

## TABLETS OF GLYCERYL TRINITRATE

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TABLETS of nitroglycerin first became official in 1885 following their introduction by Martindale in 1878 as tablets with a chocolate base containing nitroglycerin in solution. From 1885 to 1932 the monographs of the British Pharmacopœia were confined to describing the tablets as being of chocolate and stating the weight of the tablets and of the nitroglycerin content. In the Seventh Addendum (1945) to the British Pharmacopœia 1932 a detailed monograph outlined a method of preparation using chocolate basis, set limits for the content of glyceryl trinitrate at 81 to 121 per cent., described a method of assay and gave directions for storage and indicated dosage. Chocolate Basis was defined in the general monograph entitled "Tabellae" as "non-alkalised cocoa powder, of commerce, 15 parts, with Sucrose, 15 parts, and Lactose, 70 parts": the 1948 Pharmacopœia reproduces this monograph practically unchanged. Chocolate was originally used as a basis with the object of reducing the risk of explosion. This danger, however, is extremely remote even when no fat-containing substances are present.

The monograph in the 1945 Addendum was almost certainly based upon the work of Smith<sup>1</sup> and of Meek<sup>2</sup>. Both papers discussed methods of assaying the glyceryl trinitrate and suggested improvements. Meek's paper gives an interesting table showing the results of storage under laboratory conditions of tablets made with different bases. In his experiments, tablets made with lactose had retained their original nitroglycerin content for 1 year; those made with glucose lost 13 per cent. in about 5 months and then remained stable; those made with chocolate having an alkalinity of 0.2 per cent. (as  $K_2O$ ) lost 15 per cent. in 4 months and then remained stable, but when the alkalinity of the chocolate used was 1.3 per cent. the tablets lost 54 per cent. in the year. Meek recommended that when a chocolate base is used in making glyceryl trinitrate tablets the amount of water-soluble alkali should be strictly limited and as a consequence of his work the 1945 Addendum defined chocolate basis.

In February, 1945, some tablets were assayed which had been supplied to a colleague on a prescription for Tab. Glyc. Trinit. gr. 1/100; they contained approximately 1/200 grain of glyceryl trinitrate per tablet. In August, i.e., some 18 months after the Seventh Addendum became official, some glyceryl trinitrate tablets gr. 1/100 were obtained from 4 different makers, kept on a laboratory shelf for 6 months and were then assayed: the results are shown in Table I. They suggest that the introduction of non-alkalised cocoa into the official monograph for these tablets has not been as effective in preventing the dispensing of under-strength tablets as might have been expected from Meek's experi-

ments. Tablets were probably still being dispensed with, in some cases, only half the stated dose.

For longer than 20 years tablets made at these works have been made with a faintly acid chocolate basis, and it has been our experience that

TABLE I

Maker	Type of container	Strength of tablets 6 months after purchase
A	Screw-capped bottle of 100 ... ..	Per cent. 56.0
B	" " " " " " " " " " " "	63.2
C	Paper packet ... ..	36.0
D	Screw-capped bottle of 100 ... ..	79.5

such tablets have continued to lose nitroglycerin, but at a decreasing rate. The results of a number of assays on tablets of known age returned from pharmacies or stores are recorded in Table II.

TABLE II  
STRENGTH OF TABLETS AFTER PERIODS OF STORAGE IN CORKED BOTTLES

Tablets	Nominal strength	Date of assay	Age of tablets on assay	Percentage of original strength
1 ... ..	1/100 grain	August 1927	approx. 35 yrs.	30.0
2 ... ..	1/100 grain	July 1929	14 months	77.0
3 ... ..	1/100 grain	July 1929	15 months	86.0
4 ... ..	1/200 grain	July 1929	17 months	71.0
5 (1st assay) ... ..	1/50 grain	August 1935	20 months	82.0
(2nd assay) ... ..	1/50 grain	February 1936	2 yrs. 3 mths.	79.6
(3rd assay) ... ..	1/50 grain	November 1936	2 yrs. 11 mths.	69.0
(4th assay) ... ..	1/50 grain	January 1938	4 yrs. 2 mths.	61.0
6 ... ..	1/100 grain	January 1938	10 yrs. 9 mths.	40.0

All these tablets had been stored in a temperate climate. In a tropical climate the loss of activity is likely to be much more rapid.

