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Content uniformity of microdose tablets (dosage 1 μg–10 mg) produced by fluid bed granulation of interactive mixtures

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Tablets (100 mg), containing microdose quantities of micronized model drug (1 μg–10 mg), were produced from interactive powder mixtures which had been fluid bed granulated. Granulation prevents adhesion unit and constituent segregation occurring during compression. Single tablet assays were performed on 100 tablets from each batch. The content of tablets fell within ±15% of the mean, and the coefficient of variation was <5% (99% confidence) for all batches. Skewness in the content distribution showed little evidence of superpotent tablets and indicated the absence of significant agglomerates of particles of the micronized component. However, there was some indication that the mixtures produced were not totally agglomerate free. These results demonstrate that the true potential of interactive mixing may be realized, provided segregation in the mixture can be eliminated. The distribution of micronized model drug, as a function of carrier particle size, was determined for the different concentration mixtures before and after granulation. When 0·1–2% interactive mixtures were sieved gently, the proportions of micronized material adhering to the different size fractions of carrier were similar. However, the very low concentration mixtures (0·001–0·03%) proved to be relatively unstable, a significant proportion of the micronized component being transferred from the mixtures to the metal surfaces of the sieves. Granulation of the mixtures in a fluidized bed produced a uniform distribution of micronized material throughout the different sized granules. These granules were stable during vibration on the sieves and when compressed. All samples of tablets met the United States Pharmacopeia XXI content uniformity requirements.

In this paper the nomenclature proposed by Egermann & Orr (1983) and Thiel (1984) will be used. Interactive mixing is synonymous with the term ordered mixing used previously, and adhesion unit is the same as order unit.

Yip & Hersey (1977) discussed adhesion unit and constituent segregation and showed that they are major factors determining the homogeneity which can be achieved in an interactive powder mixture. Mixtures produced with polydisperse carrier particles are prone to adhesion unit segregation; Johnson (1979) concluded that to realize the benefits of interactive mixing, segregation of the carrier particles must be eliminated. Various methods have been proposed to counteract this phenomenon; Crooks & Ho (1976) recommended the use of a monosized carrier material, but this is uneconomic for large scale manufacturing. Thiel & Stephenson (1982) produced interactive mixtures at 0% r.h. and showed the build up of electrostatic charge during mixing to minimize adhesion unit segregation. However, interparticle forces of this kind may decrease the ability of the mixture to flow freely, an important consideration in a tableting operation. Thiel et al (1983) showed that fluid bed granulation of an interactive mixture could be used to overcome the problem of mixing cohesive materials, which tends to occur during conventional granulation of microdose products (Crooks & Schade 1978). This process of granulating an interactive mixture also eliminates the adverse effects caused by differential solubility and hydrophobicity of the components. Thiel & Nguyen (1982) granulated 0·1% interactive mixtures produced from a broad size range carrier material. The granules contained a very uniform distribution of micronized model drug and compressed into 100 μg dosage tablets that met the ±15% content uniformity specification (USP XX).

The critical factor determining the change in homogeneity caused by segregation, is the distribution of minor component. This can be quantified by the demixing potential (Thiel & Nguyen 1982);

$$DP\% = \frac{100}{\bar{p}} \sqrt{\Sigma \frac{w}{100} (p - \bar{p})^2} \qquad (1)$$

* Correspondence.

where p is the proportion of the minor constituent associated with w weight % of the mixture. The mean composition is calculated from

$$\bar{p} = \frac{\Sigma pw}{\Sigma w} \quad (2)$$

The demixing potential (DP%) is the coefficient of variation calculated on the grouped data describing the particle size distribution and associated mass of minor component. Theoretically, if DP% is less than the specification coefficient of variation, tablets produced from the mixture will not fail to meet specification as a result of segregation. Usually a value of 5% is used for the specification CV; Thiel & Nguyen (1982) obtained values of DP in the range 4–10% for granulated interactive mixtures.

Lai et al (1981) and Staniforth (1982) investigated the segregation induced in interactive mixtures by vibration. When a stationary column of mixture was vibrated under various conditions, constituent segregation dominated. There was no bulk flow of mixture during these experiments and negligible adhesion unit segregation occurred. Staniforth & Rees (1982) have shown that the stability of an interactive mixture can be improved by triboelectrification. Under the correct conditions, the interparticle force between carrier and micronized material can be increased, decreasing the tendency for constituent segregation.

