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Content uniformity of potent drugs in tablets

N. A. ORR* AND E. A. SALLAM

School of Pharmacy, Sunderland Polytechnic, Galen Building, Green Terrace, Sunderland, SR1 3SD, U.K.

The type of distribution of low dosage drugs that occurs in batches of commercially available tablets has been examined. The uniformity of content of ethinyloestradiol tablets 10 μg B.P. from different sources, assessed by single tablet assay showed that three batches exhibited some positive skewness and one marked positive skewness. At the high level of dilution required, the mixing theory indicates that particles of drug must be very fine if acceptable content uniformity is to be obtained. Cohesion of particles impairs the efficiency of the mixing process. It is shown theoretically that unless the drug is dispersed into its component particles the shape of the distribution curve for the content of drug per tablet, in a batch of tablets, will be positively skewed. The relation between the tensile strength of the powdered drug and the degree of skewness of the drug content is also discussed. A positively skewed distribution for tablets containing a small amount of potent drug is unacceptable because this can lead to the presence of relatively large doses of drug in a single tablet. Where one unexpectedly high result occurs in the quality control of the content uniformity of tablets containing potent drugs it is suggested that sufficient single tablet assays be performed to allow the shape of the distribution curve to be assessed. A test for skewness should be included in compendial standards.

Many regulatory authorities are exercising control over content uniformity by specifying single tablet assays for the content of active ingredient. The effectiveness of a content uniformity standard will depend upon the precision of single tablet assay data, the number of tablets examined and the statistical methods involved in the design of the specification. The specifications in both the United States Pharmacopeia (1975) and the British Pharmacopoeia (1973 and 1975, 1977 Addenda) depend upon defective tablets being detected in a numerically small sample. The effectiveness of these methods of controlling content uniformity has been discussed (e.g. Nessel, Apelian & Blodinger, 1970; Langenbucher, 1972; Oie, Frislid & others, 1971; Pederson & Torud, 1971; Pederson, Torud & Waaler, 1971; Norberg, 1972; Setnikar, 1974; Wilrich, 1976), and certain limitations pointed out.

A departure from the practice of using a standard based on defective tablets is made by the Australian Department of Health (1975) in its specification for the content uniformity of digoxin Tablets. This is based upon the statistic S_T using the formula

$$S_T = \sqrt{\frac{\overline{(X - 100)^2}}{N}}$$

where X is the amount of digoxin in a single tablet expressed as a percentage of the labelled strength and N = 30 is the number of tablets that must be assayed individually. The specification states that the calculated value of S_T must not be greater than 10·0. Setting limits to the Statistic S_T makes better use of the data available then merely stating whether a defective tablet is or is not present. This, coupled with a sample size of 30 means that the chance of making a wrong decision on the quality of a batch is much reduced.

Some authors (e.g. Train, 1960; Hersey, 1967; Johnson, 1972) have applied randomized mixing theory (e.g. Lacey, 1943; Stange, 1954; Poole, Taylor & Wall, 1964) to predict the particle size requirements of the powdered drug necessary if the dose content uniformity of the tablets is to meet certain predetermined specifications. Hersey (1975) introduced the concept of ordered mixing which takes into consideration the adherence of fine drug particles to the surface of larger excipient particles. Implicit in the application of mixing theory is the assumption that the amount of drug is normally distributed within the tablet batch. Whilst it may be desirable that the distribution is normal or at least symmetrical about the mean there is little reason to believe that this is achieved in practice.

At the high levels of dilution that occur with potent drugs, the drug must be extremely finely divided if reasonable standards of homogeneity are to be satisfied. Fine drug particles may be cohesive and adhere to themselves in the form of agglomerates; the presence of these, even after prolonged mixing, is believed to be responsible for the positively skewed distributions obtained in the studies of

* Correspondence.

Orr & Shotton (1973), Hess (1976). For the purposes of practical tablet formulations it is essential to know whether theoretical concepts of random and ordered mixing are valid. Thus the aim of this paper is to indicate the problems that exist, both in theoretical and practical terms, in incorporating a finely divided drug into a tablet.

Single tablet assay results have been obtained on commercially available samples of ethinyloestradiol tablets B.P. of labelled strength 10 μg. To enable meaningful statistical appraisal of the results made, 50 single tablet assays were performed on each batch of tablets.

