J. Pharm. Pharmac., 1978, **30**, 401–406 *Received January* 16, 1978

Multiple-scored tablets. Weight and content uniformity of subdivisions and the distribution of active constituent within and between tablets

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Using three brands of multiple-scored levodopa tablets B.P. (500 mg) and one brand of sulphamethoxypyridazine tablets B.P. (500 mg) the weight and content uniformity of the subdivisions has been examined. It is shown that quartering of such tablets can result in sub-units which do not conform to recognized standards of weight uniformity, and in some instances content uniformity may be questionable. The homogeneity of distribution of active constituent between tablets has been determined and compared with that within tablets (between quarters of individual tablets). Statistical evaluation of the results is presented.

The validity of the assumption that a tablet with a double breakline can be subdivided into two or four equal portions and that the active constituent is uniformly distributed within the tablet has been questioned (Arnold, 1973; Nash, 1973). Between-tablet dose variation and its control has attracted increasing attention (Smith, Michaels & others, 1963; Lachman & Sylwestrowicz, 1964; Cook & Hersey, 1974; Selkirk, 1974), culminating in the introduction of single-tablet assays into official monographs, with concomitant standards for content uniformity. (U.S.P. XIX. B.P. 1973). The problem of within-tablet variation does not appear to have been examined in depth within the context of the present discussion, apart from one report (Colombo, 1975), which showed that a sample of scored tablets, when hand-broken, did not provide half-tablets conforming to the uniformity of weight specifications for single-dose tablets of the Italian Pharmacopoeia (the median weight variation was $\pm 7\frac{1}{2}\%$). While such variation will usually be small and likely to be outweighed by other variables, if recommendations for the use of multiple-scored tablets are based on assumptions of homogeneity, it is not unreasonable to expect the resulting tablet fractions to conform to the same standards for weight and content uniformity as are applicable to a single-dose tablet of identical strength. We have examined these aspects of tablet uniformity.

Three proprietary brands of levodopa tablets 500 mg (A, B, C) and one brand of sulphamethoxypyridazine tablets 500 mg (D) were chosen for a preliminary study, each brand consisting of multiple-scored tablets for sub-division into halves or quarters. The average weights from samples of 20 tablets of A, B, C and D were 756·8, 743·1, 772 and 605·3 mg per tablet respectively. Using a sample of 10 tablets from each batch, the content of active constituents per quarter tablet was determined, the content per tablet being obtained from the sum of the contents of its quarters. The results have been expressed in two ways: as the weight of active constituent per unit-dose form (tablet or quarter-tablet) giving the actual dose available and also as a percentage of the weight of powdered tablet material, which indicates the extent of inhomogeneity in distribution of active constituent between and within tablets. Statistical evaluation of the data for each brand indicates the significance or otherwise of the observed differences within (between quarters) and between tablets.

Because of the large number of determinations involved, a spectrophotometric assay was chosen for reasons of simplicity and rapidity. As far as possible each tablet was divided uniformly into the quarters delineated by the scoring by a simple apparatus (see Fig. 1) consisting of two mounted steel blades, the upper blade being attached to a toggle press. A weighed tablet was placed on the lower blade with scoring uppermost, held in position and the upper blade then lowered into a groove, when the pressure was increased, breaking the tablet cleanly. The process was repeated with the separated halves to obtain the quarters. The quarters were then weighed, the sum of their weights subtracted from the weight of the original tablet giving the loss as 'fines' on cutting (Table 1, column 4). As such a method of subdivision is unlikely to be achieved in practice four colleagues were each given four weighed tablets

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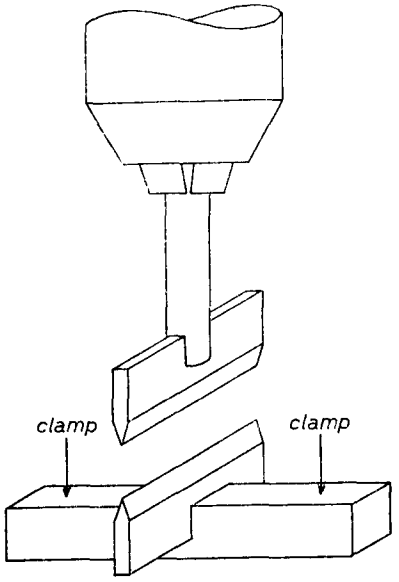

FIG. 1. Cutting apparatus for scored tablets.

of each brand and asked to break them into quarters, which were then weighed. These results are summarized in Table 1, columns 5, 6, and Table 3.

