Reliability of Accelerated Storage Tests to Predict Stability of Vitamins (A, B_1, C) in Tablets

By REAL TARDIF

Elevated temperature storage tests and a graphic method of calculation were used to determine thermodegradation rates of vitamin A, thiamine, and ascorbic acid (vitamin C) in three polyvitamin tablet formulations containing (*a*) 3–4 per cent moisture and sucrose filler, (*b*) 3–4 per cent moisture and mannitol filler, and (*c*) less than 1 per cent moisture and sucrose filler. By replacing the sucrose filler with mannitol (formulation *B*) the pseudo first-order thermodegradation rates were reduced by 35 per cent (vitamin A), 20 per cent (thiamine), and 13 per cent (ascorbic acid). If the moisture content is maintained below 1 per cent, the pseudo first-order thermodegradation rates were reduced by 78 per cent (vitamin A), 73 per cent (thiamine), and 70 per cent (ascorbic acid). Assays performed on samples of formulation *C* stored at room temperature for 15, 24, 31, 35, and 38 months confirmed that the calculated thermodegradation curve of this vitamin preparation could be used safely as an estimate of potency over a 3-year period.

UNTIL RECENTLY, the determination of vitamin stability, essential in establishing expiration dating in various polyvitamin formulations, was dependent entirely on prolonged studies at room temperature. Such an approach is time consuming, costly, and no longer adaptable to modern means of production.

In the field of accelerated storage tests, a marked theoretical advance came from the detailed work of Garrett (1) who, by applying the Arrhenius equation to the thermodegradation rates of a liquid vitamin preparation at elevated temperatures, has been able to predict the degradation rate at lower temperatures. For those who might consider the calculations rather formidable without some prior experience in this field, Campbell *et al.* (2) suggested a simplified graphical calculation to predict vitamin potency.

This paper presents the results of an investigation carried out with three different polyvitamin tablet formulations to establish the validity of the general procedure (for liquids) described by Garrett when applied to solid formulations. The Campbell (2) graphical solution was followed for this purpose.

EXPERIMENTAL

The tablet formulations investigated had the following composition: vitamin A, 7500 I.U.; vitamin D, 1500 I.U.; thiamine, 1.5 mg.; ascorbic acid, 100 mg.; pyridoxine, 1.1 mg.; riboflavin, 2.2 mg.; niacinamide, 10 mg.; filler (sucrose or mannitol), 200 mg.; weight of tablet core, 400 mg.; weight of coated tablet, 650 mg.

The differences between the formulations were in the percentage of moisture and/or the composition of the filler which accounted for approximately half the weight of the tablet core. Formulation *A* contained 3–4% moisture and sucrose; formulation *B* contained 3–4% moisture and mannitol; formulation *C* contained less than 1% moisture and sucrose.

Granulations were made by wet process using ethylcellulose and alcohol. Drying operations were performed under controlled temperature and forced air circulation. Pan coating procedure was employed; formulation *C* consists of part of formulation *A* subjected to vacuum drying before finishing the coating operation. The water content was determined on the finished coated tablets.

Three constant temperature oil baths (Fig. 1) set at 50°, 60°, and 70° were used for this investigation. The tablets were sealed in glass ampuls and submerged in the oil. When possible, the vitamin assays were performed the day the samples were taken out of the oil baths; if not possible the samples were stored at 5°. As much as possible, the samples at 70° were withdrawn and analyzed every second day, those at 60° every third day, and those at 50° every fourth day for approximately 40 days. Immersion of the sealed glass ampuls into the oil baths was accompanied by a slight air pressure build up. For formulation *A* at 70°, this pressure was increased by a release of 1 mole of CO_2 gas for each mole of ascorbic acid decomposed (3). The high incidence of breakage of these ampuls and the appearance of a dark gummy mass which leaked from the tablet motivated the removal of these tablets from the test.

