granulated ordered mixture (75–350 μm carrier). Salicylic acid distribution in the granules and mean content and standard deviation of 20 × 350 mg tablets.

| Particle size μm | Bulk Sample | |
	Weight % (w)	Content by proportion (p) × 10⁻³
>710	2·8	1·53
500–710	2·4	1·25
300–500	37·1	0·80
212–300	39·5	0·89
106–212	16·5	1·27
75–106	1·4	1·62
<75	0·2	1·97
$\bar{p} = \dfrac{\Sigma pw}{\Sigma w}$	0·96 × 10⁻³	
$\bar{p}$ theoretical	0·98 × 10⁻³	
DP%	22·5%	
	20 tablets	
$\bar{p}$ (±95% CI)	0·99 (±0·01) × 10⁻³	
S	1·9 × 10⁻⁵	
Content c.v.%	1·9	

Table 4. Granulated ordered mixture (75–350 μm carrier). Salicylic acid distribution in the granules and mean content and standard deviation of 20 × 350 mg tablets.

| Particle size μm | Bulk Sample | |
	Weight % (w)	Content by proportion (p) × 10⁻³
>710	6·4	1·16
500–710	9·1	0·94
300–500	61·7	0·90
212–300	18·0	0·97
106–212	3·8	0·98
75–106	0·5	0·98
<75	0·4	1·14
$\bar{p} = \dfrac{\Sigma pw}{\Sigma w}$	0·94 × 10⁻³	
$\bar{p}$ theoretical	0·97 × 10⁻³	
DP%	7·1%	
	20 tablets	
$\bar{p}$ (±95% CI)	0·96 (±0·01) × 10⁻³	
S	1·0 × 10⁻⁵	
Content c.v.%	1·0	

values of $\bar{p}$ measured for the bulk samples ($\Sigma pw/\Sigma w$) and for the sets of 20 tablets are within ±2% of the theoretical values (with one exception −3% $\Sigma pw/\Sigma w$ in Table 4). The value of $\bar{p}$ for the tablets should be 0·01 less than $\bar{p}$ theoretical due to addition of the lubricant. The ordered units are stable during fluidization and granulation, no significant loss of salicylic acid occurs. This confirms the proposal made by Stephenson & Thiel (1980), that it should be possible to granulate an ordered mixture in a fluidized bed.

The value of DP = 22·5% in Table 3 is due to the addition of less granulating solution. The particle size distribution indicates this batch is granulated to a lesser extent than the batch in Table 4, resulting in a greater variation of salicylic acid content in the different sized granules. The rate of addition of PVP solution was different for each batch of granules made. The addition rate can be expressed as the %PVP in the final granulation divided by the granulation time. A plot of DP% versus %PVP minute⁻¹ is presented in Fig. 1 and shows the results in Table 3 to be at the lowest rate of addition of the granulating solution. The results for the original ordered mixtures (equivalent to a granulation solution rate of zero) are also included. The 0–150 μm ordered mixture tended to give granules with a lower DP value than the 75–350 μm mixture. Fig. 1 shows a 45–80 min granulation using a rate of 5·5–7·5 × 10⁻²%PVP min⁻¹ yielded granules with a value of DP ≤ 11% for both carrier materials. Tables 4–6 give full results for three of these batches.

Table 5. Granulated ordered mixture (0–150 μm carrier). Salicylic acid distribution in the granules and mean content and standard deviation of 20 × 350 mg tablets.

Particle size μm	Bulk Sample		
	Weight % (w)	Content by proportion (p) × 10⁻³	
>710	7·8	0·87	
500–710	6·3	0·89	
300–500	8·2	0·84	
212–300	10·9	0·92	
106–212	42·4	0·96	
75–106	17·3	1·02	
<75	6·8	0·99	

$\bar{p} = \dfrac{\Sigma pw}{\Sigma w}$ $0\cdot95 \times 10^{-3}$

$\bar{p}$ theoretical $0\cdot97 \times 10^{-3}$

DP%   5·6%

     20 tablets

$\bar{p}(\pm95\% \text{ CI})$ $0\cdot96(\pm0\cdot01) \times 10^{-3}$

S $2\cdot4 \times 10^{-5}$
Content c.v.%   2·5

The values of DP for the coarser (75–350 μm) carrier material showed a minimum value at a rate of 6×10^{-2}%PVP min⁻¹, higher granulation solution rates resulted in larger DP values.