MATERIALS AND METHODS

Unopened packs of ethinyloestradiol tablets B.P. of labelled strength 10 μg from 5 sources were purchased. Single tablet assay based on the fluorimetric method of Miller & Duguid (1976), was performed on each of 50 tablets from each source.

One tablet was weighed, placed in a 100 ml separating funnel with 10 ml distilled water and 3 ml 1 M HCl and shaken in an Oxford flask shaker (Griffin and George) to complete disintegration. Ethinyloestradiol was extracted with 4 × 10 ml dichloromethane, each extract being passed through a plug of anhydrous sodium sulphate into a 50 ml volumetric flask. The extracts were made up to volume with dichloromethane and 15 ml portions pipetted into two 50 ml volumetric flasks, into each of which was added 3 ml of reagent (0·2% m/m hydroquinone in H_2SO_4–ethanol 70:30) and after 5 min of shaking, the fluorescence of the upper dichloromethane layer was measured (Baird Atomic spectrophotofluorimeter) at an excitation wavelength of 542 nm (emission wavelength 560 nm). At the same time, 15 ml portions of a standard solution of ethinyloestradiol (0·2 μg ml^{-1}) in dichloromethane was similarly treated, and 0·4 μg ml^{-1} solution was used as a reference to adjust to 100% fluorescence intensity. The mean reading of the duplicate samples was compared with that of the standard. The results were calculated as μg per tablet and also as μg g^{-1} of tablet.

The precision was found to be equivalent to a coefficient of variation of 1·5%. The efficiency of extraction of the drug was 97·3% range 96–99% n = 3. The sensitivity of the single tablet assay method was within 0·1 μg per tablet.

Chemicals used were: ethinyloestradiol (Koch-Light laboratories; Ethyl alcohol (absolute, J. Burrough Ltd); dichloromethane (Laboratory reagent, BDH) distilled over phosphorous pentoxide for 5 h then redistilled (Dufton fractionating column) before use; hydrochloric acid (Hopkin and Williams), hydroquinone, phosphorous pentoxide (laboratory reagents, BDH), sulphuric acid (Analar, BDH).

RESULTS

The single tablet assay results for each of the 50 tablets in the samples from the five sources are summarized in Table 1 in terms of μg per tablet and μg g^{-1} of tablet. The results in μg per tablet give an indication of the variation in dose that occurs. The data in μg g^{-1} of tablet give an indication of the homogeneity of the drug within the tablet mass; that is, it is independent of variation in tablet weight. Fig. 1 consists of two sets of histograms (i) results expressed as μg tablet; (ii) results expressed as μg g^{-1} tablet, each histogram being constructed on a scale chosen to best exhibit the shape of the individual distribution.

Table 1. *Summary of single tablet assays.* Summary of single tablet assay data for samples each of 50 tablets from 5 sources coded A–E. Min and Max refer to the minimum and maximum values obtained for the content of ethinyloestradiol in a tablet. C% is the coefficient of variation. $\sqrt{b_1}$ is the coefficient of skewness. For a normal distribution and a sample size of 50 the limiting values of $\sqrt{b_1}$ are 0·583 and 0·787 for $P = 0{\cdot}05$ and 0·01 respectively (Pearson & Hartley, 1958).

Source	Min	Max	Mean	C%	$\sqrt{b_1}$
(a) μg g^{-1} of tablet					
A	184	296	220	10·8	+0·87
B	161	236	185	7·1	+1·12
C	181	208	196	2·9	−0·51
D	169	227	195	6·1	+0·35
E	56	570	167	66·8	+1·40
(b) μg per tablet					
A	8·7	14·6	10·5	11·5	+1·02
B	9·3	14·2	11·3	8·3	+0·62
C	9·1	10·5	9·8	3·6	−0·08
D	8·1	11·2	9·5	6·3	+0·25
E	2·8	25·9	8·4	64·3	+1·17

DISCUSSION

Test for skewness

An inspection of the mean, minimum and maximum values in Table 1 suggests that batches A, B and E might deviate significantly from a normal distribution; the histograms in Fig. 1 for batches A, B and E all exhibit a degree of positive skewness. The degree of skewness may be assessed by calcu-