In 1938 the late James Brown suggested that the addition of castor oil to the solution of glyceryl trinitrate before it is added to the granules would probably reduce the rate of loss of nitroglycerin. A quantity of castor oil was taken equal to that of the glyceryl trinitrate present. The basis used was similar to the chocolate basis of the Seventh Addendum: it contained starch but no sucrose. The results of storage tests are given in Table III.

The results of the tests seemed to show conclusively that the addition of castor oil to nitroglycerin tablets reduces the rate of loss of activity. Since 1942 all tablets of glyceryl trinitrate made at the Wellcome Chemical Works have contained, at the time of manufacture, the maximum amount

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of nitroglycerin permitted by the British Pharmacopœia, that is 121 per cent. of label strength. By this means we have been able to ensure that all our glyceryl trinitrate tablets dispensed in a temperate climate within about 4 years would contain probably not less than the stated dose and

TABLE III  
THE EFFECT OF CASTOR OIL ON THE STABILITY OF GLYCERYL TRINITRATE TABLETS

Nominal strength			Percentage of original strength after		
			3 years at 20°C.	6 years at 20°C.	3 years at 40°C.
grain 1/100	...	With castor oil ...	77.0	68.1	61.9
	...	Without castor oil ...	49.3	54.0	41.9
grain 1/100	...	With castor oil ...	81.6	76.7	62.8
	...	Without castor oil ...	61.5	56.4	36.4
grain 1/200	...	With castor oil ...	75.5	61.7	46.6
	...	Without castor oil ...	59.3	46.0	31.3

certainly not less than the minimum permitted amount of glyceryl trinitrate. In tropical countries the tablets retained sufficient activity for not less than 18 months as indicated by assays on 2 batches of tablets returned at our request after more than a year's storage in Malaya. The results were:—glyceryl trinitrate tablets gr. 1/100 made June, 1947, returned February, 1949, contained 96 per cent. of the label strength. glyceryl trinitrate tablets gr. 1/200 made December, 1947, returned February, 1949, contained 93 per cent. of the label strength.

TABLE IV

Maker	Nominal strength of tablets	Actual strength percentage of nominal	Date of purchase and assay
A ... ..	1/100 grain	74.1	30.5.51
B ... ..	1/100 grain	71.0	30.5.51
C ... ..	1/100 grain	80.4	30.5.51
E ... ..	1/100 grain	39.0	14.2.50
F ... ..	1/100 grain	84.0	31.8.49
G ... ..	1/100 grain	85.0	11.7.49
H ... ..	1/100 grain	55.5	30.5.51
I ... ..	1/130 grain	73.0	31.5.51
J ... ..	1/130 grain	50.4	31.5.51
K ... ..	1/130 grain	40.4	31.5.51

The strength of glyceryl trinitrate tablets available in pharmacies for prescription was again investigated by assaying 10 samples made by different well-known manufacturers. The results of the assays are shown in Table IV together with the date at which the samples were obtained. The results indicate a situation little different from that disclosed in 1946.

It is possible that the tablets did not contain the nominal amount of glyceryl trinitrate when freshly made; in the case of samples E, H, J, and K this seems highly probable—unless the products were very old. This is a very unsatisfactory state of affairs. In 1935 a paper was published by Bari<sup>3</sup> in which he showed that the final concentration of nitroglycerin in the tablets was affected by the duration and temperature of drying and by the concentration of nitroglycerin solution used. It was shown, for example, that tablets dried in a current of air at 10° to 12°C. for 1 hour showed a loss of 24 per cent. of the nitroglycerin originally present, whilst drying at 50°C. for 5 hours caused a loss of 48·05 per cent. It is obviously essential that an assay of the prepared granules should be carried out before the tablets are compressed.