Because DP is defined as the coefficient of variation of salicylic acid in the different size fractions, the DP values for the granules can be directly compared to the specification coefficient of variation σ_A/π. The granules with a value of DP ⩽ 11% will be very resistant to a decrease in

Table 6. Granulated ordered mixture (0–150 μm carrier). Salicylic acid distribution in the granules and mean content and standard deviation of 20 × 350 mg tablets.

Particle size μm	Bulk Sample		
	Weight % (w)	Content by proportion (p) × 10⁻³	
>710	19·3	0·86	
500–710	5·8	0·84	
300–500	8·2	1·23	
212–300	17·3	0·85	
106–212	41·2	0·96	
75–106	6·4	0·97	
<75	1·7	0·93	

$\bar{p} = \dfrac{\Sigma pw}{\Sigma w}$ $0\cdot94 \times 10^{-3}$

$\bar{p}$ theoretical $0\cdot95 \times 10^{-3}$

DP%   10·8%

     20 tablets

$\bar{p}(\pm95\% \text{ CI})$ $0\cdot94(\pm0\cdot01) \times 10^{-3}$

S $1\cdot30 \times 10^{-5}$
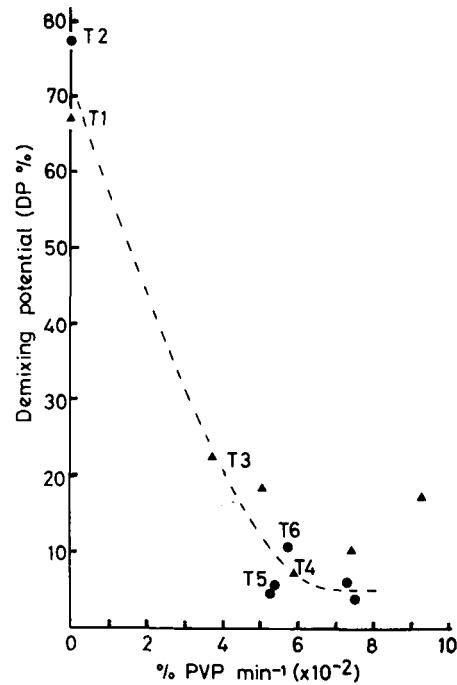Content c.v.%   1·4

Fig. 1. Demixing potential (DP%) for the granules versus the rate of addition of polyvinylpyrrolidone solution (%PVP min⁻¹). ▲ Ordered mixture, 75–350 μm carrier. ● Ordered mixture, 0–150 μm carrier. T1 indicates detailed data for this point is given in Table 1.

homogeneity caused by segregation. The values of DP ranging from 4 to 11% indicate that if segregation was so severe as to cause complete fractionation of the granules (i.e. equivalent to sieving), the mixtures in this state either meet or just fail to meet the specification value $\sigma_A/\pi = 0\cdot05$. The granule segregation which occurs during tableting, as a result of vibration and flow in the feed hopper, may never reach such an extreme. Thus these batches of granules come close to the ideal situation of a mixture totally able to resist a decrease in homogeneity caused by segregation.

Table 7 gives the results of the content and weight coefficients of variation, for 20 × 350 mg tablets, after compression of each batch of granules. The granulation time, rate of addition of granulating solution and DP% values for the granules are also tabulated. Every batch of tablets met the United States Pharmacopeia (XX) weight uniformity specification and all batches had a content coefficient of variation of less than 5%. One batch only failed to meet the specification set by equation 9 (content c.v. ⩽ 3·6%), paradoxically this batch of granules before compression had the lowest value of DP. This

Table 7. Content and weight coefficients of variation for 20 × 350 mg tablets.

Carrier particle size (μm)	Granul-ation time min	% PVP min⁻¹ × 10⁻²	DP%	Tablet content CV%	Tablet wt CV%
75–350	40	5·08	18·4	3·3	0·9
75–350 (T3)**	45	3·73	22·5	1·9	1·1
75–350	30	9·27	17·3	1·8	0·6
75–350 (T4)	45	5·88	7·1	1·0	1·5
75–350	50	7·40	10·1	1·0	1·1
0–150	80	7·31	6·1	3·3	1·2
0–150(T5)	60	5·38	5·6	2·5	1·0
0–150(T6)	80	5·73	10·8	1·4	1·0
0–150	80	7·49	3·9	4·6*	0·5
0–150	95	5·31	4·7	2·5	1·3

* Exceeds the specification set by eqn 9.
** (T3) etc: this result corresponds with the detailed results presented in Table 3 etc.

result can only be explained by the substantial contribution of the sampling (tableting) and analytical variances (S_s^2 and S_a^2 in eqn 12) to the total variance S^2, which was then used to calculate the content c.v.%.

