THE STANDARDISATION OF TABLETS

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Standardisation

The first official monograph describing a drug in tablet form appeared in the British Pharmacopœia 1885 under the title Tabellæ Trinitrini and it remained until 1945 as the only representative of this class of medicament. In comparison with the style of the monographs in the current Pharmacopœia, the original specification appears to be inadequate in that it states only the total weight of a tablet and the nominal content of active ingredient, and makes no reference to the excipient, the method of assay or the permitted limits of glyceryl trinitrate. The Seventh Addendum to the British Pharmacopœia 1932, published in 1945, described 35 tablets, with a general monograph governing the requirements laid down in the individual monographs. This marked a great advance in the control of tablets in that not only did each monograph include a method of assay and state the permitted tolerances for active ingredient but a test for disintegration was applied to all tablets except those intended to be chewed or crushed, or allowed to dissolve slowly in the mouth, or to be dissolved in water before administration. The tablet monographs for the Pharmacopœia increased to 50 in 1948, 6 more were added by the Addendum 1951 and the British Pharmacopœia 1953 has 63. It is proposed to include 72 monographs on tablets in the British Pharmaceutical Codex, 1954. A similar development has occurred with some other pharmacopœias; for example, the United States Pharmacopœia, which had described no tablets until 1936, when one monograph was added (Tablets of Glyceryl Trinitrate), now has 92 monographs. The Danish Pharmacopœia 1948, with Addendum 1952, describes 99 tablets. On the other hand, whilst there is a general monograph, there were no monographs on individual tablets in the pharmacopœias of Argentine (1943), Belgium (1951 Supplement), France (1949) and Turkey (1948).

Before considering details of the specifications given in the tablet monographs of the British Pharmacopœia it must be emphasised that, as stated in the General Notices to the book, the official standard for any particular tablet is not confined to the specified limits for the amount of active constituent. Tablets are not of pharmacopœial quality unless they comply with all the requirements described in the particular monograph or referred to in the General Monograph. These requirements include a method of preparation (which may, however, be permissive and not mandatory), identification, disintegration, limit tests for impurities, uniformity of weight and content of active ingredient when determined by the assay described in the monograph. It should be noted that the Pharmacopœia, in outlining the general methods of preparation, gives latitude to the manufacturer provided that the other ingredients are innocuous and therapeutically inert in the quantities present. Lists of suitable diluents, lubricants and moistening agents are given.

The British Pharmacopœia imposes no requirements for the dimensions of tablets or their total weight, but these aspects of standardisation have engaged, and continue to engage, the attention of the Commission. In so far as the amount of excipient and the die size for a particular tablet vary from one manufacturer to another, there is undoubtedly a source of trouble to the pharmacist and a cause for doubt in the mind of the patient as to the accuracy with which his prescription has been dispensed when he receives a second supply of tablets differing obviously in size from the first.

The trade association of the pharmaceutical manufacturers recognised some years ago the importance of uniformity and prepared and issued to its members, with a recommendation for its adoption, a detailed schedule of die sizes and total weights for some 250 different tablets and covering all the common dose-strengths. It is understood that many tablet makers now work to the recommended schedules, but unfortunately other manufacturers have not accepted their association's recommendations. The Commission continues to receive or learn of complaints which show that disparity in practice still causes embarrassment and trouble. That these conditions should persist must lead the Commission to consider whether a trade recommendation could be adequate to deal with the situation. It may prove that official standards, at least for the diameter of the punch, must be laid down. If the diameter, but not the total weight, is officially specified conspicuous distinctions in size between batches from different manufacturers might well disappear but at the same time some latitude in the amount of material to be included in addition to the medicinal ingredient would remain.

Colouring of Tablets

From the introduction of a series of monographs in the Pharmacopœia by the Seventh Addendum of 1945, the general monograph has always stated that the addition of colouring agents is not official. There are no important medical grounds for the colouring of plain or coated tablets but there are strong objections from both pharmaceutical and medical considerations. The colouring of tablets tends to give dangerous encouragement to reliance on identification by appearance instead of by the reading of the label. Further, experience has shown that some manufacturers are not always able to produce or maintain a particular shade, and variation in appearance between different batches may be conspicuous. Most important is the enhanced danger to infants and young children from brightly coloured tablets. Many references to the poisoning of children by coloured tablets have appeared in the medical journals in recent years[1,2,3].