It seemed advisable that the problem of the stability of glyceryl trinitrate tablets should be further explored and a series of experiments were started to investigate:—(1) the effect of the reaction of the cocoa on the rate of loss of nitroglycerin; (2) the effect of the size of the tablet on the rate of loss of nitroglycerin; (3) the stabilising effect of various substances and the effect of the presence of cocoa. Meek's work had been repeated in our laboratory in 1935 and 1936. Some tablets were prepared containing only lactose and glyceryl trinitrate, and others containing lactose, glyceryl trinitrate and a lubricant, and a third lot containing lactose, non-alkalised cocoa, glyceryl trinitrate and a lubricant. The tablets were assayed at intervals during a year's storage at room temperature; the results of the assays are given in Table V. The tablets containing cocoa were prepared using a slightly acid granulating medium so that any alkalinity of the cocoa was neutralised. Whilst the results confirm Meek's findings that tablets made with lactose alone keep better than tablets containing cocoa in addition, they do not confirm his findings that glyceryl trinitrate tablets made with lactose lose no nitroglycerin in 1 year.

TABLE V

Ingredients other than nitroglycerin :	Lactose	Lactose and lubricant	Lactose, cocoa and lubricant
Age of tablets on assay	Nitroglycerin present as percentage of original strength		
6 weeks ... ..	95·4	95·4	80·7
4 months ... ..	89·7	89·0	82·8
1 year ... ..	93·0	88·5	77·3

*Effect of the reaction of the cocoa on glyceryl trinitrate content.* Three commercial samples of cocoa were obtained, one "non-alkalised" and two samples of well-known "soluble" cocoas. 1 g. of each was shaken with 10 ml. of distilled water, recently boiled and cooled, the suspension was filtered and the pH value of the filtrate determined. The pH of the "non-alkalised" cocoa was 5·75 and the pH values of the "soluble" cocoas were 7·1 and 7·3. Tablets were made from each sample of cocoa using the official formula for chocolate basis and granulated with distilled water.

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Tablets were stored at room temperature (20°C.) and at 37°C. for 1 year and assayed at intervals of 3 months. The results are shown in Table VI and are expressed as percentages of the original nitroglycerin contents. The tablets made from cocoa having a low pH value retained their nitroglycerin content very much better than those having a higher pH value, particularly at 37°C.

TABLE VI  
EFFECT OF pH OF COCOA ON STABILITY OF GLYCERYL TRINITRATE

Period of storage	Tablets made from cocoa pH 5.75		Tablets made from cocoa pH 7.1		Tablets made from cocoa pH 7.3	
	Temperature of storage		Temperature of storage		Temperature of storage	
	20°C.	37°C.	20°C.	37°C.	20°C.	37°C.
3 months ... ..	100	per cent. 97.5	98.7	per cent. 74.0	99.6	per cent. 76.5
6 months ... ..	93.6	80.5	88.5	55.5	88.5	56.0
12 months ... ..	92.5	72.0	89.5	43.5	83.7	43.5

*Effect of tablet size on rate of loss of glyceryl trinitrate.* Batches of tablets were made using the official chocolate basis and a proprietary basis, and in each case tablets with a weight of 5 grains and of 2 grains were prepared. Each tablet contained 1/100 grain of glyceryl trinitrate. Each of the 4 batches of tablets was divided and one half of each was stored at room temperature (20°C. approximately) and the remainder at 37°C. Periodic assays were carried out and the results are recorded in Table VII as percentages of the original strength. The size of the tablet appears to have had no appreciable effect upon the rate of loss of the glyceryl trinitrate.