Recently, concern has been expressed about the distribution of content in batches of low dosage tablets. Hersey (1976) discussed the increased potency of modern drugs and showed it posed a significant challenge in terms of producing satisfactory mixtures for tablet production. Orr & Sallam (1978) determined that the distributions of ethinyloestradiol in some commercial batches of 10 μg tablets were positively skewed and resulted from the presence of agglomerates of particles of the cohesive drug. They discuss the implications of these results in terms of quality control procedures and recommend that a test for content skewness should be incorporated into the standards for microdose tablets. Asymmetry of the distribution of content was measured using the coefficient of skewness g_1.

$$g_1 = \frac{m_3}{m_2^{1.5}} \quad (3)$$

where the r th moment is given by

$$m_r = \sum_{i=1}^{n} \frac{(x_i - \bar{x})^r}{n} \quad (4)$$

Sokal & Rohlf (1981) describe a test of significance for the statistic g_1 using Student's *t*-distribution.

$$t_s = \frac{g_1 - \gamma_1}{S_{g_1}} \quad (5)$$

where γ_1 is the population skewness coefficient ($H_0: \gamma_1 = 0$) and S_{g_1} the standard error of g_1. The inadequacy of current testing procedures to detect the existence of small numbers of superpotent tablets is demonstrated by Egermann (1982). He recommended the use of manufacturing methods which exclude the possibility of large agglomerates of cohesive drug existing in the mixture; this may be achieved by screening drug-diluent premixes.

During tableting, a mixture will be subjected to vibration during flow in the hopper and feed frame. With an interactive mixture, both adhesion unit and constituent segregation may occur simultaneously. Fluid bed granulation of an interactive mixture is a method of minimizing both types of segregation. This investigation aimed to answer the following questions:

(a) Can the process developed previously by Thiel & Nguyen (1982) be used with a polydisperse carrier, over a wide range of concentration (0·001–10%), to produce tablets complying with USP XXI content uniformity?

(b) Do the granules prepared by this process contain agglomerates of particles of the cohesive component which will give rise to superpotent tablets? The content distribution and coefficient of skewness (g_1) were determined using a sample of 100 tablets from each batch.

(c) In the absence of adhesion unit and constituent segregation, can the true potential of interactive mixing be realized at very low concentrations (0·1–0·001%)? This was judged using the criteria set out in (a) and (b).

EXPERIMENTAL METHOD

Thiel & Nguyen (1982) and Thiel et al (1983) describe the equipment and manufacturing methods used to produce interactive mixtures and granules. The carrier material was spray-dried lactose (80 mesh) with 95% wt in the range 75–350 μm. This material has a wide particle size, a condition which will tend to promote adhesion unit segregation. Salicylic acid was chosen as the model drug because it is hydrophobic and has a low aqueous solubility, properties which have been shown to give rise to mixing problems during granulation (Crooks & Schade 1978). The micronized salicylic acid (2–5 μm optical microscopy) was mixed at various concentra-

tions (0·001–10%) with the lactose (Revolvo cube mixer, 300 min, load 3 kg, cube 17 rev min^{-1}, internal agitator 35 rev min^{-1}). A long mixing time was used to minimize the likelihood of agglomerates of particles of salicylic acid remaining in the mixture, although this situation did occur at 5 and 10%. The mixture was then transferred into the fluidized bed and granulated using a 10% aqueous solution of polylvinylpyrrolidone (PVP, BASF Kollidon 30). The granules were mixed with magnesium stearate tableting lubricant (½% weight, cube mixer, 5 min) and compressed into 100 mg tablets using a single punch Manesty F3 tablet machine. A sequential sample of 100 tablets was taken throughout the compression of the batch of granules.

The dosage of micronized model drug in the 100 mg tablets ranged from 1 μg to 10 mg. The sample of 100 tablets was assayed individually, a UV spectrophotometric method being used for the 100 μg to 10 mg tablets; further details are given by Thiel & Nguyen (1982). The 1–30 μg tablets were assayed using UV fluorescence; the tablets were dissolved in buffer solution (disodium hydrogen orthophosphate and sodium hydroxide, pH 11), passed through a 0·8 μm microporous filter to remove the magnesium stearate lubricant and the concentration of salicylic acid determined using a Perkin-Elmer 3000 fluorimeter (excitation λ 310 nm, emission λ 450 nm).

Bulk samples (70–80 g) were taken from the interactive mixtures and granules using the method described by Thiel & Nguyen (1982). A sieve analysis was performed (5 min, Endecotts test sieves, B.S. 410) running the sieve shaker at 50 V, which corresponded to the lowest level of vibrational energy used by Lai et al (1981) in studies of constituent segregation. The amount of salicylic acid present in each size fraction was determined.