Disintegration

Simple requirements for the disintegration of tablets began to appear in the pharmacopœias 20 to 30 years ago. Probably the first reference is in the Brazilian Pharmacopœia of 1926 and 4 years later the Belgian Pharmacopœia, in its general monograph, had the statement that tablets must

dissolve or disintegrate within a short time when shaken with tepid water. Within a few years other pharmacopœias adopted the same or a similar broad statement, notably those of Denmark (1933), Switzerland (1934), France (1937), Finland (1937) and Russia (1937). The method of the Swiss Pharmacopœia is typical: "pour 50 c.c. of water at 37° C. on a tablet in an 100-ml. conical flask; shake the flask gently from time to time; the tablet must completely dissolve or disintegrate within 15 minutes". Substantially the same method is used in the current pharmacopœias of Egypt (1953), Japan (6th edition), Denmark and Sweden. Many attempts have been made to find a method which will give a definite end-point whatever medicinal substance, diluent or binding agents may be present. At the 1939 British Pharmaceutical Conference, Brown[4] described a method which applied a shearing force to the tablet and on the same occasion Berry[5] suggested a method depending on a weighted wire cutting through a tablet after it had been softened in water. In a later paper Berry and Smith[6] proposed a method which was essentially a development of that given in the Swiss Pharmacopœia and it was later adopted, in its essentials, in the Seventh Addendum to the British Pharmacopœia 1932.

Other workers, including Hoyle[7], Prance, Stephenson and Taylor[8], Sperandio, Evanson and DeKay[9] and Evanson and DeKay[10], have attempted to achieve a sharp end-point by the use of a wire-gauze screen through which the particles of the disintegrated tablet must pass.

The diversity of methods used in the national pharmacopœias is shown by comparing (i) the number of tablets used in the test, (ii) the temperature and volume of the water, and (iii) the apparatus.

(i) Some pharmacopœias do not state the number of tablets to be used; in others the number ranges from 1 to 6, as shown by the following examples:—

1 tablet	Argentine, Switzerland, Japan.
2 tablets	Yugoslavia.
3 tablets	Denmark.
5 tablets	Britain, France.
6 tablets	United States of America.

There is a difference between the French practice on the one hand and the British and American on the other, in that the former uses 5 tablets in one vessel and the latter direct one tablet to be placed in each tube. Moreover the British Pharmacopœia directs that if one tablet fails to comply, the test may be repeated with 5 tablets from the same batch, when all must comply; a tolerance of 90 per cent. is thus permitted.

(ii) The volume of water varies from about 50 ml. to 1 l. but most pharmacopœias stipulate that the water shall be at about body temperature, e.g., 37° C. (B.P.), 35° to 39° C. (U.S.P.), 38° to 40° C. (Danish Pharmacopœia), 40° C. (Swedish Pharmacopœia). The French Codex has now adopted 20° C. Berry and Smith obtained more consistent results with their method at 37° C. than at 18° C.

(iii) The apparatus may consist of a flask or beaker containing the tablet or tablets and water, or a series of tubes closed with a cork, as in the British Pharmacopœia, or provided with gauze at the lower end, as in the United States Pharmacopœia. The French Codex has a metal cylinder with gauze at the bottom; 20 glass beads are used with 5 tablets and the tube is shaken with a circular movement sufficient to carry round the beads.

In an attempt to improve on the present official test, the Tablets Committee of the British Pharmacopœia Commission has examined a number of methods intended to yield consistent results and an unmistakable end-point especially when applied to tablets which tend to form a gummy mass and to coated tablets. It has also been the intention to keep the test as simple as possible. Arising from this collaborative work, the following test, which is based on that of Prance, Stephenson and Taylor[8] is now under examination and, subject to comments which may be received—and criticisms are invited from those who may try it—will be recommended to the Commission for inclusion in the forthcoming Addendum to the British Pharmacopœia 1953.

Apparatus. A glass tube 80 to 100 mm. long, with an internal diameter of about 28 mm. and an external diameter of 30 to 31 mm., is fitted at the lower end with a disc of rustproof wire gauze complying with the requirements for a *No.* 10 *sieve*, British Pharmacopœia 1953, page 853, and suspended in a volume of *water* having a depth of not less than 15 cm. and at a temperature between 35° and 39° C. in such a way that it can be raised and lowered repeatedly in a uniform manner through a distance of 75 mm.; at the highest position of the tube, the gauze just breaks the surface of the water, and at the lowest position, the upper rim of the tube remains clear of the water. The tube may be manipulated by hand or mechanically.