MATERIALS AND METHOD

A spectrophotometric method for the determination of levodopa has been reported (Nedergaard, 1970). Preliminary experiments were performed to select a suitable solvent and to determine conditions for complete extraction of the active constituents from the tablet material. Reference samples of levodopa B.P. and sulphamethoxypyridazine B.P. were dried at 105° for 3 h and used to obtain the following data.

Levodopa 0·003% w/v solution in 0·1 M HCl. Absorption maximum 280 nm. Beer's Law was obeyed over the concentration range 0·001–0·01% w/v (0·1 M HCl) A (1%, 1 cm) 135 (Nedergaard (1970) reports A (1%, 1 cm) 190 at 278 nm.

Sulphamethoxypyridazine 0·001% w/v solution in ethanol. Absorption maximum 270 nm. Beer's Law was obeyed over the concentration range 0·0002–0·001% w/v (ethanol). A (1%, 1 cm) 767.

In each case the presence of interfering impurities in the tablet extracts was tested for by comparing (a) the absorbance ratio at two selected wavelengths for solutions of the pure substances and tablet extracts; (b) a plot of the absorbance difference between two selected wavelengths *vs* concentration for solutions of the pure substances and tablet extracts: no significant amounts of interfering substances were detected by either method.

Tablet assays

Twenty tablets were selected at random from each batch and examined for uniformity of weight (B.P. 1973) (Table 1). From these, ten tablets of each brand were again randomly selected and each tablet was weighed, and cut into quarters. Each quarter was

Table 1. *Uniformity of weight and content of levodopa and sulphamethoxypyridazine tablets (500 mg).*

Tablet	Uniformity of weight: S^2 Whole tablets[a] 20 (10)	S Whole tablets[a] 20 (10)	CV* Quarters 40	F^{39}_{9} (2·83)[b] $P = 0·05$	Mean loss % on quartering 10 tablets	No. of quarters within indicated percentages of mean weight[c]: ±7½–12½%	>±12½%	Uniformity of content of cut quarters (40)[d]: ±5 and 7½%	±7½ and 10%	±10 and 12½%	>±12½%
Levodopa A	31·7 (30·61)	±5·63 (5·53) mg	84·53 ±9·19 mg	$\frac{84·53}{30·61}$ · 2·76	0·35	5 [14] 12½% [22%]	— [23] [36%]	13 (13) 32½%	1 (2) 2½% (5%)	2 (2) 5%	1 (1) 2½%
	0·74 (0·73)%		4·88%								
B	30·03 (18·13)	±5·48 (4·26) mg	22·35 ±4·73 mg	$\frac{22·35}{18·13}$ · 1·23	0·43	1 [20] 2½% [31%]	— [25] [39%]	— (8) (20%)	1 2½%	—	— — — —
	0·74 (0·59) %		2·55%								
C	26·52 (27·61)	±5·15 (5·25) mg	108·2 ±10·4 mg	$\frac{108·2}{27·64}$ · 3·91	0·69	7 [13] 17½% [20%]	— [23] [36%]	7 6 17½% (15%)	4 (8) 10% (20%)	3 (2) 7½% (5%)	— (1) (2½%)
	0·67 (0·68)%		5·42%								
Sulphamethoxy pyridazine D	65·29 (40·63)	±8·08 (6·37) mg	153·41 ±12·39 mg	$\frac{153·41}{40·63}$ · 3·77	0·04	8 [16] 20% [25%]	6 [23] 15% [36%]	6 (6) 15%	2 (5) 5% (12½%)	2 (3) 5% (7½%)	9 (6) 22½% (15%)
	1·3 (1·5)%		8·13%								

