SOME STATISTICAL ASPECTS OF THE ANALYTICAL CONTROL AND STANDARDISATION OF TABLETS

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Introduction

The problem of the standardisation of tablets has been discussed by Bandelin[1], and by Denston[2], who described many of the tests which are available. Some of the tests proposed have statistical implications which form the subject of this paper.

It is well known that tests which are of considerable use to the manufacturer may be unsuitable for incorporation in a book of standards such as the British Pharmacopœia. They may also be unsuitable for public analysts, because they work on small and not necessarily representative samples. Furthermore, each test must be so designed that it is not too difficult for the manufacturer to produce batches of tablets complying with the requirements, while adequately protecting the interests of the consumer.

Weight Variation

The function of the test for weight variation is to maintain a suitable standard of elegance, and to ensure accurate doses since provided that the granules are uniform[3], the weight of active ingredient will be directly proportional to the weight of the tablet[4]. Two factors have to be considered: (i) Gross errors, not normally distributed, due to variation in the setting of the machine, mixing of batches, etc. (ii) Small errors, probably normally distributed, due to irregular filling of the die, separation of granules in the hopper, and slackness of the compressing machinery.

The desirable criteria are therefore that no tablets in a batch shall vary from the mean weight by more than (say) 10 or 20 per cent., and that the variation shall be limited within (say) $\pm$ 5 per cent.

(*a*) *Tests based on Standard Deviation*

The most obvious test would be a specification of the permitted standard deviation or coefficient of variation of weight. This is the method of the Swedish Pharmacopœia, which states that "the variation in the weight of tablets of the same production batch shall not be greater than that corresponding to a relative standard deviation of 4·5 for uncoated tablets and 6·5 for coated tablets" (*cf.* Denston[2]).

There is a limited amount of data in the literature[4–6] on the coefficients of variation of weights of normal production batches. A graph which relates coefficient of variation and mean weight shows a rapid increase in the coefficient of variation for tablets weighing less than about 150 mg. (see Fig. 1). That is, small tablets show a greater amount of variation in relation to their weight than large tablets.

An improvement on the Swedish specification would be to vary the permitted maximum coefficient of variation according to the mean weight of the tablets. A suitable expression would be that "the coefficient of variation of the weights of tablets shall not exceed that corresponding to a standard deviation of 2 mg. plus 2 per cent. of the mean weight, or 0·06, whichever is the less". A line representing this maximum is included in Figure 1.

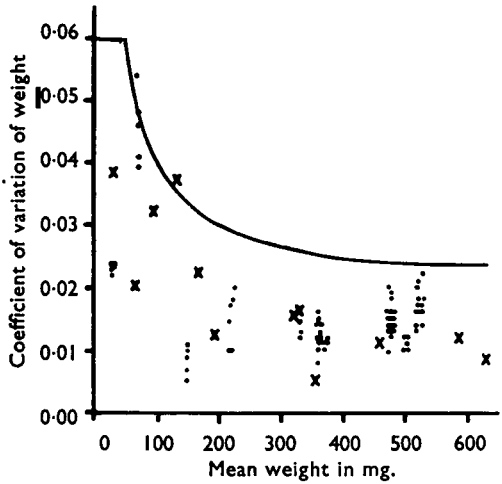

FIG. 1. Coefficients of variation of weights of production batches of tablets. × Data by Evers[4]. • Data by Dunnett and Crisafio[6]. — Suggested maximum.

It is of interest to calculate the effect on the coefficient of variation of (say) one punch out of twenty-five in a rotary compressing machine being wrongly adjusted. If σ' is the standard deviation of a mixture, in the proportion $p:(1-p)$, of two populations with means $\bar{x}_1$ and $\bar{x}_2$ respectively and the same standard deviation σ, then

$$(\sigma')^2 = \sigma^2 + p\,(1-p)\,(\bar{x}_1-\bar{x}_2)^2.$$

Consider a maladjusted machine producing 24 tablets with $\bar{x}_1 = 100$ for each tablet with $\bar{x}_2 = 105$, with $\sigma = 2$ for each population; then $\sigma' = 2{\cdot}22$. This appears to be a marked increase in the standard deviation, but allowance must be made for the errors associated with small samples. For a sample of 20 tablets, assuming normal distribution of weights, application of the t-test shows that an estimate of σ' as high as 2·22 might arise by chance 45 times in 100 even when the true value was 2·00. For $P = 0{\cdot}95$ of detecting the mixture of populations with a sample of 20 tablets, $\bar{x}_2$ would have to be at least 109 (or less than 91). That is, with a machine intended to produce tablets of mean weight 100, one punch out of twenty-five must be incorrectly adjusted to the extent of nearly 10 per cent. for there to be reasonable certainty of detecting the error by determination of the standard deviation of the weights of the tablets in a sample of twenty.