Method. Place 5 tablets in the tube and raise and lower the tube in such a manner that the complete up and down movement is repeated 30 times a minute. The tablets are disintegrated when no particle remains above the gauze which would not readily pass through it. The time required for the 5 tablets to disintegrate in the manner described is, unless otherwise stated in the monograph, not more than 15 minutes. If the tablets fail to comply, the test may be repeated using a guided disc as described below, inserted in the tube; the tablets must then comply with the test. The guided disc consists of a disc of suitable plastic material, about 26 mm. in diameter and 2 mm. thick, with 3 holes equally spaced and 10 mm. from the centre. In each hole a stainless steel wire of No. 22 Standard Wire Gauge is secured at a right-angle to the plane of the disc and the end of each wire is turned out radially and secured to a guide ring of No. 22 Standard Wire Gauge and 27 mm. in diameter. The guide ring is co-axial with the disc in a parallel plane at a distance of 15 mm. from the upper surface of the disc. The difference between the diameter of the disc and the internal diameter of the tube is not more than 2 mm. The total weight of the guided disc is not less than 1·9 g. and not more than 2·1 g.

Enteric-coated Tablets

Special coatings are applied to tablets when it is intended that the active ingredient shall not come into contact with the acid secretion of the stomach. Official specifications for the composition of such coatings are not provided. The criterion generally accepted is that the tablets should not disintegrate when immersed in an acid pepsin solution but must disintegrate in an alkaline pancreatin solution. A test for enteric coated tablets is proposed for inclusion in the new edition of the British Pharmaceutical Codex. The apparatus to be used is similar to that described above. The test consists of two parts: in the first part, a watery solution is used containing pepsin, potassium chloride, calcium chloride and hydrochloric acid, and immersion continued for 3 hours. No portion of the tablets, other than fragments of any outer coatings, passes through the gauze. The tablets are then rapidly washed with water and, as the second part of the test, they are immersed for one hour in a watery solution containing pancreatin, sodium tauroglycocholate and sodium bicarbonate. The tablets must disintegrate completely.

Durability

The pharmacopœias do not provide standards to ensure that tablets will show resistance to "wear and tear" during storage, packaging and transit. It is important that tablets should not break or crumble easily, or become chipped at the edges, and simple tests are commonly applied during production. The firmness of the tablets may be assessed by noting the amount of pressure needed to break a tablet by hand or by shaking together a number of tablets in a bottle and determining the weight of powder produced. Such simple tests can be carried out whilst the machine is running and any necessary adjustments immediately made. They are scarcely amenable to description as official standards, and no other method has so far proved acceptable for this purpose.

The application of mechanical methods has been described by Smith[11,12]. Tests were made with instruments designed for measuring the hardness of metals, such as the scleroscope which measures the height of rebound when a hammer of fixed weight is allowed to fall on the surface of the tablet; the Vickers diamond hardness testing machine measures the depth of the impression made in the surface of the tablet. Neither instrument appears to be acceptable for the routine testing of tablets. Smith regards the Monsanto pressure tester, a spring-loaded device with which the pressure required to break a tablet may be determined, as the instrument most easily and rapidly operated.

Weight Variation

Those pharmacopœias which provide, in any detail, standards for tablets usually set limits to the variation in total weight within a batch of uncoated tablets. The requirements may be stated as one figure applicable to tablets of all sizes or as graded requirements according to 3 or 4 categories of weight. Thus, the French Codex states that the average

weight, determined on 10 tablets, is not less than or more than 5 per cent. of the stated weight. The British Pharmacopœia controls the uniformity of weight by requiring that in a sample of 20 tablets not less than 18, when weighed singly, shall fall within the limits stated in a Table, and not more than 1 tablet shall deviate by more than double these limits. The pharmacopœias of the United States of America and Egypt have similar requirements with permitted limits as shown in Table I.

The Swiss Pharmacopœia has limits of ± 10 per cent. (less than 250 mg.), ± 8 per cent. (between 250 and 500 mg.) and ± 5 per cent. (more than 500 mg.), when determined on 100 tablets. The Danish Pharmacopœia also employs 100 tablets and with more detailed directions for weighing permits deviations of ± 10 per cent. for tablets weighing less than 80 mg. and ± 4 mg. + 5 per cent. of average weight for tablets weighing 80 mg. or more; the method provides a more gradual narrowing of the limits with increase in weight.