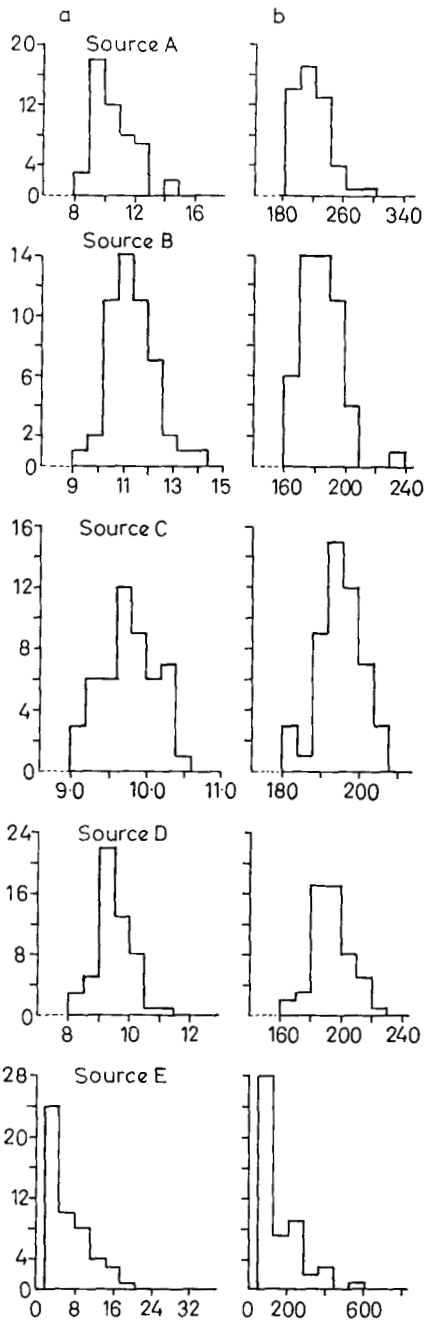

FIG. 1. Histograms based on single tablet assay results for samples of 50 tablets from sources A-E. The histograms are constructed on different scales to illustrate the shape of each distribution. Ordinate: No. of tablets. Abscissa: (a) Results expressed as μg per tablet (b) Results expressed as μg g^{-1} of tablet.

lating the statistic $\sqrt{b_1}$ often referred to as the coefficient of skewness where:

$$\sqrt{b_1} = \sqrt{\frac{m_3^2}{m_2^3}} \quad \text{with } m_r = \sum_{i=1}^{n} \frac{(x_i - \bar{x})^r}{n}$$

and n is the degrees of freedom.

For a symmetrical distribution, if all of the observations are considered, $\sqrt{b_1} = 0$, for a positively skewed distribution $\sqrt{b_1} > 0$ and for a negatively skewed distribution $\sqrt{b_1} < 0$.

The value of $\sqrt{b_1}$ calculated for a sample of observations from a symmetrical distribution will not be exactly zero. Pearson & Hartley (1958) give the probability of various departures from zero for a normal distribution. The limiting values for a normal distribution for a sample size of n = 50 are 0·533 and 0·787 for $P = 0{\cdot}05$ and 0·01 respectively. The calculated values of $\sqrt{b_1}$ for each sample of 50 tablets are given in Table 1.

Considering the results expressed in terms of μg per tablet, batches C and D produced values for $\sqrt{b_1}$ consistent with normality. Batch B produced values for $\sqrt{b_1}$ with probabilities of normality $0{\cdot}05 > P > 0{\cdot}01$ and batches A and E produced values of $\sqrt{b_1}$ with probabilities of normality $P < 0{\cdot}01$. Considering the results expressed in terms of μg per tablet, batches C and D produced values for $\sqrt{b_1}$ consistent with normality. Batches A, B and E produced values for $\sqrt{b_1}$ with probabilities of normality $P < 0{\cdot}01$.

Before discussing the implications of these results the justification for using a test for skewness must be considered. Fisher (1963) suggests this to be an excellent test for the significance of departure from normality but inefficient in estimating the shape of the distribution curve. Pearson & Hartley (1958) show how this test may be used to indicate positive skewness even for a sample size as small as 50. Orr & Shotton (1973), examining the mixing of fine cohesive powders, showed that in high dilution mixing a positively skewed distribution of the minor component could occur. Hess (1976) made a similar observation on the incorporation of reserpine into tablets by solid mixing. In both papers the positive skewness was attributed to some of the fine particles of the minor component remaining as agglomerates, even on prolonged mixing. Thus if in the manufacture of the ethinyloestradiol tablets of sources A, B and E the drug was incorporated as a fine powder that was cohesive and not readily dispersed into its component particles, it is likely

that agglomerates of drug would be present in the tablets. In such a situation a positively skewed distribution would not be unexpected, and a test for skewness in the analysis of the results would seem reasonable.