RESULTS AND DISCUSSION

Tables 1 and 2 show the distribution of micronized salicylic acid in various concentration interactive mixtures after sieving (low energy vibration). Table 1 gives the weight % (w) of carrier particles in each size range and the proportion (p) of salicylic acid associated with the carrier. The mean content after sieving ($\bar{p}$) was calculated using equation 2. The ratio $\bar{p}/\pi$, where π is the proportion weighed into the mixer, gives a measure of the stability of the mixture during sieving. For the 0·001% mixture, 27% of micronized salicylic acid transferred from the carrier particles onto the brass sieve mesh. With the 10% mixture, a large quantity of free micronized material was left adhering to the sieve when the carrier was tipped off for subsequent assay. The blinding of the mesh accounts for the different size distribution measured at 10%, compared with the 0·01–5% mixtures shown in Table 2. Washing the sieves in 50% aqueous ethanol and assaying the solution resulted in complete recovery of salicylic acid. The particle size distribution of the 0·001% mix is different because the spray-dried lactose came from another batch. The value of DP%, calculated from equation 1, uses only the proportion of salicylic acid associated with the carrier particles.

Table 1. Distribution of micronized salicylic acid in the 0·001% and 10% interactive mixtures.

Particle size (μm)	Mixture strength π 0·001% w (%)	0·001% p × 10^{-5}	10% w (%)	10% p × 10^{-1}
>300	2·6	0·21	33·5	0·72
212–300	32·4	0·58	36·3	0·81
180–212	19·6	0·68	19·2	1·08
150–180	12·3	0·65	6·1	1·09
106–150	20·6	0·81	4·5	1·13
75–106	8·3	0·93	0·5	1·27
<75	4·3	1·83	0·1	1·60
$\bar{p} = \frac{\Sigma pw}{\Sigma w}$	0·73 × 10^{-5}		0·86 × 10^{-1}	
$\bar{p}/\pi$	0·73		0·86	
DP%	(36·6%)[a]		(18·4%)[a]	
Mass drug adhering to sieves (mg/100 g mixture)	0·27		1370	

[a] A substantial transfer of salicylic acid occurred from the carrier particles to the sieves.

The distribution of micronized material in the 0·01–5% mixtures is given in Table 2. A similar weight % of carrier was retained on each sieve and only the mean and standard deviation are shown for the seven mixtures. The proportion of salicylic acid (p) associated with each size fraction is expressed as the ratio p/π, where π is the mixture strength as manufactured. For the concentration range 0·1 to 2%, the value $\bar{p}/\pi$ shows the mixtures were relatively stable when sieved, between 3 and 7% of the micronized component transferred to the sieves. With these mixtures, for a given size range, the ratio p/π is relatively constant even though the total quantity of salicylic acid varies twentyfold. In contrast, the low concentration mixtures (0·01–0·03%) were less stable, 34 and 17% of the salicylic acid being transferred to the sieve meshes. This phenomenon probably does not reflect basic differences in the force of adhesion in the various strength mixtures. A more likely explanation is the brass sieve

Table 2. Distribution of micronized salicylic acid in different concentration interactive mixtures.

Particle size (μm)	Weight % mean (s.d.)	Mixture strength π 0·01 p/π	0·03 p/π	0·1 p/π	0·5 p/π	1·0 p/π	2·0 p/π	5·0 p/π
>300	23·6 (1·3)	0·58	0·69	0·78	0·72	0·72	0·69	0·65
212–300	37·7 (1·0)	0·72	0·78	0·90	0·81	0·81	0·79	0·75
180–212	12·8 (0·3)	0·62	0·87	0·95	0·97	0·92	0·90	0·82
150–180	8·0 (0·3)	0·50	0·80	0·99	1·04	1·07	1·06	0·97
106–150	12·1 (0·4)	0·69	1·00	1·14	1·20	1·27	1·21	1·10
75–106	4·4 (0·2)	0·66	1·00	1·37	1·75	1·77	1·72	1·53
<75	1·5 (0·6)	1·19	1·82	2·27	3·28	3·89	3·33	2·86
	$\bar{p}/\pi$	0·66	0·83	0·97	0·96	0·96	0·93	0·84
	DP%	(15·5)[a]	(20·1)[a]	24·3	40·2	46·3	40·7	(27·1)[a]
Mass adhering to sieves (mg/100 g of mixture)		3·39	5·09	3·52	19·6	35·6	152·7	801·7

[a] A substantial transfer of salicylic acid occurred from the carrier particles to the sieves.

mesh competes with the carrier particles to bind a certain mass of the micronized salicylic acid, establishing an equilibrium after a few minutes sieving. In the dilute mixtures, transfer of a small mass of salicylic acid to the mesh caused a large change in the mixture proportion. This is less significant in the stronger mixes (0·1–2%). The quantity of salicylic acid which bound to the sieves is given in Tables 1 and 2, expressed as the mass per 100 g of mixture. The quantity adhering to the metal surfaces increases with increasing mixture concentration. As the amount of salicylic acid increases, a point is reached where the carrier surface has a reduced affinity for the micronized component. The stability of the various mixtures during sieving ($\bar{p}/\pi$, Table 2) indicates this point is reached between 1 and 2% for the 80 mesh lactose–salicylic acid system. Further addition produced mixtures in which both interactive and non-interactive mixing of the micronized salicylic acid occurs; Hersey et al (1979) described such mixtures as partially ordered random. With the 5 and 10% concentration, agglomerates of salicylic acid particles were still clearly visible after 5 h in the cube mixer. In the case of the 10% mix, there was sufficient unbound material to blind the meshes during sieve analysis.