If a test based on standard deviation were introduced into the British Pharmacopœia, it would be desirable to insert a safeguard against gross variations which might not otherwise be detected. A suitable expression of this type would be that "no tablet shall vary from the mean weight by an amount greater than that corresponding to five times the permitted coefficient of variation".

The particular advantage of a test based on the estimation of the standard

deviation is the freedom it allows the analyst. The same test may be used for a sample of any size. If only a small sample (*e.g.*, five tablets) is available, then the estimate based on this small sample will be subject to wide limits of error, and the batch would be rejected only if the 0·95 (say) limits of confidence did not include the coefficient of variation permitted by the specification. The manufacturer, on the other hand, could obtain a more precise estimate of the coefficient of variation of the batch by taking a large sample (e.g., 50 or 100 tablets) or by some other more convenient method of quality control.

(*b*) *Tests based on Range*

Although the range is an inefficient estimate of the standard deviation with large samples, it is of considerable convenience for samples of not more than ten. Smith[7] has referred to its use in the control of variation of weight of tablets, and some data are given by Spengler and Schenker[8], and Beeler[9].

The ratio of the mean sample range to the standard deviation can be obtained from Tables (e.g., Table XX of Fisher and Yates[10]). Consider a batch of tablets of mean weight = 1 g. with standard deviation = 20 mg. The mean of the ranges of weights in samples of ten tablets will be about 60 mg., and a sample of ten tablets with a range of weights of 120 mg. would be so unusual as to justify rejection of the batch.

If a batch is permitted a standard deviation not exceeding σ, then a suitable upper limit to the range of weights permitted in a sample of ten tablets is 6σ, or 5σ for a sample of five tablets. Using the recommended limits of section (*a*) above, the test would read "weigh five tablets individually and calculate the mean weight. The difference in weight between the heaviest and the lightest tablets shall not exceed 10 mg. plus 10 per cent. of the mean weight, or 30 per cent. of the mean weight, whichever is the less".

This test has the advantage over (*a*) that no special skill is required in calculating the range of weights, whereas it may not be desirable to rely on the accuracy of junior staff in calculating coefficients of variation. It is particularly suited to the application of a simple form of quality control by a manufacturer during the run of a batch. Its main disadvantage is its inefficiency, and it would probably not be acceptable as the basis of an official specification, since in effect the batch is accepted or rejected according to the weights of only two tablets.

The test of the British Pharmacopœia may be regarded as including a limit to the range of weight variation. The maximum variation permitted in a sample of either ten or twenty tablets with mean weight exceeding 5 grains is 10 per cent. in one direction and 5 per cent. in the other, i.e., a range of 15 per cent. of the mean weight; for smaller tablets, the permitted range is 22·5 or 30 per cent. of the mean weight. Since the greatest variations will act in the same direction in half of the samples, the test is actually somewhat less severe than these figures suggest.

(*c*) *Tests of the B.P. Type*

The majority of pharmacopœias use a test of the form: "Of a sample of n tablets, not more than 10 per cent. shall deviate from the mean weight by more than x per cent., and no tablet shall deviate by more than $2x$ per cent." (*cf.* Dunnett and Crisafio[6]). Thus, the British Pharmacopœia takes $n = 20$ (or $n = 10$ if 20 tablets are not available) and $x = 5$, 7·5 or 10 per cent. according to the size of the tablets.