Relevance of mixing theory

For the purposes of a statistical treatment, tableting may be considered as withdrawing samples of a fixed weight from a powder mixture of active ingredients. Stange (1954); Poole & others (1964) and Johnson (1972) have derived equations for estimating the coefficient of variation C_R for a random mix. When applying this theory to pharmaceutical tablets for deciding upon a maximum particle size of the drug it is necessary to consider what is the desirable maximum value of C_R. The decision is to some extent arbitrary and Johnson (1972) recommends a value for C_R of 1% or less.

If a value of $C_R \leqslant 1\%$ is to be obtained in the case of a 50 mg tablet containing 10 μg of ethinyloestradiol, the value of the mean effective particle weight of the drug, must not exceed 10^{-3} μg, equivalent to a powder consisting of monosized particles of diameter 12 μm. In practice, a powder having a limiting value of 0·001 μg for the mean effective particle weight will have a particle size distribution with most particles substantially less than 12 μm. Such a powder will exhibit cohesive properties with the result that the primary particles will agglomerate and not be readily dispersed. Although the equations of Stange (1954) and Johnson (1972) enable the coefficient of variation for a random mix to be estimated they do not necessarily indicate the shape of the distribution curve. It is implicit from Stange's derivation that the variation in fraction of minor component in a mixture between samples will be normally distributed for particle size distributions that are not markedly non-normal. This is not necessarily so for a markedly skew or multimodal particle size distribution.

The particle size distributions of many powders deviate widely from a normal distribution and often exhibit marked positive skewness. This is reflected in the fact that in particle size analysis the class widths are usually arranged in a square root of two progression. For a fine cohesive powder, in most practical situations, the size distribution is not the distribution of the sizes of the individual component particles, but will consist of some primary particles and also agglomerates. Because of the presence of agglomerates of differing size the particle/agglomerate size distribution is likely to be markedly assymetrical with a highly positive skew or possibly even distinctly bi-modal with a distribution of primary particles and a distribution of agglomerates.

Tensile strength of powdered drug

The mixing process is intended to distribute the component drug particles within the diluent and it will be unsatisfactory if any of the particles are in the form of agglomerates. Considerable energy will be required to detach each particle from its neighbours. An indication of the magnitude of this energy can be deduced from the tensile strength of the powder. Cheng (1968) has developed a theory for the tensile strength of powders incorporating the effect of density, particle size distribution and interparticle force. Application of this theory enables an estimate of tensile strength to be predicted from particle size data. Orr & Shotton (1973), in their study on the mixing of fine cohesive powders in a ratio 1 in 1000, showed that when the minor component consisted of a fine but cohesive powder of high tensile strength, the distribution of minor component was positively skewed even on prolonged mixing under vigorous conditions.

Flow properties of the diluent powders

From the above it can be assumed that the rate-determining step in the mixing of small amounts of a fine cohesive powdered drug will be the rate of breakdown of agglomerates into their component particles. Hence factors influencing the breakdown of the agglomerates will also influence the rate of mixing. There are two main factors that influence the rate of breakdown, direct mechanical action and interaction between drug particles and diluent particles. The extent of this interaction has been shown by Orr & Shotton (1973) and Egerman (1974) to be dependent upon a combination of the type of mixing process and the flow properties of diluent. Generally, the more free flowing the diluent, the faster the rate of mixing, this is believed to be due to the abrasive qualities of free flowing powders in that they mechanically disperse the agglomerates. However, Orr & Shotton (1973) showed that if a very cohesive powder (particle size <2 μm) was used to represent the diluent, the rate of mixing was dependent upon the nature of the mixing machinery. When a Lodige–Morton mixer which has double plough shaped shovels connected to a shaft rotating at 240 rev min^{-1} was used, the rate of mixing was relatively slow and this was attri-

buted to the cohesive nature of the diluent as well as of the drug. When the same powder system was mixed in a Y-cone mixer rotated at a speed of 26 rev min^{-1} a relatively rapid mix was achieved. The cohesive powders exhibited the phenomenon of 'balling' ('spontaneous granulation') in the Y-cone but not in the Lödige–Morton mixer and the following mechanism for the rapid mixing process is proposed. During rotation of the Y-cone mixer the powder is subjected to forces that cause compaction in certain areas of the powder mass. Once formed, these 'compacts' will be subjected to disruptive forces during tumbling, from stresses within the powder mass and collision with the walls of the mixer. The powder resulting from the disintegration of 'compacts' will have a slightly increased bulk density and can be regarded as ball nuclei. Nuclei present on the free surface of the powder mass may roll down the slope, increasing in size as they do rather like a rolling snowball. These balls will disintegrate into ball nuclei as a result of the same disruptive forces that broke up the original balls. These nuclei in turn will produce a further generation of balls. If the build up and breakdown of these 'balls' is rapid, the increase in shear and convection mixing will be considerable causing rapid dispersion of agglomerates followed by the subsequent mixing of the component particles.