TABLE I

VARIATION IN WEIGHT OF TABLETS

PHARMACOPŒIAL TOLERANCES

Percentage deviation	Average weight		
	B.P. 1953 mg.	U.S.P. XIV mg.	Egypt. Ph. 1953 mg.
±15	—	13 or less	25 or less
±10	130 or less	more than 13 and including 130	26 to 150
± 7·5	more than 130 less than 324	more than 130 and including 324	151 to 300
± 5	324 or more	more than 324	more than 300

The pharmacopœias which have been cited refer only to uncoated tablets, except 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.

CONTENT OF MEDICAMENT

A few of the monographs of the B.P. 1953 provide a formula for one strength of tablet, as for example Codeine Compound Tablets and Sodium Bicarbonate Compound Tablets, but most of the monographs are framed to cover all strengths which may be prepared. Consequently, in laying down a standard for the amount of medicament contained in each tablet, the tolerances are intended to apply to all dosage strengths. In selecting these tolerances, three main factors have been taken in account, namely:— (a) a manufacturing tolerance in recognition of the variation to be expected when reasonable care and skill is exercised in the preparation of the granules and in compression. The figure may be about ± 5 per cent.; (b) any tolerance allowed in the monograph on the medicinal agent itself. Thus, official acetylsalicylic acid may contain 99·5 per cent. of $C_9H_8O_4$ and the lower figure for the content in the tablets is 94·5 per cent., not 95·0 per cent. It has not been considered necessary to observe

this factor in all tablets and indeed the principle may need reconsideration, due to the growing practice among manufacturers of assaying the granules before compression, and adjusting the total weight in accordance with the result; (c) the error inherent in the assay, due either to the very small amount of the substance present in each tablet or to the nature of the assay method. Ergometrine maleate tablets provide an example of tablets with a small dose (0·5 mg.) and a colorimetric method of assay leading to the specification of a wider tolerance, namely 85·0 to 110·0 per cent. In the British Pharmacopœia 1948, aneurine hydrochloride tablets were assayed by a fluorimetric method and it was necessary to allow a tolerance of 85·5 to 119·0 per cent. The same tablets are assayed by a silicotungstate method in the British Pharmacopœia 1953 and the tolerances are narrowed to 92·5 to 107·5 per cent.

Apart from any allowance for the purity of the medicament, official tolerances fall into three main groups, 95·0 to 105·0 per cent., 92·5 to 107·5 per cent. and 90·0 to 110·0 per cent., with a minority in the last group. It has been the practice to narrow the tolerances on revision of the Pharmacopœia when data has become available to show that it was reasonable to do so. The following are examples of such changes.

Tablet	*Tolerances (per cent.)*	
	B.P. 1948	*B.P.* 1953
Acetomenaphthone	89·0 to 110·0	92·5 to 107·5
Atropine Sulphate	89·5 to 112·5	90·0 to 110·0
Ephedrine Hydrochloride ..	89·5 to 110·0	90·0 to 107·5
Mepacrine Hydrochloride ..	88·0 to 111·0	92·5 to 107·5
Nicotinamide	88·0 to 110·0	92·5 to 107·5
Nicotinic Acid	88·5 to 110·0	92·5 to 107·5
Phenobarbitone	90·0 to 110·0	92·5 to 107·5
Phenobarbitone Sodium ..	85·5 to 110·0	90·0 to 110·0
Sodium Citrate	89·0 to 112·0	92·5 to 107·5

References

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4. Brown, *Quart. J. Pharm. Pharmacol.*, 1939, **12**, 489.
5. Berry, *ibid.*, 1939, **12**, 501.
6. Berry and Smith, *ibid.*, 1944, **17**, 248.
7. Hoyle, *ibid.*, 1946, **19**, 279.
8. Prance, Stephenson and Taylor, *ibid.*, 1946, **19**, 286.
9. Sperandio, Evanson and DeKay, *J. Amer. pharm. Ass., Sci. Ed.*, 1948, **37**, 71.
10. Evanson and DeKay, *Bull. Nat. Form. Comm.*, 1950, **18**, 45.
11. Smith, *Pharm. J.*, 1949, **163**, 194.
12. Smith, *ibid.*, 1950, **73**, 132.

