J. Pharm. Pharmac., 1974, **26**, 298–303 *Received November* 19, 1973

Powder mixing in the tableting of fenfluramine hydrochloride; evaluation of a mixer

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A vertical cone mixer has been used to mix a single active component, fenfluramine hydrochloride, with a number of diluents used for production batch-scale tablet preparation. The mixing operation was followed by the analysis of fenfluramine hydrochloride in a number of samples equivalent to the final tablet size. The results may be suitably analysed by treating the diluent materials as a single component in a binary mixture.

Considerable literature is now available on the theory and practice of powder mixing. The completely randomized system has been evaluated for simple single sized particles (Lacey, 1943), for particle size distributions (Stange, 1954; Buslik, 1950) and for multicomponent systems (Stange, 1963; Harnby, 1967a). However, there are still various criteria of homogeneity, index of mixing or "degree of mixedness" applied to the analysis of a single mixing operation (Valentin, 1967; Hersey, 1967; Buslik, 1973).

Most of the reported work has used simple binary systems and frequently, the results were obtained using laboratory or pilot-scale equipment. We have examined an actual tablet blend at the production size level, and even though it consisted of many different materials, it was decided to analyse the results as a binary system, in which the diluent materials were grouped as a single component.

A mixer† that has the capability of both dry and wet mixing and that has found wide use (Harnby, 1967b; Williams & Khan, 1973), although not pharmaceutically, was considered suitable since it could be usefully employed for tablet formulations involving dry blending and granulation operations. The capability of the mixer for producing a suitable multicomponent blend meeting pharmaceutical requirements in production conditions has therefore been evaluated.

METHODS

A dispersion containing approximately 20% fenfluramine hydrochloride in standard tablet diluents (starch 20, sucrose 30, lactose 30% and a small quantity of tragacanth) was chosen for the evaluation. The mixer is a verticle cone mixer with a rotating orbital screw having a horizontal sliding discharge port and no bottom bearing to facilitate discharge without subsequent segregation.

The materials were subjected to particle size analysis using a Pascall sifter. The reproducibility of the sieving operation was ±2% from 36–60 mesh and ±5% for

An abstract of this paper was given at the F.I.P. Meeting, Stockholm, September 3rd–7th, 1973.

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† Nauta DX600 with 600 litre capacity.

smaller particle size fractions. Their densities were either determined using liquid displacement or air displacement (Beckman air comparison pycnometer) or taken from the literature. Measured density values compared to within $\pm 0{\cdot}1$ of the literature values, which were also measured using the air-pycnometer.

The materials were loaded into the mixer in such a way as to locate the fenfluramine hydrochloride in a horizontal layer in the middle of a total load of approximately 300 kg. The rotating screw of the mixer was operated in the lift orientation and twenty samples (nominal sample size 100 mg, equivalent to tablet weight) were removed at each of 1, 5, 10, 20, 50 and 100 min during the preliminary dry mix operation. Two concentric cylinder sample thieves were used for this. The longer thief sampled randomly from ten positions at the apex of the cone, whilst the shorter thief was used to sample ten positions randomly at the base of the cone.

A wet mixing operation was undertaken on the mix with the addition of approximately 27 litres of water over 20 min and mixing continued for a further 40 min. The screw was maintained in a lift orientation throughout the kneading process. No samples were removed during the wet mixing operation. The mass was discharged under gravity, granulated using a Colton Wet Extruder and tray-dried at 120° F for 18 h.

The mixer was then reloaded with the granule and lubricants and a final blend carried out. During this period 30 samples were taken at 2, 7 and 15 min.

The mixed granules were then compressed on a Manesty tablet machine (Type BB3A operating at 1000 tablets min^{-1}) and thirty single samples were taken at fixed time intervals to represent the whole of the batch and assayed spectrophotometrically at 265 nm for fenfluramine hydrochloride content.