Quality control considerations

A question that arises in quality control is what does the analyst do with an exceptionally high result, especially if it is from a single tablet assay where the test is destructive. Johnson (1966) discussed this dilemma and posed the question whether a single high result could be due to variation in content within a batch or to an error in the assay. He suggested that a high result could quite probably be due to analytical error, but this could not be proved because of the destruction of the tablet. The present work suggests that a tablet assaying at a high value may be taken as possible evidence of a distribution for drug content that differs markedly from normality. In such an event it is suggested that sufficient single tablet assays be performed to enable the shape of the distribution curve to be assessed. This would then provide the analyst with enough information to decide whether the content uniformity of the batch was or was not pharmaceutically acceptable.

If skewed distributions, whatever their cause, do exist in commercially available tablets, then there is a distinct likelihood of tablets containing a relatively enormous dose of active drug being present in a batch. Batches of tablets containing small amounts of highly potent drugs should be regarded as unacceptable if the distribution of drug throughout the tablet mass is shown to be positively skewed. In testing for positive skewness the single tablet assay data should be expressed in terms of $\mu g\ g^{-1}$ of tablet since the weight of the tablets will itself vary.

At present there is no content uniformity test specified for ethinyloestradiol tablets B.P. There are content uniformity tests included in monographs of tablets of: dexamethasone, digoxin, nicoumalone (B.P. 1973); glibenclamide (B.P. Addendum 1975); colchicine, ergometrine and ergotamine (B.P. Addendum, 1977). Of these tablets, those that contain the smallest dose of drug and are commercially available are digoxin tablets B.P. of labelled strength 62·5 μg. The specification for digoxin tablets is based on the single tablet assay of 10 tablets, 9 must be within the range of 80 to 120% of the average content of the tablets and none must be outside the range 75–125% of the average content of the tablets.

In the absence of a B.P. content uniformity specification for ethinyloestradiol tablets B.P. the single tablet assay data from these tablets were checked against the B.P. specification for digoxin tablets. This was done by dividing the results from each sample of 50 tablets into 5 consecutive groups of 10, each group of 10 results being subjected to the test. Tablets B, C and D passed the test. Tablets 11–50 of source A passed while 1–10 failed the test. All five groups of 10 tablets from source E failed.

Using the above test as a criterion for adequate content uniformity, the batch of tablets from source E were substandard, those from source A were substandard only on the basis of the first group of 10 tablets, while batches from sources B, C and D performed satisfactorily. The test for skewness performed on the groups of 50 single tablet assays for both A and B batches exhibited significant positive skewness. We believe that it would be undesirable to pass either batch A or B on the basis of the data available.

The magnitude of the problem is illustrated by the following example. A spherical agglomerate of ethinyloestradiol of porosity 0·5 and of diameter 320 μm would contain 10 μg of drug. If this agglomerate was present in an otherwise 'ideal' tablet mix for the manufacture of ethinyloestradiol tablets of labelled strength 10 μg, the tablet which contained the agglomerate would contain double the

labelled strength of drug. If the content uniformity were assessed by the single tablet assay of 10 tablets it is highly unlikely that in a batch, for example, of 5×10^6 tablets that the tablet with an agglomerate would be in the sample. However, it is also unlikely that in a tablet batch only one agglomerate would remain undispersed, rather it is more likely that a number of agglomerates of ranging size would remain undispersed. If a large enough sample of tablets were assayed the presence of agglomerates would be identified by a positively skewed distribution. To safeguard against batches of tablets with a positively skewed distribution for the content of drug we recommend that a test for skewness should be incorporated into pharmaceutical content uniformity specifications. This would necessitate increasing the number of individual tablets assayed since no meaningful test for skewness can be performed on the results for 10 tablets.