(a) Figures in parentheses are corresponding data for the 10 tablets subsequently quartered and assayed.
(b) Upper significance limit (Snedecor).
(c) Figures in parentheses indicate number of hand-broken quarters falling within ranges indicated. Total number of cut quarters, 40; broken quarters, 64.
(d) These columns give numbers and percentages of cut quarters within the indicated percentage deviations from the mean content. Figures in parentheses are the numbers deviating from the stated content (125 mg per quarter).

* Abbreviations: variance, S^2; standard deviation, S; coefficient of variation, CV; variance ratio, F; analysis of variance, anovar; $P = 0·05$.

weighed, the difference between the weight of the whole tablet and the sum of the weights of the quarters giving the loss as 'fines' on cutting. Each quarter was then powdered and the content of active constituent (Table 2) determined as follows.

Tablets A, B, C (levodopa). Two replicates of about 80 mg of powdered tablet (equivalent to approximately 50 mg levodopa) were weighed from each quarter, transferred to 100 ml volumetric flasks, shaken (15 min) with 0·1M HCl (25 ml) and adjusted to volume with the same solvent. The resulting solutions were filtered and 10 ml aliquots diluted to 100 ml with 0·1 M HCl. The absorbances were measured at 280 nm (0·1 M HCl in reference cell) and the content of levodopa per quarter-tablet calculated [A (1%, 1 cm) 135].

Tablets D (sulphamethoxypyridazine). Two replicates of about 50 mg (equivalent to approximately 40 mg sulphamethoxypyridazine) were weighed from each quarter, transferred to 100 ml volumetric flasks, shaken (20 min) with spectroscopic grade ethanol (80 ml) adjusted to volume with the same solvent and filtered. Two further dilutions of each replicate were made, 10-fold and 5-fold, the absorbances measured at 270 nm (ethanol in reference cell) and the sulphamethoxypyridazine content per quarter-tablet calculated [A (1%, 1 cm) 767].

For each brand, the content of active ingredient per tablet was taken as the sum of the contents of the constituent quarters. With tablets A, B and C, a correction was made for the loss in 'fines'; with tablets D, since the loss due to this source was negligible (mean loss per tablet 0·04%) this correction was not made.

RESULTS AND DISCUSSION

Uniformity of weight and content

All four tablet batches conformed to the B.P. standards for uniformity of weight (Table 1) and of the 10-tablet samples taken for assay, that for batch D gave one tablet with a *content* of sulphamethoxypyridazine outside the range of ±5% of the *stated* quantity of 500 mg.

Quarter tablets gave different results. When 10 tablets from each batch were cut by the method described, a large proportion of the quarters were outside acceptable limits for uniformity of weight; with tablets broken by hand the non-uniformity was more marked. The distribution of quarters outside acceptable limits is summarized in Table 1, along with the numbers in each sample deviating from both the *mean* and the stated content (125 mg). Brand B proved to be the most satisfactory in uniformity of weight of cut quarters, only one of 40 being outside the limits of ±7½% of the mean weight. Although only one quarter in this batch had a *content* of active constituent more than 7½% in excess of the mean content, eight of these quarters were outside a limit of ±5% of what must be regarded as the stated content, i.e. 125 mg. Batches A, C and D all gave a greater number of cut quarters with deviant contents; of the nine quarters of tables D outside the