DISCUSSION

MR. D. N. GORE (Dorking) suggested a test for durability of tablets based on rotating them in a horizontal fluted cylinder at a standard speed for a certain number of revolutions, separating the resulting powder from the tablets and weighing it. He did not see why it was not as accurate a measure of durability as the disintegration test was a measure of disintegration. He had simulated the traditional hardness test of exerting pressure on the tablet between the finger and thumb, by the use

of a bridged anvil and a weight travelling along a scale. There was no correlation between durability and resistance to snapping.

MR. M. TEEMAN (Leeds) asked the authors to comment on the various shapes used for tablets and their possible advantages.

MR. W. TRILLWOOD (Oxford) drew attention to the difficulty of rapidly identifying tablets in hospital when they had been dispensed under the National Health Service in a container labelled only with the name of the patient and the pharmacist. He suggested that N.H.S. prescriptions might be in duplicate, one copy to be retained by the pharmacist. He was glad that Mr. Denston disapproved of coloured tablets. Did manufacturers realise that 0·4 per cent. of the female population and about 4 per cent. of the male population were colour blind? Shape, colour, smell, appearance or any other device which detracted from label reading should be deplored.

DR. J. G. DARE (Leeds) referred to the accidents occurring to children and adults by the consumption of tablets in excessive doses or for purposes for which they were not intended. More should be done, in co-operation with the medical profession, to emphasise to the public that any medicine was potentially dangerous. For instance, in antenatal clinics in small towns and villages iron tablets were often supplied without adequate supervision of dispensing. It might be better if people were compelled to go to a pharmacy for all their tablets.

MR. J. B. LLOYD (Manchester) protested against the colouring of tablets, for which he said no adequate pharmaceutical reason had been given. He asked whether there was evidence that the *in vitro* tests of enteric-coated tablets gave an indication of what happened to the tablets *in vivo*. Would following the passage of an enteric-coated barium sulphate tablet through the body radiographically show what would happen to any other enteric-coated tablet? There was some evidence that certain proprietary enteric-coated tablets which had passed these tests in fact passed through the body unchanged.

MR. T. D. WHITTET (London) criticised the practice of stamping initials on tablets. He described the use of relatively cheap kitchen equipment for making tablets. The standard cake mixer made an excellent granulation machine. Powders, after mixing in a bowl and adding a moistening agent were put through a soup strainer, which gave moist granules, and then the coffee bean grinder attachment was used, giving granules ready for tabletting. Another excipient, which had not been mentioned, was bentonite, which had been found excellent where an entirely inorganic tablet, such as potassium perchlorate, was required. Magnesium trisilicate was a satisfactory disintegrant where its pharmacological properties were not contra-indicated. It seemed impossible to make a good tablet of aminophylline by the moist granulation process recommended in the B.P. It became very dark after 2 or 3 months' storage and smelled of ammonia and acetamide.

MR. S. DURHAM (Sheffield) asked whether it would be possible to specify in the official monographs the exact punch size for each tablet.

MR. A. F. CALDWELL (Singapore) spoke of the packing of tablets for tropical countries. Transparent cellulose sheeting collected dust and also grew moulds, although there was nothing wrong with the tablets. An excess of filling agents and excipients which were hydrophilic colloids might cause difficulty in that the tablets, whilst not becoming damp, swelled until it was impossible to get them out of the bottle.

MR. E. SHOTTON (London) thought it right to resist the use of coloured coatings. He asked for a clear definition of the properties which were being measured in durability. Engineers had already defined what they meant by hardness, which involved more of a surface property by indentation than breaking or crushing.

MR. C. W. ROBINSON (Liverpool) said that the conscience of the profession had been disturbed by the many deaths of infants due to eating tablets, in particular tablets containing ferrous sulphate. Tablets of ferrous sulphate and compound tablets of ferrous sulphate, which looked like ordinary white uncoated tablets, could be made by the compression coating technique. The June issue of the *Practitioner* contained an admirable review by Dr. Fraser, lecturer in child health in the University of Aberdeen, and it was clear from his analysis of many cases of accidental poisoning in children that it was by no means certain that colouring and sugar-coating played a decisive part in accidental poisoning. Therefore the question of whether tablets should be coloured ought not at this stage to be related to the causation of accidents until there was clearer evidence that it was the colour or the sugar which caused this fatal attractiveness. With the co-operation of the chief pharmacist of a large children's hospital, the organisation with which he was associated was in the process of organising some planned experiments with inert white sugar-coated, coloured sugar-coated and plain uncoated tablets to try to determine differences in attractiveness to infants. Plastic strip packs were easy for adults to undo and difficult for infants' fingers to open, but cost a little more.