RESULTS

The particle size results are recorded in Table 1. From the density figures for fenfluramine hydrochloride of 1·23 g cm^{-3} (determined using the Beckman pycnometer), for lactose of 1·55 g cm^{-3} (from Thurn, Soliva & Speiser, 1971), for starch, sucrose and tragacanth of 1·49, 1·66 and 1·55 g cm^{-3} respectively (liquid displacement

Table 1. *Particle size classification of ingredients determined by Pascall sifter.*

B.S.S. sieve size	Sieve aperture μm	Mean particle size	% retained on sieve				
			Fenfluramine HCl	Lactose	Starch	Sucrose	Tragacanth
36	420		0	0	0	0	0
		388					
44	355		0·9	0·1	0	0	0
		303					
60	250		0·9	0	0	6·0	0
		220					
90	190		0·9	0·4	0	2·1	0
		170					
100	150		0·9	0·4	0·2	4·9	0
		113					
200	75		21·8	49·2	2·4	31·2	17·0
		64					
300	53		70·0	29·9	46·8	37·2	40·0
		27					
<300	0		4·6	20·0	50·6	18·6	43·0

Table 2. *Effective mean weight of fenfluramine hydrochloride.*

Sieve aperture μm	Mean size μm	Particle wt μg	Mean wt w μg	Wt fraction undersize	Range fraction f	fw μg
420		47·73		1·000		
	388		42·68		0·009	0·38
355		37·63		0·991		
	303		27·78		0·009	0·25
250		17·92		0·982		
	220		12·39		0·009	0·11
190		6·86		0·973		
	170		5·02		0·009	0·05
150		3·17		0·964		
	113		2·05		0·218	0·45
75		0·93		0·746		
	64		0·55		0·700	0·39
53		0·17		0·046		
	27		0·09		0·046	0·01
0		0·0		0·000		

$\Sigma(fw) = 1{\cdot}64$ μg

method), the effective mean weights of the fenfluramine hydrochloride (Table 2) and of the other components (Table 3), estimated as a single constituent (Table 4), were calculated by the method of Stange (1954) as modified by Poole, Taylor & Wall (1964). Since there is only one active material in the preparation, the data were treated as a binary mixture. The diluents were thus grouped together with allowances for particle weight contributions from each size fraction of each of the diluents used (Table 3). The theoretical standard deviation for the completely randomized mixture (σ_R) was calculated from the expression of Lacey (1943):

$$\sigma_R = (xy/N)^{0.5}$$

where x is the proportion of fenfluramine hydrochloride, y is the proportion of the combined diluents, and N is the number of particles per sample weight (100 mg). N was calculated from the expression of Poole & others (1964):

$$N = \frac{\text{Sample weight}}{x.\Sigma(fw)_y + y.\Sigma(fw)_x}$$

Table 3. *Combination of diluents to a single component.*

	% of total material in each size range				
Sieve aperture μm	Lactose	Starch	Sucrose	Tragacanth	Combined
420	0	0	0	0	0
315	0·03	0	0	0	0
250	0	0	2·33	0	2·3
190	0·13	0	0·82	0	1·0
150	0·13	0·06	1·91	0	2·1
75	16·33	0·66	12·14	0·07	29·3
53	9·93	12·87	14·47	0·16	37·4
0	6·64	13·92	7·24	0·17	28·0
Proportional composition	0·33	0·28	0·39	0·004	1·00
Density contribution	0·515	0·410	0·646	0·006	1·58

where Σ(fw) is the effective mean particle weight of fenfluramine, x, and the combined diluents, y.

$$N = \frac{100 \times 10^3}{0{\cdot}216 \times 2{\cdot}19 + 0{\cdot}784 \times 1{\cdot}64}$$

$$= 5{\cdot}69 \times 10^4 \text{ particles}$$

thus $\sigma_R = 0{\cdot}00173$

The standard deviation, s, for the amount of fenfluramine hydrochloride in each group of samples taken from the mixing was then calculated. The ratio of s/σ_R was used to demonstrate the mixing achieved during the preliminary dry blending operation. Subsequent processing involves particle size changes due to solubilization and grinding and the addition of a small quantity of lubricant. These changes are not easily followed and allowance for them has not been made in the value of σ_R used to evaluate the mixing achieved during the final blending and tableting operations. Fig. 1 includes an indication of the necessary standard deviation to comply with possible limits allowable on content uniformity. Assuming these to be $\pm 15\%$ for at least 95% of the samples for a normal distribution (as might be taken from the U.S.P. XVIII), then

$$\pm 1{\cdot}96\ \sigma_A = \pm 0{\cdot}20 \times 0{\cdot}15$$

thus $\frac{\sigma_A}{\sigma_R} = 8{\cdot}85$

Similarly a more strict, within manufacturer control might exist such that limits of $\pm 10\%$ are imposed for 99·7% of the results for a normal distribution, then

$$\pm 3\ \sigma_B = \pm 0{\cdot}20 \times 0{\cdot}10$$

and $\frac{\sigma_B}{\sigma_R} = 3{\cdot}85.$

Table 4. *Effective mean weight of the combined diluents.*

Sieve aperture μm	Mean size μm	Particle wt μm	Mean wt w μg	wt fraction undersize	Range fraction f	fw μg
420		61·32		1·000		
	388		54·83		0·000	0·00
355		48·34		1·000		
	303		35·69		0·023	0·82
250		23·03		0·977		
	220		15·92		0·010	0·16
190		8·81		0·967		
	170		6·44		0·021	0·14
150		4·07		0·946		
	113		2·63		0·292	0·77
75		1·19		0·654		
	64		0·71		0·374	0·27
53		0·22		0·280		
	27		0·12		0·280	0·03
0		0·00		0·000		