Table 2. *Statistical data. Content distribution between and within tablets.*

	Constituent average contents, S*, S, CV‡				F† ($P = 0.05$)		Within tablet and between tablets anovar F† ($P = 0.05$)		
	Whole tablets (10)		Quarter tablets (40)						
	Content (mg)	Content %	Content (mg)	Content %	Constituent content (mg)	Constituent content %	Wt. of tablet	Wt. of active constituent	Percentage of active constituent
Levodopa A	501* 31·95 ±5·65 mg 1·13%	66·1* 0·17 ±0·41% 0·62%	124·8 50·175 ±7·08 mg 5·67%	66·1 2·15 ±1·47% 2·22%	$F^{39}/_{9}$ $\frac{50{\cdot}175}{31{\cdot}95} \cdot 1{\cdot}57$	$F^{39}/_{9}$ $\frac{2{\cdot}15}{0{\cdot}17} \cdot 12{\cdot}65$	$F^{30}/_{9}$ $\frac{107{\cdot}3}{7{\cdot}33} \cdot 14{\cdot}64$	$F^{30}/_{9}$ $\frac{62{\cdot}96}{7{\cdot}72} \cdot 8{\cdot}14$	$F^{30}/_{9}$ $\frac{2{\cdot}58}{0{\cdot}66} \cdot 3{\cdot}89$
B	487·8* 14·135 ±3·76 mg 0·77%	65·6* 0·22 ±0·46% 0·71%	121·5* 9·60 ±3·1 mg 2·55%	65·6 0·49 ±0·70% 1·07%	$F^{9}/_{39}$ $\frac{14{\cdot}135}{9{\cdot}61} \cdot 1{\cdot}47$	$F^{39}/_{9}$ $\frac{0{\cdot}49}{0{\cdot}22} \cdot 2{\cdot}22$	$F^{30}/_{9}$ $\frac{52{\cdot}28}{4{\cdot}28} \cdot 12{\cdot}20$	$F^{30}/_{9}$ $\frac{11{\cdot}5}{3{\cdot}1} \cdot 3{\cdot}77$	$F^{9}/_{30}$ $\frac{0{\cdot}88}{0{\cdot}37} \cdot 2{\cdot}36$
C	489·5* 17·0 ±4·12 mg 0·84%	63·4* 0·18 ±0·43% 0·68%	121·5 42·53 ±6·51 mg 5·36%	63·4 0·41 ±0·64% 1·01%	$F^{39}/_{9}$ $\frac{42{\cdot}43}{17} \cdot 2{\cdot}5$	$F^{39}/_{9}$ $\frac{0{\cdot}41}{0{\cdot}184} \cdot 2{\cdot}23$	$F^{30}/_{9}$ $\frac{136{\cdot}14}{4{\cdot}83} \cdot 28{\cdot}19$	$F^{30}/_{9}$ $\frac{53{\cdot}9}{2{\cdot}9} \cdot 18{\cdot}67$	$F^{9}/_{30}$ $\frac{0{\cdot}72}{0{\cdot}36} \cdot 1{\cdot}98$
Sulphamethoxypyridazine D	488·1 74·45 ±8·6 mg 1·76%	80·1 2·72 ±1·65% 2·06%	122·0 113·54 ±10·65 mg 8·73%	80·1 3·73 ±1·93% 2·41%	$F^{39}/_{9}$ $\frac{113{\cdot}5}{74{\cdot}45} \cdot 1{\cdot}53$	$F^{39}/_{9}$ $\frac{3{\cdot}73}{2{\cdot}72} \cdot 1{\cdot}37$	$F^{30}/_{9}$ $\frac{199{\cdot}4}{10{\cdot}2} \cdot 19{\cdot}53$	$F^{30}/_{9}$ $\frac{141{\cdot}8}{19{\cdot}1} \cdot 7{\cdot}44$	$F^{9}/_{30}$ $\frac{11{\cdot}0}{0{\cdot}97} \cdot 11{\cdot}33$

* Corrected for loss as 'fines' on quartering.
† Upper Significance Limits (Snedecor). $F^{39}/_{9}$ 2·83; $F^{9}/_{39}$ 2·13; $F^{30}/_{9}$ 2·86; $F^{9}/_{30}$ 2·21.
‡ Abbreviations as for Table 1.

$\pm 12\frac{1}{2}\%$ limit, four contained less than 85% of the stated content, which would put them at the limits of conformity with U.S.P. requirements for single tablet assays. Table 2 summarizes some statistical data on the results.