With the mixtures that best resisted constituent segregation (0·1–2%) the DP% values in Table 2 show there is considerable potential for adhesion unit segregation to decrease the homogeneity. The values of DP for the low and high concentration mixtures ($\pi < 0{\cdot}1$ and $\pi > 2\%$) are less meaningful, since they are calculated using only the proportion of salicylic acid adhering to the lactose carrier and substantial losses occurred. The lack of stability of this system was noted by Thiel et al (1983), but in that study 20 min sieving at 240 V was used, giving rise to larger DP values. Thiel & Nguyen (1982) suggested that the salicylic acid which transferred to the sieves could be treated as unbound material under these vibration (segregation) conditions and assigned to the <75 μm interval. This increases the value of DP%, but this approach may not be realistic. Recently, Staniforth & Rees (1983) have shown that complicated constituent segregation patterns occur, which are very dependent on the frequency of vibration. In some situations, unbound fine particles will concentrate in bands within the mixture or move upward to the surface of the powder. The mechanism of adhesion and distribution of micronized particles on the carrier surface are poorly understood. Egermann (1980) has proposed that the distribution is random. The results in Table 2 show that under the low energy vibration conditions used for sieving, a twentyfold increase in strength (from 0·1 to 2%) resulted in similar p/π values. The smallest carrier particles were associated with 3 to 4 times the proportion by mass found in the coarsest fraction. This result shows that as the concentration of salicylic acid is increased, uptake by the lactose carrier particles proceeds in a regular way.

When subjected to vibration, all the interactive mixtures underwent some constituent segregation. The values of DP% (Table 2) also indicate that significant decreases in mixture homogeneity may result from adhesion unit segregation. Fluidized bed spray agglomeration was used to randomize and granulate the adhesion units. An ideal granulation results in an equal proportion of micronized component in each size fraction (DP% = 0). The values measured in the 0·001 to 10% granulations are given in Tables 3 and 4; granulation reduced the demixing

Table 3. Granulated interactive mixtures; content variation of granules and tablets.

Mix %	Ref. (Fig. 1)	Sieve analysis granules $\bar{p}$ (eqn 2)	$\bar{p}/\pi$ %	DP% (eqn 1)	Tablet mean content (proportion), coefficient of variation, skewness and range (as % mean) n	$\bar{p}$	$\bar{p}/\pi$ %	CV %	Skewness t_s (eqn 5)	Range Max %	Min %
0·001		$1·01 \times 10^{-5}$	104·3	10·4	50	$9·59 \times 10^{-6}$	98·8	4·3	+1·9	110·0	92·0
0·001	A	$1·00 \times 10^{-5}$	103·8	8·0	100	$9·41 \times 10^{-6}$	97·0	2·7	+3·5**	109·2	95·1
0·01					100	$9·60 \times 10^{-5}$	99·3	1·2	+1·1	103·2	97·8
0·01	B	$9·71 \times 10^{-5}$	100·4	7·6	100[1]	$9·52 \times 10^{-5}$	98·4	1·5	−2·9**	102·7	95·7
0·01	C	$9·66 \times 10^{-5}$	99·8	12·3	100	$9·33 \times 10^{-5}$	96·4	1·5	+1·7	105·1	96·9
0·03	D	$2·76 \times 10^{-4}$	96·8	7·7	100	$2·83 \times 10^{-4}$	99·3	1·5	+4·9**	106·9	96·9
0·1	E	$9·21 \times 10^{-4}$	96·3	6·3	100	$9·41 \times 10^{-4}$	98·4	2·2	+2·8**	110·0	95·6
0·5		$4·54 \times 10^{-3}$	96·0	7·9	20	$4·57 \times 10^{-3}$	96·6	0·8	—	102·1	98·9
1	F	$9·45 \times 10^{-3}$	99·9	6·9	100	$9·25 \times 10^{-3}$	97·8	1·2	+0·2	103·2	97·4
2	G	$1·80 \times 10^{-2}$	93·8	12·1	100	$1·81 \times 10^{-2}$	94·3	1·2	−0·9	102·8	96·8
5		$4·54 \times 10^{-2}$	94·8	12·4	50	$4·53 \times 10^{-2}$	94·6	1·8	−2·3	103·0	95·8
10		$9·30 \times 10^{-2}$	97·2	19·8	50	$9·03 \times 10^{-2}$	94·4	1·9	−0·2	103·3	96·4

** t_s Significant ($P < 0·01$). [1] 60 mg tablets compressed from half the batch.

Table 4. Distribution of micronized salicylic acid in three batches of 0·01% granules.