MR. G. RAINE (Manchester) said that he had recently drawn attention to the unsatisfactory nature of many soluble aspirin tablets. There had been some improvement, but many, although labelled soluble, in fact were not. Manufacturers of some antibiotics would not supply the pure materials, and soluble tablets had to be used in making mixtures. Experience showed that these so-called soluble tablets, in water, gave inelegant liquids with a good deal of suspended matter. If manufacturers labelled anything as soluble, it should be soluble; or any insoluble ingredient should be in such a form that it readily dispersed and produced an elegant suspension in water.

PROFESSOR H. BRINDLE (Manchester) said that some years ago, at Manchester University, an enteric-coated capsule was devised which resisted a test similar to that mentioned by Mr. Denston. By using different gelatin mixtures and various formalin treatments a capsule was devised which resisted acid pepsin solution at body temperature for

3 hours and dissolved in alkaline pancreatin solution in 1 hour. A number of capsules were filled with barium sulphate, administered to volunteers, and the passage of the capsules was followed through the body. To their surprise only about one capsule out of 50 behaved as it should have done, i.e., resisted the action of the stomach juices and dissolved in the upper intestine—which suggested that the tests mentioned were not an accurate guide to what happened in the body.

MR. F. BERRY (Nottingham) emphasised the need for careful storage of tablets. Was liquid paraffin ever used nowadays in tablet manufacture? He thought a great need was for a water-soluble lubricant, and he agreed that coating by the new pressure technique was of value for incorporating medicaments in tablet coatings. Mr. Burlinson had mentioned the use of gelatin in a coating process. Had the tendency to mould growth in such tablets been overcome? He had found that incorporating gelatin made the product rather brittle. Commenting on the size of tablets he said that some tablets containing, for example, only 5 mg. of medicament weighed 4 grains, which seemed unnecessarily bulky. The general principle he followed was to use as little added diluent as possible, a 5 mg. tablet weighing about 1 grain. He had found the Monsanto hardness tester useful for comparative experiments.

MR. A. R. G. CHAMINGS (Horsham) said that a large proportion of British pharmaceutical products were exported, and in discussing tablet diameters the profession could not restrict its outlook to British pharmacy. The originator of the product determined in the first instance not merely the ingredients but also the physical characters of the tablet.

MR. A. W. BULL (Nottingham) said that two different processes of coating by compression were already being operated in this country. Mr. Burlinson had said that coating by compression did all that was required of it, but one process which had been described fell down when compared with the traditional pan coating. There was no opportunity to put on a sub-coat, which was an important coat in giving protection, particularly for tablets for export to tropical countries. He had tested tablets of cascara extract stored under hot, humid conditions, where temperatures were fluctuating, and found that the traditionally coated tablet was better than that coated by one particular compression process. Referring to cellulose sheeting, he pointed out that even the so-called moisture-proof film had an appreciable transmission rate for water vapour. Better foils were available for strip packaging of tablets where complete moisture protection was required. He had had occasion to investigate the tabletting of a quaternary ammonium compound where bactericidal effect was important, and, in that case, tablet lubricants which were normally regarded as innocuous had a material effect on the biological efficiency of the resulting tablets. The choice of suitable lubricants in such cases was a difficult problem. Mr. Burlinson had said that certain chemical substances could be compressed without a granulation process and had given aspirin as a typical example. He had examined many specimens of aspirin and had found that the crystal form

varied considerably. He felt that more work was required on crystal shape of many chemicals and that this might greatly assist tablet making. Commenting on Mr. Whittet's remarks on aminophylline, he said that a great deal could be done by attention to the excipients. Sugar should not be used and it was also important to observe official requirements for storage in a well-closed container protected from light.

MR. R. HENRIKSEN (Epsom) asked for statistics showing the number of infant fatalities which had been caused by non-coloured tablets. Referring to the standardisation of tablets, he emphasised that manufacturers had to consider the export market, where conditions might be very different from those in this country, but where 50 per cent. of the output might be sent. It was not feasible to make a tablet of one size and shape for this country and a tablet of a different size and shape for export. A good deal of money had been spent on tablet punches and dies, and these could not simply be thrown away.