Tablets A

There is no significant difference in the variation of weight [F_9^{39} 2·76 (2·83)] or of content [F_9^{39}, 1·57(2·83)] between tablets and quarters considered as individual dose units, whereas the difference in content expressed as a percentage of the tablet material is significantly greater for the quarters [F_9^{39} 12·65 (2·83)]. An analysis of variance showed that in terms of weight, content and percentage [F_9^{30} 14·64, 8·14 and 3·89 (2·86) respectively] the within-tablet variation (i.e. between the quarters of individual tablets) was significantly greater than the between-tablet variation. The agreement between weight and content is to be expected and the variation in percentage persists in the analysis of variance data, implying differences in homogeneity of the matrix between and within the tablets.

Tablets B

The sample of these tablets shows no significant difference in the variation of weight, content or percentage between tablets and quarters considered as individual dose units [F_9^{39} 1·23 (2·83), F_{39}^{9} 1·47 (2·13), F_9^{39} 2·22 (2·83) respectively]. An analysis of variance showed that the variations in weight and content of broken tablets were significantly greater than the corresponding variations between tablets [F_9^{30} 12·20, 3·77 (2·86)] whereas the variation in percentage between tablets was significantly greater than that within the tablets (i.e. between individual quarters of a tablet). [F_{30}^{9} 2·36 (2·22)]. An estimate of the between-tablet variance components was calculated as 0·135, in reasonable agreement with the value of 0·22 previously calculated for the whole tablet.

Tablets C

This sample showed a significantly greater variation in weight between quarters compared with whole tablets considered as individual dose units, whereas in terms of content and percentage there was no significant difference [F_9^{39} 3·91, 2·5, 2·23 (2·83) respectively]. Analysis of variance reflected this pattern in weight differences within and between tablets [F_9^{30} 28·19 (2·86)] and also revealed a significantly greater difference in the variation of content within as compared with that between tablets [F_9^{30} 18·67 (2·86)] despite non-significant differences in the percentages of active constituent within and between tablets [F_{30}^{9} 1·98 (2·21)], indicating homogeneity of distribution. These results show a serious lack of uniformity between quarters of individual tablets, due to failure of the cutting process to produce uniform quarters. Of the 40 quarters produced by cutting, 7 ($17\frac{1}{2}\%$) were outside the limits of $\pm 7\frac{1}{2}\%$ of the mean weight (Table 1). Excessive friability or variation in density of the tablet material could be contributory factors, as indicated by the observation that this brand provided the greatest loss as 'fines' on quartering (0·69% Table 1) and on hand-breaking (15·6% Table 3).

Tablets D (sulphamethoxypyridazine)

As with batch C, these tablets showed a significantly greater variation in weight between quarters compared with the variation between whole tablets, considered as individual dose-units. [F_9^{39} 3·77 (2·83)] with no signficant difference in the variation between quarters and tablets with respect to content and percentage [F_9^{39} 1·53, 1·37 (2·83) respectively]. Here again, analyses of variance revealed highly significant differences in the within-tablet and betweeen-tablet variation in terms of uniformity of weight and content [F_9^{30} 19·53, 7·44 (2·83) respectively]. Also in terms of percentage, the between-tablet variation was significantly greater than the within-tablet variation. [F_{30}^{9} 11·33 (2·21)], indicating a highly uniform distribution of active constituent within individual tablets compared with the distribution between tablets. Also, despite the very small loss in 'fines' compared with tablets A, B and C (mean losses: 0·04% on cutting. Table 1; 0·72% on breaking, Table 3), it is still evident that uniform 'quarters' cannot be produced even with the aid of a mechanical device.