TABLE VII  
EFFECT OF TABLET SIZE ON RATE OF LOSS OF GLYCERYL TRINITRATE

Period of storage	5 grain tablets				2 grain tablets			
	B.P. basis		Proprietary formula		B.P. basis		Proprietary formula	
	Temperature of storage		Temperature of storage		Temperature of storage		Temperature of storage	
	20°C.	37°C.	20°C.	37°C.	20°C.	37°C.	20°C.	37°C.
3 months ... ..	per cent. 95.8	89.5	per cent. 94.5	90.5	per cent. 98.0	81.5	per cent. 93.5	83.0
6 months ... ..	92.0	72.0	89.7	79.5	96.0	75.8	96.0	78.0
12 months ... ..	88.5	67.5	82.0	66.5	93.0	67.8	89.5	67.5

*Effects of various "stabilising" agents and the effect of the presence of cocoa.* On theoretical grounds glycerol would appear likely to have a greater stabilising effect than castor oil, which had been previously shown to have some value. As other polyhydric alcohols might have a greater stabilising action than glycerol, mannitol and sorbitol were included in the experiments. A proprietary brand of polyethylene glycol

was also tested. A series of glyceryl trinitrate (gr. 1/100) tablets were made, using the following bases:

- A. B.P. basis.
- B. B.P. basis with 0.5 per cent. of castor oil added.
- C. Lactose with 20 per cent. of cocoa and 5 per cent. of glycerol.
- D. Lactose with 20 per cent. of cocoa and 10 per cent. of mannitol.
- E. Lactose with 20 per cent. of cocoa and 5 per cent. of polyethylene glycol.
- F. Lactose with 20 per cent. of cocoa and 10 per cent. of sorbitol.
- G. Dextrose with 20 per cent. of cocoa and 0.5 per cent. of castor oil.
- H. Lactose with 0.5 per cent. of castor oil added.
- I. Lactose with 5 per cent. of glycerol.
- J. Lactose with 10 per cent. of mannitol.
- K. Lactose with 10 per cent. of sorbitol.

Only "non-alkalised" cocoa was used in these experiments; a slightly acid granulating solution was used throughout. Dextrose was included (G.) because Meek reported that "tablets made with glucose had kept remarkably well." Tablets were stored in corked bottles in the dark at room temperature (20°C. approximately) and at 37°C. for 18 to 21 months and assayed at intervals. The results are recorded graphically, those for tablets stored at 20°C. in Figure 1 and those for tablets stored at 37°C. in Figure 2.

With the exception of the tablets containing the polyethylene glycol all samples had retained more than 85 per cent. of their original strength for 12 months at room temperature (Figure 1). The official tablets had lost strength steadily and would probably have fallen to 81 per cent. of nominal strength in 2½ years. The addition of 0.5 per cent. of castor oil had reduced the rate of loss a little (3 per cent. in 18 months). In general the tablets containing cocoa had lost strength more rapidly than those without cocoa (Figure 1). The case of the lactose with castor oil is surprising; the loss of glyceryl trinitrate at room temperature is greater than we would have expected. The tablets containing lactose with added glycerol, mannitol or sorbitol have all retained their activity remarkably well, no tablets containing less than 95 per cent. of the original glyceryl trinitrate content after 18 months. When we consider the tablets stored at 37°C. the difference is much more marked. No tablets containing cocoa retained 81 per cent. of the original glyceryl trinitrate for much more than 6 months; after 18 months all tablets containing cocoa had less than 65 per cent. In the tablets without cocoa the higher alcohols have again proved to be very effective stabilisers. The tablets made with lactose and 5 per cent. glycerol and those made with lactose and mannitol still had 95 per cent. of the original glyceryl trinitrate after 18 months storage at 37°C. (Figure 2).

In the cases of the mannitol and sorbitol tablets the experiments had been repeated a number of times, the method of incorporating the mannitol and nitroglycerin into the tablets being varied. In the Figures the mean of the results is shown.