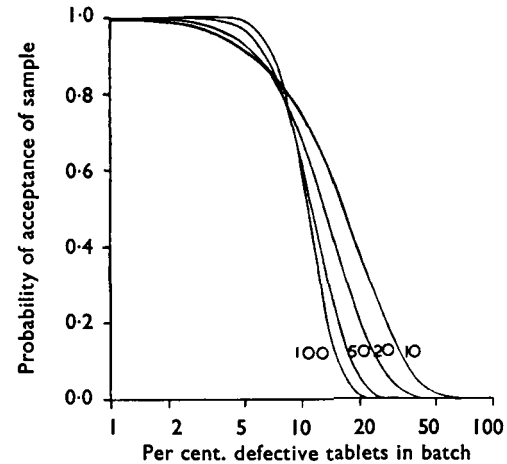

FIG. 2. Operating characteristic curves for samples of the stated size with not more than 10 per cent. of defective tablets in the sample.

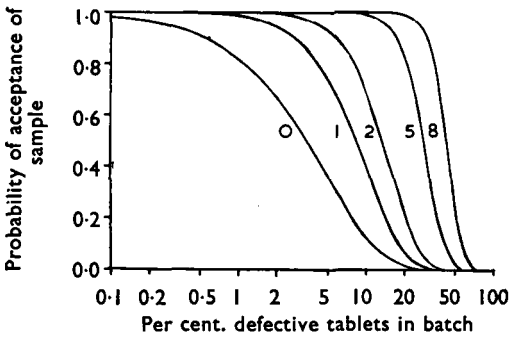

FIG. 3. Operating characteristic curves for samples of 20 with not more than the stated number of defective tablets in the sample.

The proportion of samples which will pass the test for a given percentage of faulty defective tablets in the batch can be calculated by expansion of the appropriate binomial, which for large batches is a satisfactory approximation to the hypergeometric variable which should be used. Dunnett and Crisafio[6] gave curves showing the relation where $n = 10$, 20, 50 and 100, although they used an approximate and complicated method of calculation. Evers[11] gave some related data in tabular form.

Curves of this type, known as "operating characteristic curves", are given in Figures 2 and 3. In calculating the data, the proportion of tablets deviating from the mean by more than $2x$ per cent. has been ignored. The effect of considering them would be to increase very slightly the probability of acceptance of batches by the official test (*cf.*, for example, Figure 3 of this paper with Table I of Smith's paper[7] in which the proportion of "double defectives" has been calculated by assuming normal distribution of weights).

A good test will show a high probability of accepting satisfactory batches and a low probability of accepting unsatisfactory batches. In terms of operating characteristic curves, the greater the sigmoid character

of the curve, the greater the ability of the test to discriminate between satisfactory and unsatisfactory batches.

Values of x given by various pharmacopœias have been tabulated by Smith[12] and Denston[2]. They are shown in a diagrammatic manner in Figure 4. The method of calculating x given by the Danish Pharmacopœia (namely, x is 4 mg. plus 5 per cent. of the mean weight, or 10 per cent., whichever is the less) provides a gradual narrowing of the limits with increase in mean weight, and is probably to be preferred. In any case, it would seem desirable for the British Pharmacopœia to specify mean weights in metric rather than in imperial units, when tabulating values of x.

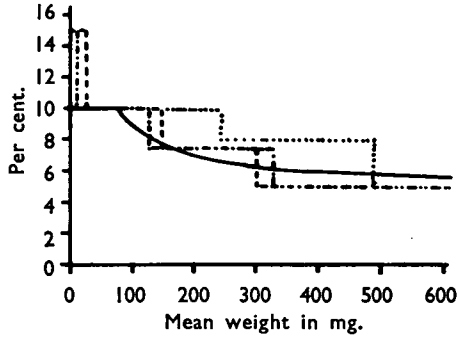

FIG. 4. Limits of deviation from the mean weight of not more than 10 per cent. of tablets in the sample permitted by various pharmacopœias. —— Denmark IX (1948). – – – Egypt 1953. .–.– B.P. 1953; U.S.P. XV (1955). .... Finland VI (1937); Norway V (1939); Switzerland V (1933).

It is clear from Figure 2 that large sample sizes improve the ability of the test to discriminate between satisfactory and unsatisfactory batches. Reference to Figure 3 shows that the curve can also be made more markedly sigmoid by increasing the proportion of tablets in a sample of fixed size which are allowed to deviate from the mean weight by a stated percentage x. In the latter instance, the probability of acceptance of a batch increases whether the percentage of defective tablets in the batch is large or small. This may be corrected by a decrease in the value of x; thus a test approximately equivalent to that now official would be that not more than eight tablets out of a sample of twenty should deviate by more than $0{\cdot}67x$ per cent. of the mean weight, and that none should deviate by more than $2x$ per cent.