Σ(fw) = 2·19 μg

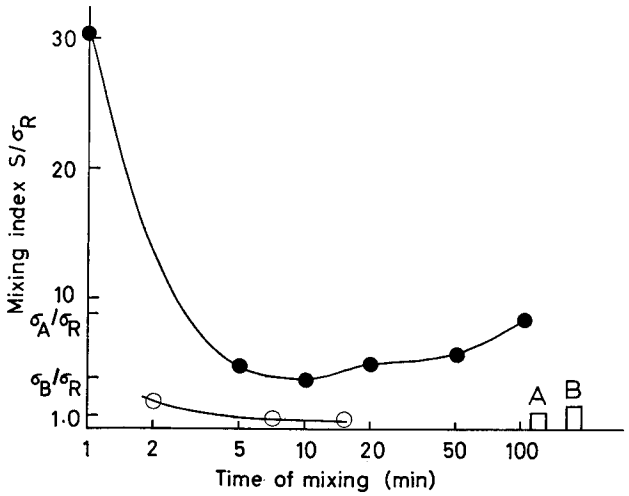

FIG. 1. Mixing of fenfluramine hydrochloride. ● preliminary ingredient blending; ○ final blending. A, content uniformity of tablets produced (based on 100 mg tablet weight, excluding weight variation). B, overall content uniformity of tablets produced (based on actual tablet weights). When $s/\sigma_R = 1{\cdot}0$ mixing to theoretical completely randomized system has been achieved. $s/\sigma_R = \sigma_A/\sigma_R$ mixing to pharmacopoeial specification has been achieved. $s/\sigma_R = \sigma_B/\sigma_R$ mixing to the manufacturer's specification has been achieved.

The presence of these values in Fig. 1 is a useful indication of when these two criteria are obeyed during the mixing operation and is extremely useful for the evaluation of the mixer with respect to its practical performance.

DISCUSSION

Mixing of the preblend is sufficient to satisfy the pharmacopoeia requirements of σ_A given above and, after approximately 10 min, reaches an optimum mixing condition at the within manufacturer control level. Subsequent mixing causes a partial segregation of the components.

The difference between the preblend and final blend curves may be attributed to the wet mixing, extrusion and drying stages (granulation operation) as well as to the addition of lubricant. It is evident that the granulation operation causes a significant degree of mixing in the process under consideration. This may be due to a variety of factors including the solubility of the fenfluramine hydrochloride and some of the excipients in the aqueous granulating solution, and the further solubility and possible size reduction achieved on drying.

During the final blending, the optimum mixing condition was again attained after some 10 min, when the mixture obtained appeared to be better than that which is theoretically possible on the basis of the calculation of the completely randomized mixture. This may be accounted for by a change of particle size, resulting in an increased number of particles, which occurs during the mixing operation, notably at the wet mixing stage. Other contributing factors are the addition of lubricants and the fact that during granulation and dry blending with the lubricants some degree of ordered mixing may have taken place.

As observed by Tawashi & Speiser (1964), subsequent processing, e.g. tableting, results in some degree of segregation. Since tablets vary not only in content but

also in weight, the overall dose variation will be larger than that suggested by actual content uniformity (based on 100 mg tablet). This may be expressed by

$$E_o^2 = E_c^2 + E_w^2$$

assuming analytical errors to be negligible where E_o^2 = overall dose variance; E_c^2 = variance due to content uniformity;
E_w^2 = variance due to weight uniformity.
This mixer is evidently well suited to the mixing of this tablet preblend and for the final blending with tablet lubricant, since it is both rapid and produces a mixture well within specifications for content uniformity.

Acknowledgements

We wish to acknowledge the assistance of Mr. M. Smyth, Control Manager of D.H.A. and his staff, who carried out the sample analyses, the sieve analysis and some of the density determinations used in this work. We also wish to thank C.S.I.R.O., Division of Applied Chemistry, for the loan of the Beckman air-comparison pycnometer.

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