MR. D. F. SMITH (Bournemouth) said he had been struck by the anomalous therapeutic results from enteric-coated tablets. A satisfactory test for disintegration was needed, but a test which satisfied an *in vitro* specification and which could be checked *in vivo* with volunteers might not necessarily mean that the product would give similar results with sick patients, for the secretions of the alimentary tract of a sick patient were not necessarily the same as those of a healthy volunteer.

MR. J. R. ELLIOTT (London) dealing with enteric-coated tablets, said that pancreatin was given in a number of cases where pancreatic deficiency existed in the patient. There should be another method of testing enteric-coated pancreatin tablets so as to ensure that they would disintegrate in the alimentary tract where pancreatic deficiency existed.

DR. G. BROWNLEE (London) said that anyone who considered the problems of enteric-coating would recognise that the physiological aspect had the last word. What might justifiably be asked of an enteric-coated product? Contrary to what might have been suggested, it was reasonably easy to coat a tablet so that it passed intact through the stomach, even when allowance was made for the enormous variation in emptying times of stomachs. But what of the requirement implied by the *in vitro* test to restrict the contact time with the pancreatic juices in the upper third of the small intestine to 1 hour? There were those who emptied their gut in as little as 6 hours and those who emptied it in 48 hours. That was a rough and ready measurement of the speed with which products passed through the upper third. Anybody who had studied blood levels with such preparations as penicillin, the sulphonamides or aspirin would appreciate the wide normal range which existed. The manufacturer's problem was therefore physiological. All that should be expected of him was that he should make an enteric-coated tablet. He should not be blamed if the tablet sometimes passed through.

MR. H. HOYLE (Leeds) said he thought the suggested new disintegration test was more satisfactory than the present test. A more definite dividing

line was drawn between tablets which passed and those which failed, and the test would give similar results with different operatives. Referring to coated tablets, he urged the B.P. Commission to continue to use caution in connection with the disintegration time of coated tablets. The best solution to the problem of child fatalities was education of the public, but a degree of success had been obtained with a tablet having a harmless and colourless bitter in the coating. Some of the standards needed revision, for example the requirements for aneurine hydrochloride tablets seemed to be a little more stringent than those for nicotinic acid tablets. In the case of ferrous sulphate, this drug was assayed by the permanganate method, but the tablets by the iodate method. It would be better if the same method were adopted for the raw material and for the finished product.

MR. H. E. BROOKES (Nottingham) said he was concerned about the chronic toxicity of some tablet ingredients. Mr. Burlinson had suggested that the excipients used in tablet manufacture should be pharmacologically inert. Boric acid had been used as a tablet lubricant, although its use as a preservative of foods was not permitted. He was concerned with the considerable number of new wetting, suspending and lubricating agents which were coming into use, and he thought that some of these products might later be found to show chronic toxicity. Thorough pharmacological tests should be carried out on these agents.

MR. D. STEPHENSON (Dartford) said that the suggested new test for enteric-coated tablets in the B.P.C. was better than no test at all, and would probably help to remove from the market entirely unsatisfactory tablets. Barium sulphate tablets had been treated with a coating similar to that which complied with the suggested B.P.C. test, and the results on volunteers had been excellent. After 2½ hours the tablets could be seen in the stomach. Later they could be seen breaking up. Part of a batch of similarly coated tablets was sent to Africa and part to South America. Most of the Africans passed the majority of the tablets entire, and many of the Brazilians vomited!

MR. A. BRAGG (Liverpool) suggested that one system only should be adopted for recording the content of active principle in tablets, either the metric or the Imperial system.

MR. E. LOCKER (Reading), speaking as a retail pharmacist, said that the colouring of tablets was an assistance, and did not lead to carelessness. It had been suggested that certain types of drugs should have certain colours so that people would know immediately what type of drug had been used.

DR. G. E. FOSTER (Dartford) said that there was something to be said for the manufacturer being allowed to put a mark on the tablet so that people might know by whom it had been manufactured.

MR. D. STEPHENSON (Dartford) disagreed with Mr. Locker on the question of colouring. If they were to adopt the practice of trying to

identify tablets by colour there would soon be difficulty in distinguishing between the slight variation of successive batches of one tablet.