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*Assay.* The method of assay used prior to 1932 was a modification of Method II of the "Report on Nitroglycerin" in the Journal of the Association of Official Agricultural Chemists<sup>4</sup> for 1926 which involved the extraction of the powdered tablets with ether, evaporating the ether, and distilling off the nitrogen as ammonia from caustic potash and

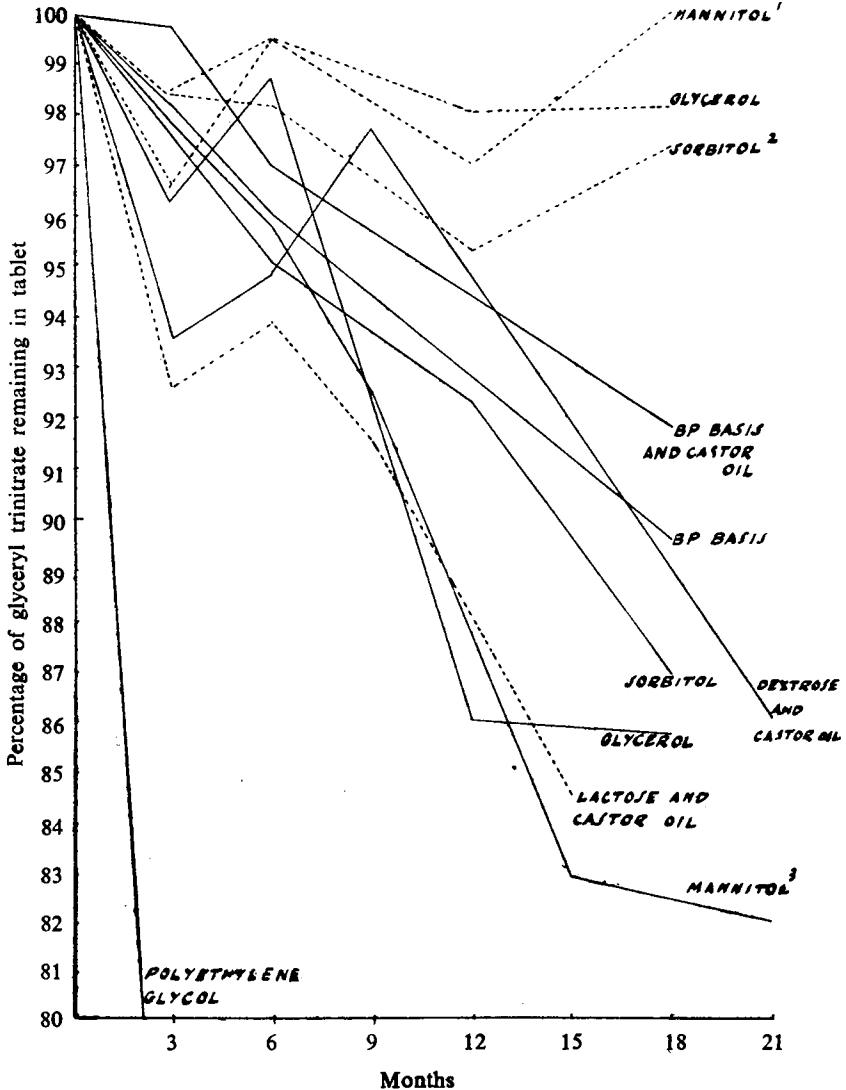


FIG. 1. Keeping properties of tablets of glyceryl trinitrate prepared with various bases and stored at room temperature.

With cocoa ——— Without cocoa - - - - -

Polyethylene glycol base showed 31.5 per cent. loss after 3 months.