Particle size (μm)	Batch I w (%)	I p/π	II w (%)	II p/π	III w (%)	III p/π
>710	5·6	0·94	2·6	0·99	2·1	0·95
500–710	20·3	0·94	13·1	0·94	9·8	0·91
300–500	53·8	0·95	59·3	0·97	57·6	0·92
212–300	16·2	1·23	20·2	1·10	24·2	1·16
106–212	3·9	1·25	4·7	1·20	6·0	1·26
75–106	0·1	1·39	0·1	1·40	0·2	1·38
<75	0·01	1·85	0·05	1·79	0·05	1·54
Wt% PVP	4·1%		3·5%		3·3%	
$\bar{p}/\pi$ (%)	100·5%		100·4%		99·8%	
DP% (eqn 1)	11·5		7·6		12·3	

potential to 6–12%, with the exception of the 10% mix (which contained a large quantity of free agglomerates of salicylic acid when manufactured). Demixing potential values of 6–7% indicate the micronized component is sufficiently uniformly distributed, so the mixture is close to meeting the specification value (5%) in a totally segregated (i.e. sieved) condition. In a previous study Thiel & Nguyen (1982) obtained values of DP less than 5% with a finer, narrower size range carrier.

The $\bar{p}/\pi$ values for the sieve analysis of the granules ranged from 94 to 100%; the 0·001% mix assayed at 104%. There are two potential sources of loss of micronized salicylic acid, elutriation from the fluidization chamber during processing, and loss caused by abrasion of the granules during sieve analysis. With the exception of the 0·001% mix, Table 3 shows the content of granules determined from the sieve analysis were within 3% of the mean content of the tablets sampled from the batch during compression. This indicated that the loss did not occur during sieving, but was caused by micronized material being blown out of the fluidized bed through the overhead filters. Losses can be minimized by rapid addition of the granulating solution at the start of the process, this technique was particularly effective with low concentration mixtures. Three replicates of 0·01% granulations are presented in Table 4, the mean content ($\bar{p}$) was within ±1% of the theoretical mixture strength π (as manufactured and corrected for the PVP added during granulation).

The uniform distribution of minor component in the granules (DP < 12%) is reflected in the content variation results for the tablets, presented in Table 3. In most cases 100 tablets were assayed and the content expressed by proportion to eliminate the effect of tablet weight variation. The content coefficient of variation (CV) was calculated from

$$CV = \frac{s}{\pi} \qquad (6)$$

where s is the sample standard deviation of the content by proportion and π the theoretical proportion. Table 3 shows the values of CV ≤ 2·2% for all batches, except the lowest dosage which was 2·7 and 4·3%. If the content is approximately normally distributed, the upper 99% confidence interval for the coefficient of variation can be calculated (Thiel 1982); this was <5% for all batches. The CV results for the tablets indicate a very uniform dispersion of salicylic acid. The content distributions for a number of sets of samples are shown in Fig. 1, these justify the use of a normal distribution during calculation of the CV confidence interval.

In Fig. 1 the content of the tablets is presented, firstly, calculated by proportion, and secondly, as the mass of salicylic acid in each tablet. The content by

proportion is the preferred measure for assessing the adequacy of mixing. One lot of 60 mg tablets was compressed from half a batch of 0·01% granules, the sample of 100 tablets having a mean content (mass salicylic acid) of 5·9 μg and a CV of 1·5% (B in Fig. 1). Table 3 shows the content range calculated as a maximum and minimum percentage of the mean proportion; all samples fell within the ±15% content uniformity specification (USP XX). Significant skewness (t_s) scores (eqn 5) occurred in four of the