The particular advantage of this test is that it operates relatively near to the inflexions of the distribution curve, whereas the test of the British Pharmacopœia operates relatively near to the "tails". Provided that the distribution is normal, this is of little importance, but it is common for unsatisfactory batches to show deviations from normality. Batches showing platykurtosis, i.e., a preponderance of weights remote from the mean, such as might be caused by maladjusted punches in rotary compressing machines, would be likely to be rejected by the test, although the sample might pass the test of the British Pharmacopœia. Conversely, leptokurtic batches, with a preponderance of weights close to the mean (a desirable characteristic) would be likely to be accepted by this test.

The tests of the British Pharmaceutical Codex for uniformity of weight of pastilles and of lozenges may also be considered here, since the problems are similar. The pastille test appears to be incorrectly stated: "The average weight is determined by weighing 20 pastilles. When weighed

singly not more than one of the pastilles deviates from the average weight by more than 15 per cent., and none of the remainder deviates by more than 10 per cent.". This implies that not more than one pastille may deviate from the mean weight by more than 10 per cent., but that one pastille may deviate by an unspecified amount. It is presumably intended to require that not more than one pastille shall deviate by more than 10 per cent., and no pastille by more than 15 per cent. Reference to Figure 3 shows that this test gives a curve which is even less sigmoid than that of the British Pharmacopœia test applied to tablets, whereas a more markedly sigmoid curve would be desirable.

The lozenge test is similar to the test of the British Pharmacopœia for tablets weighing not more than 2 grains (i.e., $x = 10$ per cent.), except that no lozenge is permitted to vary by more than 15 per cent. (i.e., $1{\cdot}5x$ compared with $2x$ for tablets). This will not make the test appreciably more severe on satisfactory batches, but will reject a greater proportion of unsatisfactory batches, and so is to be preferred.

(*d*) *Sequential Analysis Tests*

Smith[7] recommends application of the methods of sequential analysis to the problem, on the grounds that it allows uniform batches to be accepted with fewer weighings than the test of the British Pharmacopœia and removes the rigid division between acceptance and rejection in borderline cases.

He selects as the important criteria the probabilities of accepting batches which contain $p_0 = 5$ per cent. and $p_1 = 25$ per cent. of defective tablets respectively. Using the data of Figures 2 or 3 (or of Table I of Smith's paper[7]) relating to the test of the British Pharmacopœia, the desired probability of rejection of the more acceptable quality p_0 is $\alpha = 0{\cdot}08$, and the desired probability of acceptance of the less acceptable quality p_1 is $\beta = 0{\cdot}08$, giving the acceptance and rejection numbers $0{\cdot}128\ m \pm 1{\cdot}323$ for a sample of size m, and this leads to the Table I (*cf.* Table II of Smith's paper[7]).

If the probabilities at the $p_0 = 5$ per cent. and $p_1 = 30$ per cent. levels are considered, then the acceptance and rejection numbers are $0{\cdot}146\ m - 1{\cdot}632$ and $0{\cdot}146\ m + 1{\cdot}190$ leading to Table II. Table III gives the data for $p_0 = 15$ per cent. and $p_1 = 20$ per cent. The criteria for acceptance and rejection of batches can thus be varied by using data from different parts of the operating characteristic curve based on the specification of the British Pharmacopœia.

Just as a test of the B.P. type can be improved by use of a greater number of tablets in the sample, so the sequential analysis test can be improved by altering the probabilities desired. Table IV gives the criteria for $\alpha = \beta = 0{\cdot}01$, with $p_0 = 5$ per cent. and $p_1 = 25$ per cent.; it is clear that a greater number of tablets is required before a decision can be made.