Hand-breaking of tablets

When the tablets were broken by hand, the resulting 'quarters', despite the score-marks to facilitate breaking, lay far outside B.P. limits for uniformity of weight for whole tablets of equivalent weight (Table 1). Table 3 gives further data on the 64 quarters obtained by hand-breaking of four tablets of each brand by four different persons. The results show some inter-brand variation. Tablets C were more friable than either of the other two brands with the same content, or the sulphamethoxypyridazine (D). The latter showed the least overall loss in fines both on breaking and cutting. Whether this was due to the difference in constituent or to the manufacturing process or, as is more probable, to a combination of both, cannot be decided at this stage.

Table 3. *Hand breaking of tablets.*

Quantities measured	Tablets															
	A Breaker				B Breaker				C Breaker				D Breaker			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
$\bar{X}$, mg	188·95	190·4	186·0	187·4	183·2	184·3	185·0	180·2	190·4	190·05	190	190·2	150·9	149·0	148·8	150·6
S ± mg	33·8	21·3	24·7	26·1	32·65	30·74	37·6	18·2	24·5	38·3	35·2	31·1	18·1	30·1	18·75	25·7
CV%	17·9	11·2	13·3	16·6	17·5	16·6	20·3	10·1	12·9	20·15	18·5	16·35	12·0	20·2	12·6	17·1
Overall																
$\bar{X}$ mg	188·3				183·2				190·2				151·85			
S ± mg	27·8				29·7				32·3				23·2			
CV%	14·75				16·2				17·0				15·3			
Mean losses 'fines'	8·6 mg 4·6%				10·2 mg 5·6%				29·6 mg 15·6%				1·1 mg 0·72%			

Also, despite this apparent advantage, tablets D could not be regarded as superior to the other brands in producing uniform quarters.

Summary and conclusions

The multiple-scored tablets examined conformed to recognized standards for uniformity of weight and content. Subdivision of these either by hand or a mechanical device although facilitated by the score marks, did not result in sub-units of acceptable standards in uniformity of weight, and with at least one example conformity to acceptable standards for uniformity of content was questionable.

Statistical evaluation of the results generally reflected these findings but also revealed some unexpected differences between the tablets and their quarters.

Considered as individual dose-units, tablets A and B showed no significance in the weight variation between whole tablets and cut quarters, suggesting that these tablets should be capable, under reproducible conditions, of being subdivided into acceptable quarters. With tablets C and D, however, the variation in weight between quarters was found to be significantly greater than that between tablets, despite the fact that tablets D yielded the smallest loss as fines on cutting or breaking, predisposing in favour of uniform subdivisions, whereas tablets C provided the greatest loss under similar circumstances, a characteristic which might be expected to lead to disparate sub-units. Analyses of variance, however, revealed that for all brands, the within-tablet variation (i.e. the variation between quarters of an individual tablet) was significantly greater than the between-tablet variation, confirming that in no instances were the tablets being uniformly subdivided by the cutting device.

Examination of the distribution of active constituent expressed as a weight (mg per tablet) revealed that for each brand there was no significant difference in the variation between tablets and quarters considered as individual dose-units. Again, analyses of variance showed that in each case the within-tablet variation was significatly greater than the between-tablet variation, which, assuming a uniform distribution of constituent within the tablet matrix is a corollary of the previous findings.

The content of constituent expressed as a percentage of the weight of tablet taken (i.e. a measure of the homogeneity of the tablet matrix) showed with tablets B, C and D no significant difference in the variation between tablets and quarters considered as individual dose-units, indicating a uniform tablet matrix. Rather surprisingly, tablets A showed a highly significant difference in the variation of percentage of constituent between quarters as compared with that between tablets. An analysis of variance reflected these findings implying less homogeneity of the matrix within tablets than between tablets, although without further data it would perhaps be unwise either to draw firm conclusions from this or to attempt an explanation. With tablets B and D between-tablet variation was significantly greater than the within-tablet variation (highly so with tablets D) and non-significant with tablets C. These results are consistent with homogeneity of matrix within the tablet.

Acknowledgements

We thank Roche Products Ltd and Parke Davis & Co. respectively for samples of levodopa B.P. and sulphamethoxypyridazine B.P. One of us (A.A.) thanks the British Council for a study award, during the tenure of which much of this work was performed.

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