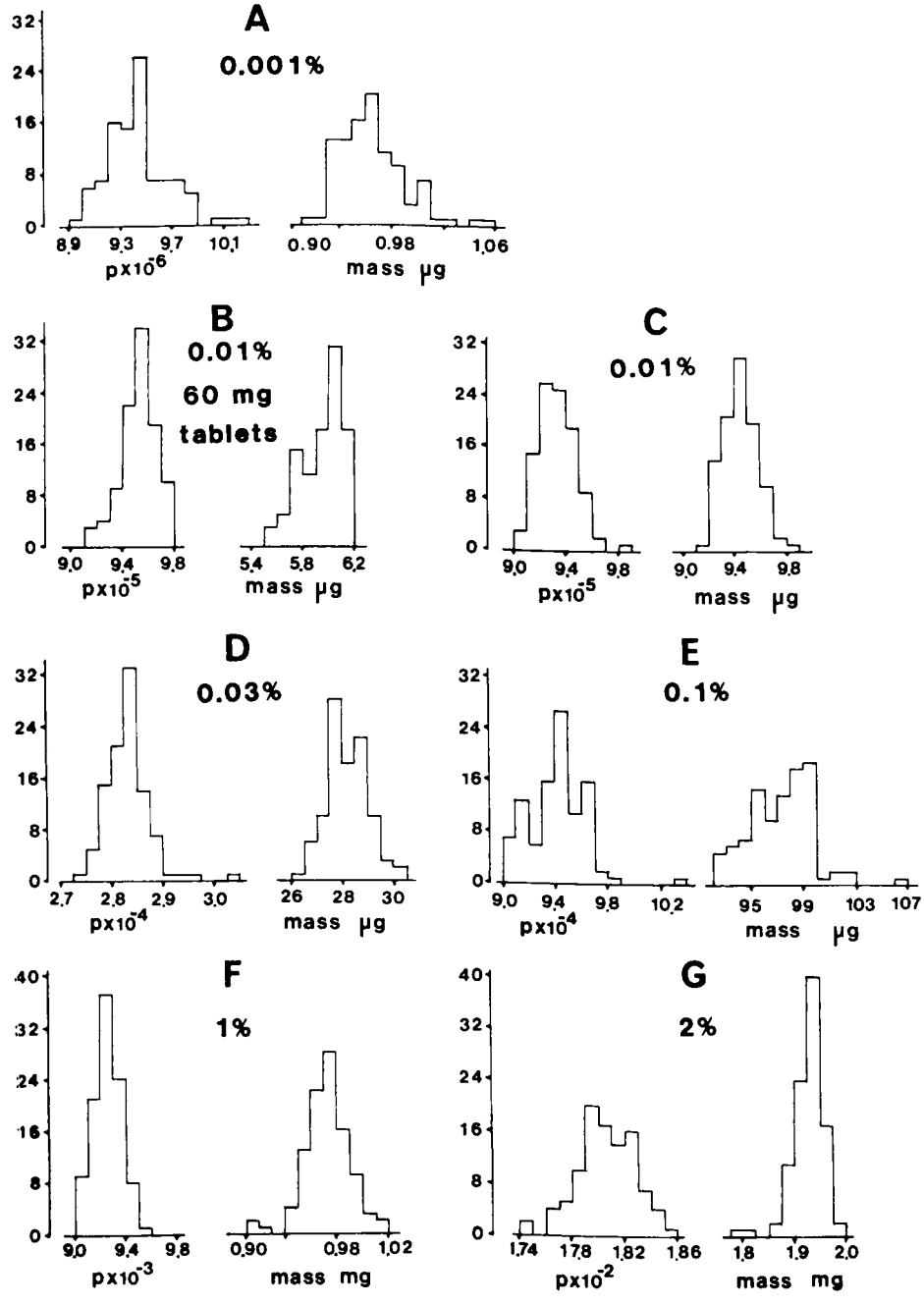

FIG. 1. Distribution of micronized salicylic acid in samples of 100 tablets. The content is shown expressed by proportion and mass. The letters A–G refer to the results presented in Tables 3 and 5.

samples; in three cases this was positive and for the batch of 60 mg tablets it was negative. The significant positive values resulted from the presence of one or two tablets containing a higher proportion of salicylic acid (see Fig. 1) indicating the presence of small agglomerates of particles of the micronized drug. The cube mixer used to produce the interactive mixtures does not supply sufficient energy to break up the cohesive agglomerates totally. The variance and skewness of the results presented in Fig. 1 and Table 3 are less than those reported by Orr & Sallam (1978) for 10 μg ethinyloestradiol tablets, and very much less significant than the case cited by Hersey (1976). The 5 and 10% mixtures contained clearly visible agglomerates of salicylic acid after interactive mixing, because of carrier particle saturation. However, the values of t_s in Table 3 are not statistically significant and indicate that after wet granulation in the fluid bed the size of the agglomerates is not sufficient to produce content skewness.