Smith also describes an "improved" procedure, involving counting the numbers of "half-defectives", and gives data based on the assumption of normal distribution of tablet weights. This procedure is equivalent to reducing x in tests of the B.P. type to $0{\cdot}5x$, and has certain advantages

TABLE I

CRITERIA FOR ACCEPTANCE AND REJECTION WHERE $p_0 = 5$ PER CENT., $p_1 = 25$ PER CENT., $\alpha = \beta = 0{\cdot}08$

Number of defectives observed	Accept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not more than:
0	11	—
1	19	—
2	26	5
3	34	13
4	42	20
5	50	28
6	58	36

TABLE II

CRITERIA FOR ACCEPTANCE AND REJECTION WHERE $p_0 = 5$ PER CENT., $p_1 = 30$ PER CENT., $\alpha = 0{\cdot}08$, $\beta = 0{\cdot}03$

Number of defectives observed	Accept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not more than:
0	12	—
1	19	—
2	25	5
3	32	12
4	39	19
5	46	26
6	53	32

which have been discussed above. The particular advantage here is the reduction in the number of weighings when there is evidence of uniformity.

As Smith himself has pointed out, "decisions with a small number of weighings would be possible only when the batch was uniform", and so the test is unsuited to inclusion in an official book of standards, since evidence of uniformity of a batch would not in general be available to a public analyst or other small-scale consumer. The method is well-suited for use by manufacturers, especially in well-controlled production units.

TABLE III

CRITERIA FOR ACCEPTANCE AND REJECTION WHERE $p_0 = 15$ PER CENT., $p_1 = 20$ PER CENT., $\alpha = 0{\cdot}61$, $\beta = 0{\cdot}19$

Number of defectives observed	Acept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not more than:
0	12	—
1	18	—
2	24	6
3	30	12
4	35	18
5	41	24
6	47	29

TABLE IV

CRITERIA FOR ACCEPTANCE AND REJECTION WHERE $p_0 = 5$ PER CENT., $p_1 = 25$ PER CENT., $\alpha = \beta = 0{\cdot}01$

Number of defectives observed	Accept if number of tablets weighed is not less than:	Reject if number of tablets weighed is not more than:
0	14	—
1	23	—
2	32	4
3	41	13
4	50	22
5	59	31
6	68	40

Coated Tablets

The foregoing discussion relates to uncoated tablets. While it is true that the weights of pan-coated tablets are not directly proportional to the weights of active ingredient contained in them, there is a positive correlation, and a high standard deviation of the coated weights would indicate a poorly-made batch. In the case of tablets coated by compression, there should be no difficulty in securing uniformity of weight.

If it were considered desirable to extend the test for uniformity of weight to coated tablets, wider limits would need to be set, at any rate at first. Suitable values would be twice the deviations allowed for uncoated tablets. Thus for tests of type (*a*), a suitable limit would be that "the coefficient of variation of the weights of coated tablets shall not

exceed that corresponding to a standard deviation of 4 mg. plus 4 per cent. of the mean weight".

DISINTEGRATION

The function of the test for disintegration is to ensure adequate release of the active ingredient[13].

Apparatus and methods have been described by many workers[14–33], and reviews are given by Brown[16], Hoehn[34], Sperandio, Evanson and DeKay[24], Smith[12], Denston[2] and Münzel and Kägi[35]. Mention must also be made of the apparatus described by official bodies, including the American Pharmaceutical Manufacturers' Association, the Association of Official and Agricultural Chemists, the American Pharmaceutical Association, the Fédération Internationale Pharmaceutique, and pharmacopœia commissions of many countries. Other related papers have been published[36–39] suggesting suitable time limits for disintegration, and Bukey and Brew[40] have given information about *in vivo* disintegration times as measured by X-ray methods. The method of setting the specification has been discussed by Hoyle[21], Prance, Stephenson and Taylor[22], and Evers[11]. Enteric and hypodermic tablets lend themselves to the same statistical treatment.

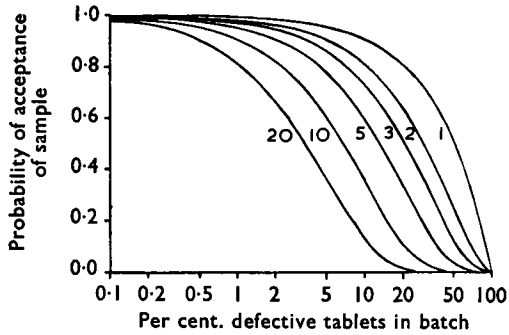

FIG. 5. Operating characteristic curves for samples of the stated size with no defective tablets in the sample.