CONCLUSION

When assessing the content uniformity of a solid dosage form containing a small amount of potent drug, an examination of the type of distribution is desirable. A positively skewed distribution should be regarded as unacceptable since, owing to the nature of the distribution, it is highly likely that a number of tablets in the batch will contain relatively enormous doses of drug. If the rationale behind content uniformity standards is to ensure the dose is within well defined limits a positively skewed distribution is unacceptable.

Theoretical treatments of mixing based on a normal distribution, such as randomized mixing theory, are useful simple models. Their usefulness is limited in predicting content uniformity of tablets containing small amounts of highly potent powdered drugs owing to the cohesiveness nature of very fine powders. The agglomerates that occur in such powder can lead to markedly positively skewed distributions of drug content per tablet in a batch of tablets unless agglomerates are dispersed into their component particles, the rate of mixing being dependent upon the rate at which the agglomerates are broken up into the component particles. The tensile strength and flow properties of both the powdered drug and diluents are factors in assessing the degree to which the agglomerates can be readily dispersed, that is the rate of mixing that can be achieved in given processing conditions.

Further progress must therefore be made in characterizing skewness and in understanding the processes leading to its occurrence. This is of particular relevance to good manufacturing practice and quality control specifications for content uniformity of tablets and capsules.

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REFERENCES

Australian Department of Health (1975). *Therapeutic Goods Act* 1966, *Therapeutic Goods Order No.* 1 *Digoxin Tablets.*

British Pharmacopoeia (1973). London: H.M.S.O.

British Pharmacopoeia Addendum (1975). London: H.M.S.O.

British Pharmacopoeia Addendum (1977). London: H.M.S.O.

CHENG, D. C. -H. (1968). *Chem. Engng Sci.*, **23**, 1405–1420.

EGERMAN, H. (1974). *Scientia Pharm.*, **42**, 1–19.

FISHER, R. A. (1963). *Statistical methods for research workers*, pp. 315. London: Longman.

HERSEY, J. A. (1967). *J. Pharm. Pharmac.*, **19**, Suppl. 168S–176S

HERSEY, J. A. (1975). *Powder Technology*, **11**, 41–44.

HESS, H. (1976). *Acta pharm. Technol.*, **22**, *Suppl.* 2, 49–64.

JOHNSON, C. A. (1966). *Symposium on the dosage of medicines*, 29–38. London: Pharmaceutical Society.

JOHNSON, M. C. R. (1972). *Pharm. Acta Helv.*, **47**, 546–559.

LACEY, P. M. C. (1943). *Trans Instn. chem. Engrs*, **21**, 53–59.

LANGENBUCHER, F. (1972). *Pharm. Acta Helv.*, **47**, 142–151.

MILLER, J. H. & DUGUID, P. (1976). *Proc. Analyt. Div. Chem. Soc.*, **13**, 9–13.

NESSEL, R. J., APELIAN, H. M. & BLODINGER, J. (1970). *J. pharm. Sci.*, **59**, 254–257.

NORBERG, R. (1972). *Pharm. Acta Helv.*, **47**, 710–718.

OIE, S., FRISLID, K., WAALER, T., ARNESEN, E. & ENGER, E. (1971). *Ibid., Pharm. Acta. Helv.*, **46**, 701–707.

ORR, N. A. & SHOTTON, E. (1973). *Chem. Engr*, issue No 269, 12–19.

PEARSON, E. S. & HARTLEY, H. O. (1958). *Biometrika Tables for Statisticians*, Vol. 1 Table 34B and text tables 34 A-C. Cambridge: University Press.

PEDERSON, A. O. & TORUD, Y. (1971). *Pharm. Acta Helv.*, **46**, 114–120.

PEDERSON, A. O., TORUD, Y. & WAALER, T. (1971). *Ibid.*, **46**, 21–30.

POOLE, K. R., TAYLOR, R. F. & WALL, G. P. (1964). *Trans Instn. chem. Engrs*, **42**, T305–T315.

SETNIKAR, I. (1974). *Pharm. Acta Helv.*, **49**, 302–308.

STANGE, K. (1954). *Chem.-Ing.-Yech.*, **26**, 331–337.

TRAIN, D. (1960). *Pharm. J.*, **131**, 129–134.

United States Pharmacopeia XIX (1975). United States Pharmacopoeial Convention Inc.

WILRICH, P. (1976). *Acta Pharm. Technol.*, **22**, Suppl. 2, 99–114.