MR. R. GILLHAM (Leeds) said his Company placed in every box of tablets a circular reading "These tablets, being in a form likely to attract children, should be kept beyond their reach." A simple test for durability was to place the tablets inside a bottle and rotate them in a revolving drum. Another test was to transport them under severe conditions.

MR. L. H. BOARDMAN (Manchester) said he was convinced that the colouring of tablets was to be deprecated, but he would not be dogmatic. The question of fixing standards for colouring was difficult. From the point of view of dispensing in this country he was convinced that B.P. and B.P.C. tablets should be of fixed diameter.

MR. W. A. PARK (Aberdeen) said that his firm micro-photographed all prescriptions, which gave a ready means of tracing them. Some of the more potent drugs were dispensed, by his firm, in tubes with screw caps, which were more difficult for children to open, but the real problem was in the homes and it was a question of education. Many pharmacies and surgeries in Aberdeen carried cards emphasising that medicine should be kept away from children, and 20,000 copies of a booklet on Home Safety, containing a feature on child poisoning, were to be distributed.

MISS M. C. ISLIP (Harrow), speaking as a children's hospital pharmacist, agreed that publicity and education were the answer to the question of child poisoning. Colour and taste had little effect, for a small child would put anything into its mouth.

MR. T. JAMES (London) said he was perturbed about the containers in which many tablets were dispensed. Containers which could be well sealed should be used.

MR. H. WILLIAMS (Reading) complained of the tendency to supply smaller and smaller tablets, which were difficult to handle.

MR. FITCH, in reply, said that relying on a sign or a colour in identifying tablets was to be deplored: the only way to identify them was by reference to the person who dispensed them.

MR. BURLINSON, replying to Mr. Teeman on the shapes of tablets, said they should distinguish between the shapes of the official B.P. or B.P.C. tablets and those offered as proprietaries, where the shape could be anything the manufacturer wished. Mr. Whittet had raised an interesting point on the use of culinary equipment. He had come across bentonite only as a disintegrant and not as an adhesive. Mr. Caldwell had mentioned excipients which caused tablets to swell in the tropics. When tablets were to be exported, special packaging conditions were required. Dealing with hardness tests, he said that the ultimate test was how well the tablets travelled. Actual hardness did not convey very much. Replying to Mr. Berry, he said that liquid paraffin was still used, but it was important to incorporate a solubiliser to prevent an oily film appearing on the surface of the solution. He was still looking for a satisfactory

water-soluble lubricant. Reference had been made to gelatin and mould growth. Possibly, in the case in question, too much was being used. He thought gelatin was intended to give a certain elasticity, and he had not experienced cracking due to its use. His experience of coating by compression was no more than that of Mr. Bull. He did not think that a tablet which had a sugar coating pressed round it differed greatly in properties from the original tablet. There were physical forms of material more suitable for tablet making than others, and chemical manufacturers should bear that in mind when making drugs which were primarily used for tabletting. Mr. Brookes should know that boric acid would not be used internally, but only for making solution-tablets. As for the newer excipients, manufacturers should satisfy themselves that the substance was not harmful in the proportions used.

MR. DENSTON, in reply, dealing with the introduction of the metric system, said that the B.P. had simplified the position in a logical manner by deleting all reference to Imperial dosage from tablets and medicaments which had never been presented in Imperial quantities, e.g., the sulphonamides and sex hormones. Dr. Capper could rightly claim that the enteric-coating test included in the B.P.C. was the best available at present. Replying to Mr. Whittet on aminophylline tablets, he said that he thought the moist granulation process could be used satisfactorily, but careful drying was necessary. To label a package of tablets to the effect that they were dangerous for children and should be kept out of their reach might create the danger that other tablets would be regarded as not dangerous at all, and would be treated with less care than otherwise would be the case. He agreed with Mr. Whittet that the surface of a tablet should not be used as an advertising medium. He said that regarding tablet identification, the B.P. tried to assist by including a simple identification test which required nothing more than reagents and test tubes. In 1946, Mr. Hoyle had published a useful paper on tablet disintegration, and was one of the first to advocate the use of the wire screen to determine the end-point. In fixing limits for the percentage of medicaments, the figures had to take into consideration the degree of accuracy obtained by the assay method used. He agreed that where appropriate they attempted to adopt the same method for the assay of the tablet as that applied to the medicament in the tablet.