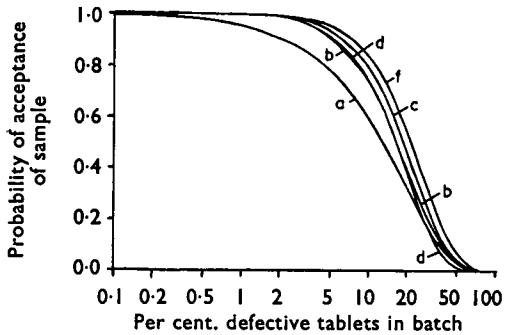

FIG. 6. Operating characteristic curves for tablet disintegration tests (a) (sample of five tablets), (b), (c), (d) and (f).

(*a*) The usual form of specification is to require that no tablet out of five (or ten, etc.) shall fail to disintegrate in the specified conditions and time. Operating characteristic curves similar to those for the weight variation test can be constructed, and some relevant data are given in Figures 5 and 6. In order to be sure that the chance of a sample from a satisfactory batch failing the test is negligible ($P = 0{\cdot}005$), the manufacturer must work to a maximum of about 0·1 per cent. of defective tablets in the batch, with

samples of five tablets; this is a high standard. On the other hand, a batch containing as many as 10 per cent. of defective tablets has a chance of 3 in 5 of being accepted.

(*b*) To avoid rejecting a batch containing an occasional abnormal tablet, Prance, Stephenson and Taylor[22] suggested that if the first sample of five tablets is rejected, a further ten should be taken and must all pass. Figure 6 shows that the manufacturer must work to not more than about 1 per cent. of defective tablets in the batch; a sample from a batch containing 10 per cent. defective has 3 chances in 4 of passing the test.

(*c*) The test of the British Pharmacopœia 1948 has been analysed by Evers[11]. It has about the same stringency as the test of Prance, Stephenson and Taylor, although a maximum of only ten tablets is needed (*cf.* fifteen for the latter). Note: The data on which curve (*c*) of Figure 6 are based are different from those in column 4 of Table II of Evers' paper[11], since he neglected the proportion of tablets which fail on the first sample and do not qualify for a second sample, i.e., those with two or more defective in the first sample of five tablets.

Evers[11] suggested two alternative tests: (*d*) Not more than one defective tablet shall be permitted in a sample of ten tablets.

(*e*) Not more than two defective tablets shall be permitted in a sample of 20 tablets. The latter, in particular, is more discriminating than test (*c*), since it is more severe on unsatisfactory batches and less severe on satisfactory batches (see Fig. 6). However, the gain in discrimination is not sufficient to compensate for the need to expend a greater number of tablets in the sample. The suggestion by Evers that the same 20 tablets which are used for the test of uniformity of weight should be employed is not really valid, because these are normally required in the assay.

(*f*) The test of the 1955 Addendum to the British Pharmacopœia 1953 must be considered in relation to two types of tablets. Certain tablet formulations give gummy masses which fail to break up in conventional disintegration tests, and with these a guided disc may be used to assist in breaking up the residue[2]. Gummy tablets will almost always fail in the first half of the test, so that curve (*a*) of Figure 6 applies. The non-gummy tablets, however, may fail or pass the first half, and so the second half of the test, involving the use of the disc, must be considered in addition. Assuming that the presence of the disc does not facilitate rapid disintegration of a non-gummy tablet, then curve (*f*) of Figure 6 applies; a sample from a batch containing 10 per cent. of defective tablets has 5 chances in 6 of being accepted by the double test. In practice, the disc will facilitate rapid disintegration, and so even fewer batches will be rejected. This anomaly could be overcome by requiring the guided disc to be inserted in all cases, and accepting or rejecting the batch on the evidence of the first sample of five tablets. In addition, to allow for instances in which ten tablets are available for disintegration testing, it could be required that all of a sample of ten tablets (or of two samples of five tablets each) must disintegrate within the stated time with the disc fitted; if ten tablets are not available, five may be used and all must disintegrate.