1. Mean of 4 experiments. 2. Mean of 2 experiments. 3. Mean of 3 experiments.

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Devarda's alloy via a Murray scrubber and a Kjeldahl trap into standard acid. Since March, 1932, all the determinations referred to in this paper have been carried out using the method of assay published by Anderson<sup>5</sup> in preference to the official method. In our experience the former gave more consistent results, and for our purposes the larger number of tablets required for the assay was no disadvantage. The method depends upon the steam distillation of the nitroglycerin from a

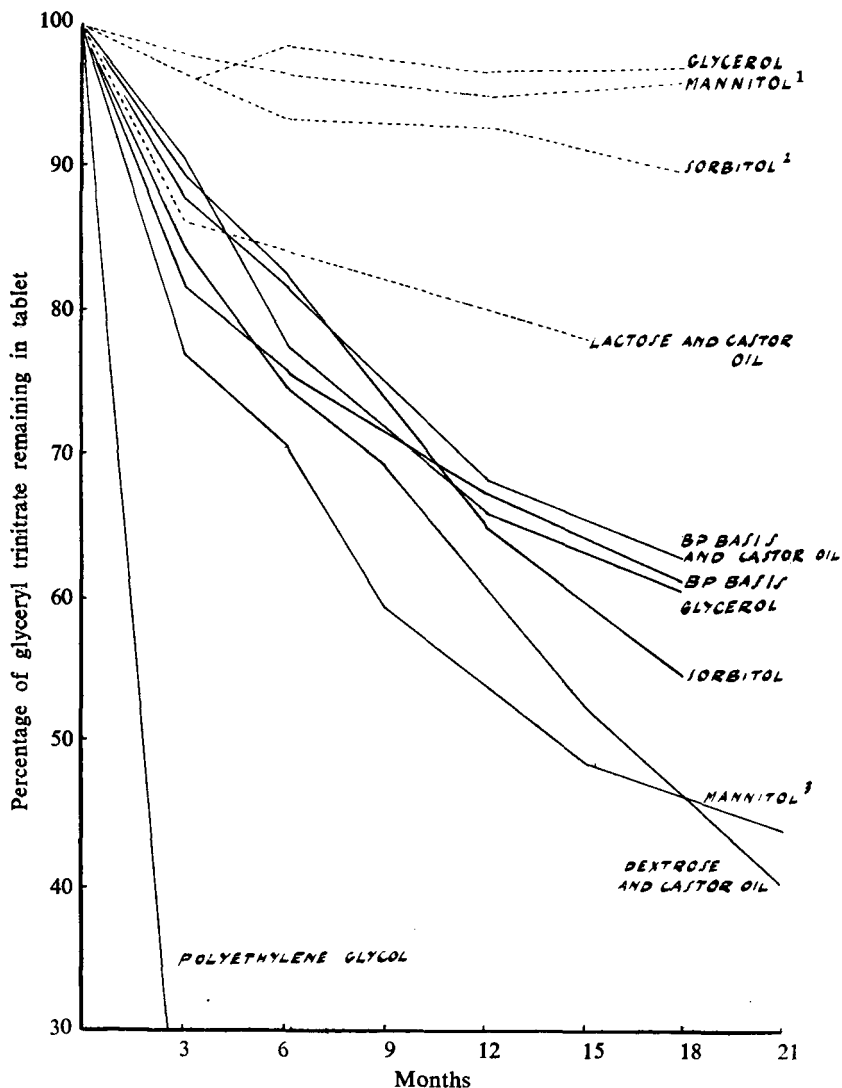


FIG. 2. Keeping properties of tablets of glyceryl trinitrate prepared with various bases and stored at 37°C.

With cocoa ——— Without cocoa - - - - -

1. Mean of 4 experiments. 2. Mean of 2 experiments. 3. Mean of 3 experiments.



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slightly acid solution or suspension of the tablets and collection in alkali. The alkaline distillate is redistilled via a Murray scrubber and a Pyrex Kjeldahl trap into 0.02N acid and back titrated with 0.02N alkali using a screened methyl red indicator. The only modifications introduced into the published method are the use of the screened indicator and elimination of the use of a 300 ml. Kjeldahl flask as a water trap in the ammonia distillation.