Finally, five different lots of tablets (formulation *C*) stored at room temperature for 3 years were assayed at various intervals to check the reliability of the calculated thermodegradation rates. Only the three most critical vitamins (A, B_1, and C) with respect to adherence to label claim were studied. Vitamin A was analyzed by the hexane-destruction method (4), thiamine by the thiochrome method (5), and ascorbic acid by titration with 2,6-dichlorophenolindophenol dye (5).

RESULTS

In Fig. 2, the three tablet formulations, stored for 40 days at 50°, are compared with corresponding formulations kept at room temperature during the same period. In formulation *A*, the tablets were cracked, a dark brown gummy mass had leaked out,

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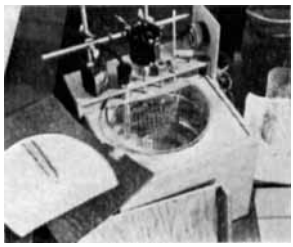

Fig. 1.—Constant temperature oil baths.

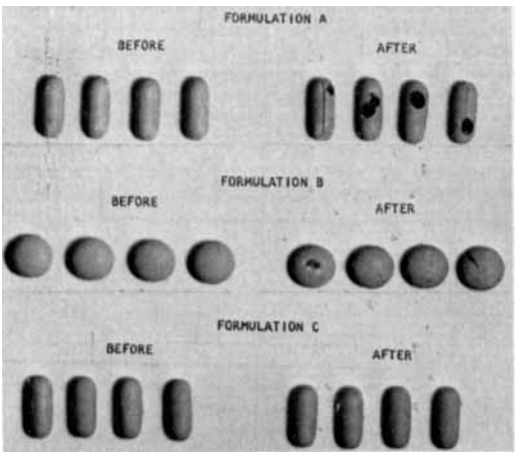

Fig. 2.—Comparison of formulations *A*, *B*, and *C* after 40 days' storage at 50°C.

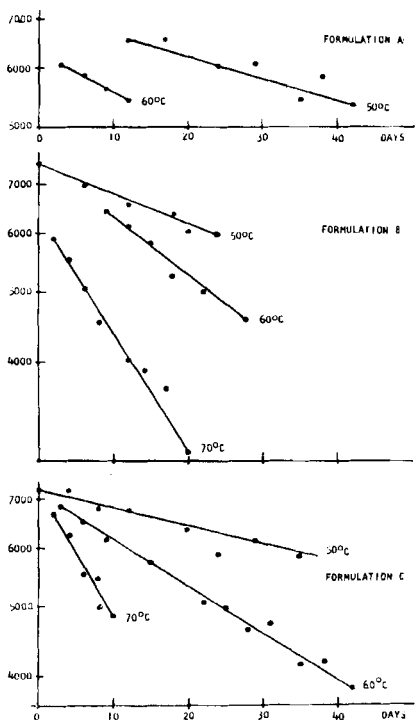

Fig. 3.—Pseudo first-order plots of the thermodegradation of vitamin A.