The variation of total tablet weight and content (mass salicylic acid) is shown in Table 5, for the same samples presented in Table 3 and Fig. 1. The tablet weight CV was ≤2·2% and all batches met the ±10% weight uniformity specification (USP XX). The linear correlation coefficient was calculated on each sample for content by proportion with tablet weight (r_{pw}) and content expressed as mass of salicylic acid with tablet weight (r_{mw}). As would be expected, there was no significant positive correlation between proportion and tablet weight (r_{pw}). However, a significant positive correlation between mass of salicylic acid and the tablet weight occurred in seven of the eleven samples. The mass of salicylic acid in three samples had a skewed distribution, positive in one case (A, Fig. 1) and negative in two cases, B and G. The negative skewness of mass of salicylic acid results from negative skewness in the tablet weight distribution (Table 5); the two batches for which this occurred also showed high values of correlation r_{mw}. The positive skewness of mass in 0·001% tablets was due to the presence of agglomerates of salicylic acid particles; the tablets containing a high proportion were the same as those that contained an excess mass of salicylic acid.

Table 6 presents a theoretical calculation of surface area and number of particles in different size fractions of carrier. The lactose particles are assumed to be smooth spheres of various mean diameters and the micronized salicylic acid 3·5 μm spherical particles. Microscopic examination revealed both materials had approximately spherical shapes. Column (vi) in Table 6 gives the ratio of the mass of salicylic acid adhering to the surface area. This ratio shows that the quantity adhering to the coarser carrier particles is greater than the smooth sphere area calculations would predict; this may be due to adhesion of fine lactose (<75 μm) and associated salicylic acid to the coarser carrier particles, or differences in the number of adhesion sites on the surface of the lactose. Table 6 column (iv), pw × 10^{-3} shows the <75 μm fraction contains only 3·4% of the total salicylic acid in the mixture; this suggests there is insufficient fine lactose to cause the observed

Table 5. Coefficients of variation for tablet weight and content (mass salicylic acid), tablet wt and content skewness, and linear correlation of content with tablet wt.

Mix %	Ref. (Fig. 1)	Sample size n	Tablet wt CV %	Tablet wt skewness t_s (eqn 5)	Tablet content (mass drug) CV %	Tablet content mass skewness t_s (eqn 5)	Correlation r_{pw}[1]	Correlation r_{mw}[2]
0·001		50	0·8	−1·5	4·3	+1·7	−0·25	−0·04
0·001	A	100	0·8	−1·1	2·7	+4·3**	−0·14	+0·18
0·01		100	1·1	−2·0	1·6	−1·3	+0·28	+0·65*
0·01	B	100[3]	2·0	−3·1**	2·8	−3·1**	−0·02	+0·86*
0·01	C	100	0·9	+1·6	1·4	+0·7	−0·40*	+0·19
0·03	D	100	2·2	+0·5	2·8	+0·3	+0·11	+0·85*
0·1	E	100	1·3	−0·5	2·4	+1·8	−0·12	+0·40*
0·5		20	1·1	—	—	—	—	—
1	F	100	1·7	+0·8	2·1	0·0	−0·01	+0·83*
2	G	100	1·1	−3·6**	1·6	−5·4**	−0·01	+0·69*
5		50	1·0	−2·0	1·7	−2·0	−0·38	+0·19
10		50	1·3	−3·0**	2·3	−0·2	−0·04	+0·54*

[1] r_{pw} linear correlation content (proportion) with tablet weight.
[2] r_{mw} linear correlation content (mass drug) with tablet weight.
[3] 60 mg tablets compressed from half the batch.
** t_s significant ($P < 0·01$). * Significant correlation ($P < 0·01$).

Table 6. Theoretical calculations for a 0·1% interactive mixture: Ratio, adhering salicylic acid to carrier surface area; Ratio, number of micronized drug to lactose carrier particles.

(i) Carrier mean diameter μm	(ii) Weight % (w)	(iii) Proportion drug (p) × 10^{-3}	(iv) Mass drug per 100 g mix pw × 10^{-3}	(v) Surface area per 100 g mix cm^2	(vi) Ratio (iv) ÷ (v) × 10^{-3}	(vii) No. particles per gram of mix
350	23·6	0·78	18·4	3677	5·0	9 500
256	37·7	0·90	33·9	8033	4·2	39 000
196	12·8	0·95	12·2	3562	3·4	29 500
165	8·0	0·99	7·9	2645	3·0	30 900
128	12·1	1·14	13·8	5156	2·7	100 200
90	4·4	1·37	6·0	2667	2·3	104 700
50	1·5	2·27	3·4	1636	2·1	208 200
						Σ = 313 800[d]
[a]	[a]	[a]		[b,c]		Σ = 522 000[e]

Salicylic acid, 3·5 μm particles, density 1·44 g cm^{-3}, 3·10 × 10^{10} particles g^{-1}.
Drug to carrier ratio 100 : 1 using [d].
Drug to carrier ratio 60 : 1 using [e].
[a] Taken from Table 2.
[b] Lactose particle density 1·1 g cm^{-3}.
[c] Assuming smooth sphere.
[d] Sum of particles excluding <75 μm.
[e] Sum including <75 μm fraction.

trend in the ratio, column (vi). The more probable explanation is changing surface characteristics of the different sized spray-dried lactose particles.