### DISCUSSION

It seems to be established that there is a factor in cocoa other than the alkalinity which accelerates the loss of glyceryl trinitrate from tablets. What this factor may be or what is the mechanism of its action we have as yet no evidence. It may be connected with the conversion of the labile isomer to the more stable form. Experiments carried out some years ago, of which data are no longer available, indicated that the use of fat-free "non-alkalised" cocoa did not increase stability of the tablets nor did the solution of glyceryl trinitrate in oil of theobroma and its re-incorporation into defatted cocoa have any appreciable effect upon the rate of loss of nitroglycerin. Agents which appear to reduce the loss of glyceryl trinitrate in the presence of lactose are not effective in the presence of cocoa, this is particularly marked at tropical temperatures. The information which has been gained suggests that it would be advisable to discontinue the use of chocolate basis in the preparation of these tablets. We would recommend that the British Pharmacopœia should direct that tablets of glyceryl trinitrate should be prepared with lactose and should contain 5 per cent. of glycerol. It should then be practicable to set narrower limits for the glyceryl trinitrate content of these tablets. The use of lactose and glycerol should also ensure that tablets of glyceryl trinitrate B.P. in whatever part of the world they are dispensed will contain more nearly the stated dose than is the case at present.

### SUMMARY

1. Analyses of commercial samples of glyceryl trinitrate tablets have shown that the tablets may contain as little as 40 per cent. of the nominal strength.

2. Tablet size appears to have no significant effect upon the rate of loss of glyceryl trinitrate.

3. Earlier reports that the alkalinity of commercial "soluble" cocoa will cause rapid loss of nitroglycerin have been confirmed. The use of "non-alkalised" cocoa or even slightly acid cocoa will still result in unstable tablets, particularly at tropical temperatures.

4. The use of certain stabilisers such as glycerol is very effective in reducing the rate of loss of glyceryl trinitrate in the absence of cocoa.

5. It is recommended that the chocolate basis be replaced by lactose and glycerol in the official tablet.

We should like to express our thanks to Mr. W. F. Grove, of the Control Laboratories, Wellcome Chemical Works, for help with the

earlier assays, and to the Directors of The Wellcome Foundation Limited for permission to publish this paper.

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#### DISCUSSION

The paper was presented by MR. D. STEPHENSON.

MR. H. DEANE (Long Melford) observed that the tablets of glyceryl trinitrate prepared originally by Martindale were quite different from those which were official in the B.P. The 10 per cent. alcoholic solution of glyceryl trinitrate now used was not available to Martindale, and it would be of interest to know how the stability of tablets prepared by the two methods compared.

MR. A. NUTTER SMITH (Nottingham) pointed out that there were two B.P. methods of preparing the tablets. Either the granules could be prepared separately and the solution of glyceryl trinitrate incorporated subsequently, or the glyceryl trinitrate could be incorporated during the process of granulation. He asked which method had been used. It would also be interesting to know whether the tablets containing glycerin became hygroscopic on storage and whether any kind of tropical storage tests had been carried out. As a tablet maker he would probably have chosen mannitol as the basis, although it was less readily available than glycerin, because it would be easier to handle in the granulation process. He asked how the tablets referred to in Table IV were packed.

MR. STEPHENSON, in reply, said that the effect of dissolving glyceryl trinitrate in melted cocoa butter (as used by Martindale) had been investigated with very similar results, as decomposition of the glyceryl trinitrate seemed to result. The glyceryl trinitrate solution had been incorporated in the tablets by both the official methods. Although more was lost during the direct method of incorporation, he considered that a more even distribution could be obtained in that way. It was important at that stage to make sure that the granules were quite dry. The tablets were not hygroscopic; indeed, some which had been stored at 37°C. were brittle and hard. In comparison with lactose tablets the glycerin tablets remained firm and hard at 60 to 70 per cent. relative humidity, but at 80 per cent. they appeared to be more hygroscopic. Glycerin was recommended rather than mannitol as the alcohol of choice on the basis of mass action. All the tablets referred to in Table IV had been bought on prescription and the authors had not been concerned with the way in which they had been stored.