(*g*) Bull[41] stressed the importance of variation from mean disintegration

time when comparing formulations; Linnell[42] has also raised this point. Satisfactory batches of tablets show a coefficient of variation of disintegration time which is less than 25 per cent., although not much information on this point is available in the literature. (Analysis of Tables III and IV of the paper by Hoyle[21] gives values of 24 and 9·8 per cent. respectively.) Where the mechanics of the disintegration test permit measurement of the disintegration times of individual tablets, it should be possible to specify a maximum permitted standard deviation (or coefficient of variation). However, to ensure rejection of those batches containing a proportion of tablets which might not disintegrate within hours or days, it would be more expedient to require that all tablets should disintegrate within twice the limit allowed for the bulk of the tablets in those tests such as (*b*), (*c*), (*d*) and (*e*) which allow a small proportion to exceed the standard disintegration time limit.

Durability

Spengler and Kaelin[43] listed eight desirable mechanical properties of tablets, namely resistance to wear, rolling, shaking, impact, rubbing, pressure, bending and indentation. Smith[44] reviewed some of the equipment available for testing some of these properties. More recent work has been published by several authors[37,45–49].

Three criteria are in use in different types of tests: (*a*) The tablet must not show any significant change when subjected to specified misusage. (*b*) The tablet must not lose more than a certain weight, or proportion of its weight, when subjected to specified misusage. (*c*) The tablet must withstand a specified stress. Adequate replication must be ensured, since the between-tablets variation is frequently large; Webster and Van Abbé[47] specify a maximum permitted coefficient of variation of loss of weight in their test.

The test of uniformity of weight of the British Pharmacopœia is to some extent a check that the tablets are mechanically sound, since (unlike the U.S.P. XV) it does not specify the use of unbroken tablets. Batches containing a high proportion of chipped or broken tablets would almost certainly be rejected by the test of uniformity of weight.

The number of tablets taken for a test of durability depends mainly on the mechanical construction of the apparatus used, although tests of type (*c*) normally involve only one tablet at a time. With tests of types (*a*) and (*b*), more tablets are required if their size is small. Since the tablets are expended in the test, and since large samples (e.g., 100 tablets) are often needed for useful results, tests of durability are more likely to be applied by a manufacturer as a form of quality control than to be included in a book of official standards.

The various criteria discussed in the two previous sections can be applied, with obvious modifications, to tests of mechanical properties. If official standards were contemplated, data showing the characteristics of large numbers of satisfactory and unsatisfactory batches of different formulations of tablets would be required before detailed recommendations could be made.

Dimensions and Weights

Several foreign pharmacopœias specify the weights and die sizes of official tablets[12,50]. The Wholesale Drug Trade Association (now the Association of British Pharmaceutical Manufacturers) has issued schedules of recommended weights and die sizes to its members for many years[51]. Smith[50] and Firth[52] have tabulated the dimensions and weights of many tablets commercially available.

Smith[50] compared possible methods of standardising these properties, and put forward specifications as a basis for discussion. If a specification were to be adopted by an official body (possibly as a first step only for tablets newly introduced into a book of standards), it might take the form of a statement either of die size[2] with a tolerance of (say) $\pm$ 0·05 cm. or of total weight with a tolerance of $\pm$5 per cent.

Conclusions

Control of the quality of tablets is required at two stages (at least) of their life-history. The manufacturer should maintain production under statistical control, in order to detect, and so be able to correct, abnormalities as soon as they develop. The consumer should inspect some or all of the tablets at the time of purchase, in order to be sure that the alleged quality has been maintained.

For the control of variation of weight by the production unit, tests based on range are probably the most useful; tests based on sequential analysis carried out by the analytical control department may be a useful supplement. For the control of variation of weight by the consumer, the test of the British Pharmacopœia, modified in one or more of the ways suggested in this paper, or (better) a test based on standard deviation, is recommended.

For the control of disintegration, the test of the 1955 Addendum to the British Pharmacopœia 1953, modified as suggested in this paper, is recommended.

There is a lack of sufficient data for detailed recommendations on standards for durability and for weights and dimensions.

Summary

1. The statistics of tests of weight variation, disintegration and durability, and standards of dimensions and weights of tablets are discussed.

2. The specifications laid down in the British Pharmacopœia are criticised, and alternatives are suggested.

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DISCUSSION

The paper was presented by MR. A. R. ROGERS.