The ratio of micronized to carrier particles is calculated in Table 6 for a 0·1% interactive mixture. The ratio is in the range 60 : 1 to 100 : 1 dependent on the inclusion of the lactose <75 μm particles. They might reasonably be omitted from the calculation, as they are likely to adhere to coarser lactose particles (this unit being treated as a single entity). Extrapolating this result to 0·01 and 0·001% mixtures, which were used to produce 10, 6 and 1 μg tablets, the particle ratio in these mixtures was found to be 10 : 1 and 1 : 1 (<75 μm lactose excluded). In the 1 : 100 000 mixture this calculation reveals the minor component has been diluted to the extent of approximately one micronized particle to each carrier particle. The values of tablet content CV of 2·7 and 4·3% (Table 3) indicate that homogeneous mixtures were still achieved at this high dilution, although the skewness (t_s) value was significantly positive for one batch. From Table 6, a 100 mg tablet containing 1 μg of model drug, will contain approximately 3·1 × 10^4 adhesion units, with a micronized to carrier particle ratio of 1 : 1 (assuming <75 μm lactose excluded). A 15% increase in dosage occurs if an extra 4650 micronized salicylic acid particles are contained in a tablet. If this were caused by a single entity, assuming a density of 0·7 g cm^{-3}, this would constitute an agglomerate of salicylic acid of 75 μm diameter. A similar calculation has been presented by Egermann (1982) to demonstrate the usefulness of sieving drug-diluent premixes to prevent superpotent tablets.

CONCLUSION

The distribution of micronized model drug adhering to different sized carrier particles was found to be independent of mixture concentration in the range 0·1–2·0%. Calculations for a theoretical interactive mixture revealed that micronized salicylic acid adhered to the coarser carrier particles to a greater extent than a simple surface area calculation would predict. The calculation also showed that in the most dilute mixtures (1 : 100 000), the micronized to carrier particle ratio was approximately 1 : 1.

The low concentration interactive mixtures (0·001–0·03%) were relatively unstable, between 15 and 35% of the micronized model drug transferred to the surface of the metal sieve during 5 min vibration. In contrast, the granulated interactive mixtures were stable at all concentrations. Compression of the granules, during which no adhesion unit or constituent segregation occurred, realized the true potential of interactive mixing.

Batches of tablets (dosage 1 μg–2 mg), showing very good content uniformity, were compressed from granulated 0·001–2% interactive mixtures. All samples of 100 tablets had a content CV <5% with 99% confidence and met the content uniformity specification of the United States Pharmacopeia XXI, providing the measured mean content was taken to be the label strength required. This assumption is necessary as USP XXI measures the deviation

from the label strength, not about the actual sample mean. In this work, no target (label) content was set for each batch of tablets. When the tablet content was expressed by proportion, significant positive skewness in three of the nine batches indicated the presence of one or two tablets containing small agglomerates of particles of the micronized component. This indicates the cube mixer does not completely disperse the cohesive salicylic acid as individual particles during the interactive mixing operation (5 h duration).

A balance must be struck between the clinical and statistical significance of these results. All batches produced in this study met the ±15% specification, indicating the batches probably contained no super-potent tablets likely to cause overdoses of clinical significance. However, a positively skewed content (proportion) distribution indicates that micronized salicylic acid is not being completely dispersed. The actual sample taken is unlikely to contain the tablet with the highest proportion (i.e. largest agglomerate of minor component) and so positive skewness must be taken as a warning that a potentially dangerous situation may exist with respect to the mixing process.

The processing method described produces homogeneous granules, containing small quantities of micronized materials, which are very resistant to the effects of segregation. The two stage process used ensures the cohesive component is uniformly mixed with the excipient, by formation of an interactive mixture, before granulation. Homogeneity problems caused by differential solubility and hydrophobicity are avoided. The fluidized bed is an efficient mixer for randomizing and granulating the preformed adhesion units, thereby preventing adhesion unit and constituent segregation occurring during compression. It may be possible to use other methods, such as mixing at 0% r.h. (Thiel & Stephenson 1982) or triboelectrification (Staniforth & Rees 1982), to achieve similar results with lower processing costs.

This investigation is the first to attempt to quantify the degree of content skewness in dosage units produced from interactive mixtures. The results obtained sound a note of caution when applying interactive mixing to microdose preparations. In addition to the adverse effects of adhesion unit and constituent segregation, the mixer selected must be able to disperse totally the cohesive component during interactive mixing. To establish this requires large numbers of individual assays to be performed.

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