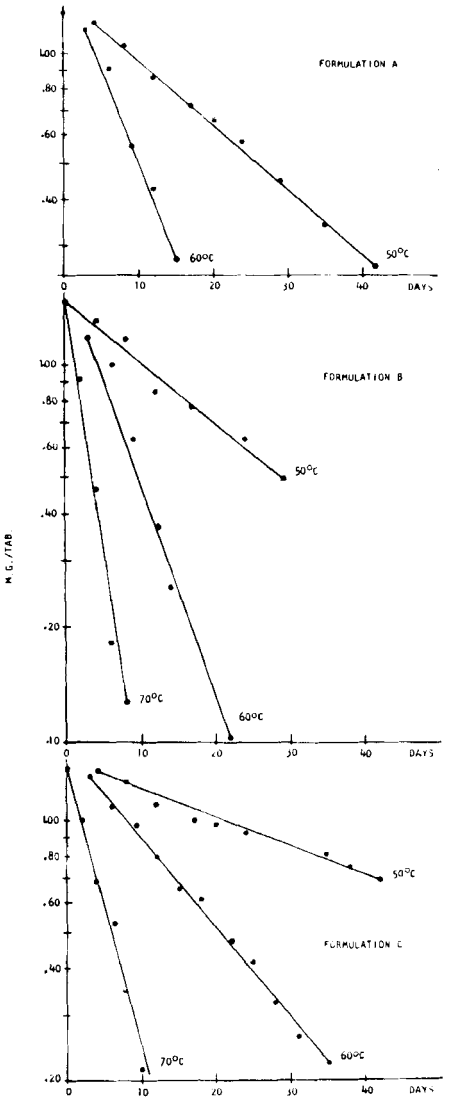

Fig. 4.—Pseudo first-order plots of the thermodegradation of thiamine.

and the yellow coating had faded; in formulation *B*, the tablets were cracked, chipped, and faded; in formulation *C*, the only change was a slight fading of color. As formulation *B* was a pilot plant size lot, a different shape (round) was adopted to enable the coater to sort them once coated with regular formulation *A*.

Figures 3, 4, and 5 show pseudo first-order plots (semilog) of the thermodegradation (potency *versus* time) of vitamin A, thiamine, and ascorbic acid for the three formulations. The calculated slopes (2) corresponding to each linear curve are reported in Table I. The best fit of most of the determined points and the agreement between initial assays, determined by analysis and as given by extrapolation of the line to zero time, were considered the most important guides in tracing the curves.

Figures 6, 7, and 8 illustrate the Arrhenius plots of calculated thermodegradation rates K^1 (solid lines) for vitamin A, thiamine, and ascorbic acid with their

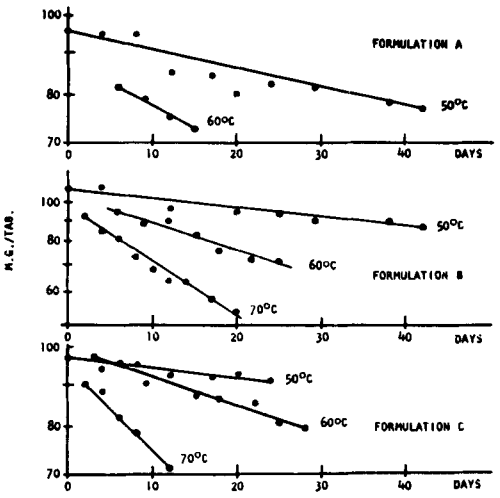

Fig. 5.—Pseudo first-order plots of the thermodegradation of ascorbic acid.

TABLE I.—VALUES OF CALCULATED SLOPES (K^1) FOR EACH THERMODEGRADATION CURVE

Formulation	Storage Temp., °C.	Vitamin A	Thiamine	Ascorbic Acid
A	50	0.0031	0.0174	0.0024
	60	0.0056	0.0516	0.0058
	70	...	...	...
B	50	0.0039	0.0167	0.0023
	60	0.0078	0.0473	0.0065
	70	0.0162	0.1330	0.0140
C	50	0.0024	0.0074	0.0013
	60	0.0065	0.0241	0.0035
	70	0.0159	0.0767	0.0103