MR. K. L. SMITH (Nottingham) said that as worded the paper meant that a sample would be failed if it had such uniformity that the upper confidence limit did not exceed the critical coefficient of variation. When considering tests based on range the author suggested that the range in weights to be observed in five tablets may be as great as five times the standard deviation which is not to be exceeded. This is the order which would indicate that there was a 95 per cent. probability that the standard deviation did exceed the critical value. To ensure, with 95 per cent. probability, that this was not so, the range in weights of five tablets should not exceed the critical standard deviation. He could not understand how

the author found that in a sample of 20 the range of the B.P. test could be 15 per cent. of the mean weight. Under the B.P. test, batches of tablets weighing five grains would be accepted with 95 per cent. probability if 4 per cent. of them had weights deviating from the mean by 5 per cent. or more. The standard deviation of such populations, if they are normally distributed, is about 2·5 per cent. of the mean weight, from which it could be calculated that the average range in weight of 20 tablets should be 9·3 per cent. On the subject of sequential sampling, he was surprised that the author considered the values calculated using other points on the operating curve for the B.P. test differed markedly from those given by him. He thought it more reasonable to calculate from points towards the extremities of the curve, and it could be shown that the points chosen by him gave an operating curve closer to that of the B.P. test than Table III. It was unfortunate that in the discussion of his paper at the Aberdeen conference a misquote led Mr. Rogers to suggest he considered that the suitability of the sequential sampling test depends on other information regarding the uniformity of the batch being available. This was certainly not the case: it stands on its own as efficiently as any equivalent procedure. Mr. Rogers suggests that the test based on sequential analysis could provide a useful supplement for the analytical control department, presumably to quality control tests. There is a good argument for the claim that where quality control charts are available these could provide sufficient evidence for everybody that the batches have the desired uniformity.

MR. E. W. RICHARDS (Upminster) suggested that manufacturers should release for publication the large amount of information in their files on tablet weights. There appeared to be no direct reference in the paper to batch size, which might be up to 10^6, and in such cases a sample of 20 tablets could only be regarded as a spot check. The tablet maker would make frequent checks during the run of a batch. It was difficult to understand the author's remark on page 1109 that the weights of pan-coated tablets were not directly proportional to the weights of active ingredient contained in them. Provided variations between tablets and batches were not so obvious as to be readily noticed by the customer, there did not appear to be a need for the uniformity test for coated tablets. The recommendation that the disc should be used in all cases was not sound. With certain formulations there was a tendency for tablets to clump together or stick to the disc itself, and the disintegration time could then be considerably longer with the disc than without it. He suggested that tests might be made, with the disc and without, and the shorter time recorded. It would be almost impossible to devise a single durability test which could be related to the behaviour of a tablet in all the hazards it met from the die to the consumer.

MR. G. R. WILKINSON (London) asked for some amplification of whether "slackness" applied to the machine rate or to the operator. With reference to the author's remark concerning one punch out of 25 in a rotary compressing machine being wrongly adjusted, he said that he had yet to find a rotary machine where the punches could be individually adjusted. A

feature of the compression coated tablet was the time delay experienced between checking and the actual adjustment of the machine to rectify any fault found. He had found that a chargehand working with a pair of calipers could produce much better control than many of the statistical methods.

MR. D. STEPHENSON (Dartford) said that many rotary tablet machines had adjustable punches. He supported Mr. Richards' comment on the disintegration test. Many tablets containing vegetable extracts tended to stick to the under side of the disc.

MR. N. J. VAN ABBÉ (Loughborough) said that from the point of view of the consumer or of the public analyst it was not the remaining length of life for the tablet which mattered. The durability test was essentially a quality control for the manufacturer and not a test for the tablets at the time of use.

MR. A. R. ROGERS, in reply, said that he felt that the figures in the paper with reference to the ratio of range to standard deviation were correct. He was prepared to stand by his figure of 15 per cent. for a sample of 10 tablets. With regard to sequential analysis tests he maintained that his figures, even as amended, were different, but perhaps in practice the difference was not very important. He agreed that the sequential analysis test could supplement other tests and that the analyst in a manufacturing concern should make control charts available to the public analyst, but it was difficult to see how a body such as the Pharmacopoeia Commission could take cognizance of such a procedure. He also agreed that it would be useful to have more of the data which were in manufacturers' files. He had emphasised that it was desirable for tablet manufacturers to keep their products under statistical control in regard to weight variation. He had not a very wide experience of the new disintegration apparatus. He agreed that it would be better to leave the durability test as unofficial. Perhaps "slackness" was a loose term; it might have been better to say "worn punches".