Since the value of DP measures the content dispersion as a function of granule particle size, this might be expected to correlate with the tablet content coefficient of variation. Fig. 2 plots c.v.% for the content of 20 × 350 mg tablets versus the value of DP for each batch of granules. The linear correlation coefficient of −0·256 indicates no significant correlation at the 5% level. However, the analysis of the experimental errors (eqn 12) shows a content c.v. as high as 3% can be due only to sampling and analytical variance. This will tend to mask any trend in the data presented in Fig. 2.

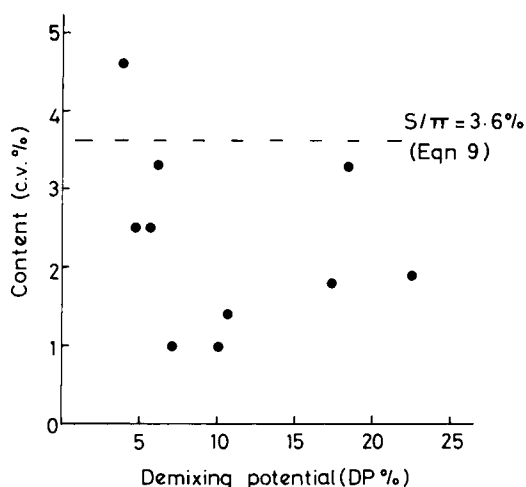The weight and content uniformity results for the

FIG. 2. Content coefficient of variation for 20 × 350 mg tablets versus the demixing potential (DP%) for the granules.

100 mg tablets are shown in Table 8. The value of DP for the granules, the content and weight c.v., and the mean proportion of salicylic acid in the 20 tablets is given. The three sets of samples had a weight c.v. ≤ 1·3% and each set met the USPXX weight uniformity specification. The 95% CI for the mean proportion was close to the value of p̄ theoretical and the content c.v. was ≤4·4% for the three batches.

Table 8. Weight and content uniformity of 20 × 100 mg tablets.

Granules DP%	Tablets Wt c.v.%	Tablets Content c.v.%	Tablets p̄ (±95% CI) × 10⁻³	Tablets p̄ theor. × 10⁻³
18·7	1·3	4·4	0·97 (±0·02)	0·95
4·8	1·3	2·3	0·98 (±0·01)	0·95
4·0	1·0	1·8	0·95 (±0·01)	0·96

These results verify that the processing method used is capable of producing microdose tablets which conform to the current weight and content uniformity specifications.

CONCLUSIONS

A 0·1% ordered mixture of cohesive salicylic acid and spray dried lactose excipient is stable when fluidized, no significant loss of salicylic acid occurs during fluidized bed granulation. As proposed by Stephenson & Thiel (1980), granulation of the ordered mixture fixes the ordered units in a random pattern. The salicylic acid is much more uniformly distributed in the granules than in the original ordered mixtures. Granulation offers a viable method of greatly reducing the effect of ordered unit segregation, thus eliminating the need to use closely sized carrier materials. All batches of 100 and 350 mg tablets produced had a content c.v. ≤ 4·6%, a weight c.v. ≤ 1·5% and met the U.S. Pharmacopeia (XX) weight uniformity specification.

The demixing potential (DP%, eqn 11) is a useful index for measuring the distribution of minor component in a mixture as a function of particle size. The value of DP is directly comparable to the specification coefficient of variation σ_A/π. Theoretically if DP < σ_A/π it is not possible for the mixture to fail to meet the required homogeneity specification as a result of segregation.

The analysis of the experimental errors indicates little margin between the specification standard deviation (σ_A) and the standard deviation of the experimental errors. An analysis performed by u.v.

spectrophotometry is both simple and accurate. This shows that a more complicated technique or less precise chemical assay could easily give rise to the situation where the experimental variance $(S_a^2 + S_s^2)$ was comparable to or larger than the specification variance (σ_A^2).

A fluidized bed is a very efficient mixer for randomizing non- or slightly cohesive materials, but the level of energy input may not be sufficient to break down agglomerates of highly cohesive particles. The two stage process used in this investigation has the advantage of ensuring the cohesive component is uniformly mixed with the excipient, by formation of an ordered mixture, before the granulation stage. Dissolution and bioavailability requirements often dictate the use of very fine active ingredients, the processing method described is ideally suited to producing very homogeneous granules containing small quantities of active material.

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