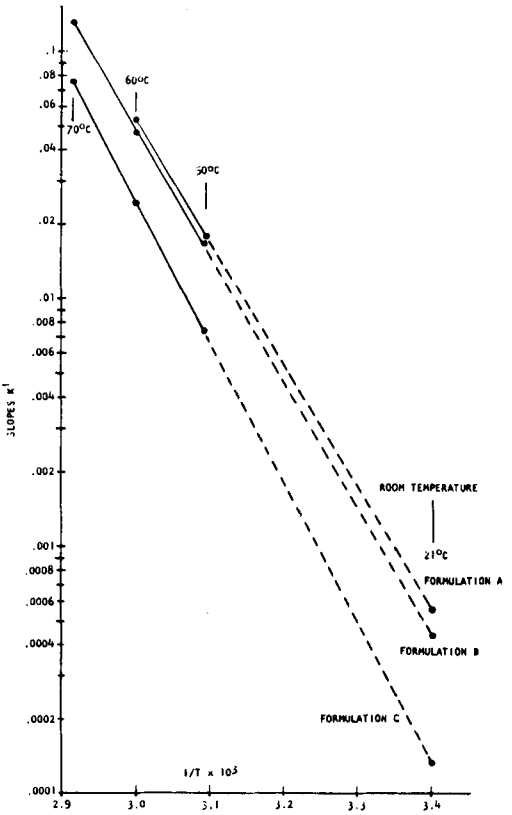

Fig. 7.—Arrhenius plots of slopes K^1 (solid lines) with extrapolations to room temperature (broken lines) for thiamine.

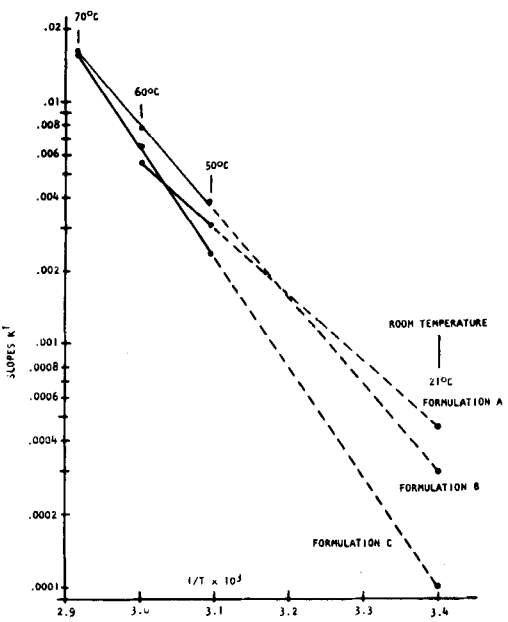

Fig. 6.—Arrhenius plots of slopes K^1 (solid lines) with extrapolations to room temperature (broken lines) for vitamin A.

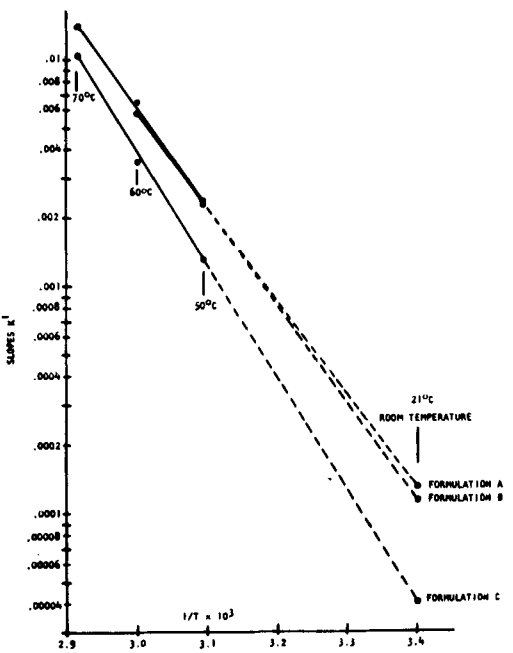

Fig. 8.—Arrhenius plots of slopes K^1 (solid lines) with extrapolations to room temperature (broken lines) for ascorbic acid.

TABLE II.—VALUES OF THERMODEGRADATION RATES (K^1) AT ROOM TEMPERATURE FROM EXTRAPOLATED CURVES

Formulation	Vitamin A	Thiamine	Ascorbic Acid
A	4.6×10^{-4}	5.6×10^{-4}	1.3×10^{-4}
B	3.0×10^{-4}	4.4×10^{-4}	1.1×10^{-4}
C	1.0×10^{-4}	1.3×10^{-4}	0.4×10^{-4}

TABLE III.—MONTHS OF MAINTENANCE AT ROOM TEMPERATURE FOR 90% LABELED POTENCY

Vitamins	Formulation *A*	Formulation *B*	Formulation *C*
Vitamin A	13	19	58
Thiamine	10	13	38
Ascorbic acid	24	28	82

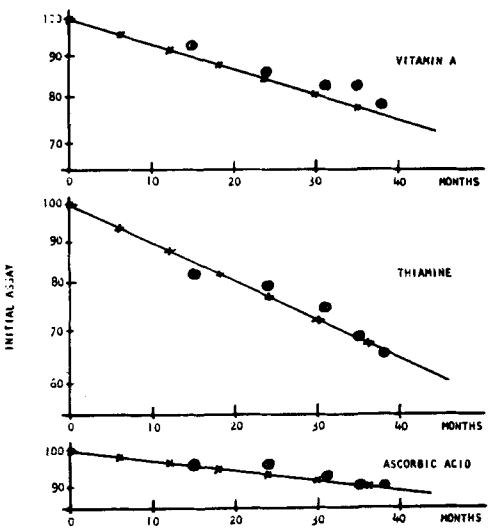

Fig. 9.—Prediction of stability of vitamin A, thiamine, and ascorbic acid in tablet formulation *C*. Asterisks represent the calculated prediction by graphical method and the circles the actual values of five different lots stored at room temperature for the times shown.

respective extrapolations (broken lines) to prevailing room temperature (21°) in Canada. Values of the thermodegradation rates obtained from the graphs are reported in Table II.

Using the thermodegradation rates of Table II, the months of maintenance at room temperature for a 90% label claim were calculated by the Campbell simplified method (2). Results of this prediction are reported in Table III.

Figure 9 shows the calculated thermodegradation plots for the three vitamins, represented by asterisks and solid lines. The actual analytical values obtained on samples (formulation *C*) stored at room temperature for the period of time shown are represented by circled dots.

DISCUSSION

The above results corroborate previous findings (1, 2, 6, 7) and demonstrate that it is not necessary to determine the mechanism of degradation. If some property of the degradation is followed as a function of time, and the findings are then linearized, a good estimate of the thermodegradation rates will be obtained from the slope. Statistical procedures suggested by Garrett (1, 6) and Campbell (2) are recommended to establish a certain degree of confidence in predicting stability. When possible, it also is recommended that the data be fitted by the least-squares method.

It is evident that the moisture in excess of 1% in formulations *A* and *B* was responsible for the thermal instability of these three vitamins. Liquefaction occurred (appearance of brown gummy mass), and the pyrolytic degradation was greatly accelerated (8). When the tablet formulation was thoroughly dried (less than 1%), the pyrolytic stability was greatly enhanced. For example, by reducing the moisture content of formulation *A* (3%) to less than 1% (formulation *C*), thermodegradation rates were reduced by 78, 73, and 70%, respectively, for vitamin A, thiamine, and ascorbic acid.

Experimental results (circled dots of Fig. 9) obtained on five different lots of formulation *C*, stored at room temperature for the periods shown, are all very close to the potencies predicted (solid lines through asterisks) by calculation with their respective thermodegradation rates shown in Table II. That these predictions were verified five times gave confidence in this method.

Garrett's comment in his recent review (9) might be repeated here: "The prediction of solvolytic stability of drugs in solid forms is also based on good science just as for liquids."

SUMMARY

A stability study of vitamin A, thiamine, and ascorbic acid was made on three polyvitamin tablet formulations.

The thermodegradation rates were determined and found to be pseudo first-order for the three vitamins.

A reduction in moisture content from 3 to 1% showed a reduction in thermodegradation rates by 70 to 80%.

Validity of the prediction made on formulation *C* (less than 1% moisture) was checked over a 3-year period with five different lots of the same formulation.

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