THE STABILITY OF LIQUID MULTIVITAMIN PREPARATIONS DURING USE

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The stability during normal use of vitamin A, vitamin C and thiamine in 6 liquid multivitamin preparations has been examined. Three samples were below label claim when purchased but no further losses occurred during storage of unopened bottles. Destruction of the vitamins was increased by daily removal of a portion of the contents and the stability of most samples stored at room temperature was unsatisfactory. The study suggests that the results of stability tests should be examined more critically to ensure not only that the products meet label claim when purchased, but also maintain a satisfactory potency during normal use. From the consumer's point of view the use of expiration dates which take account of loss during normal use would be most valuable. The finding of retrovitamin A in one preparation suggests the need for more detailed study of the complex changes which may take place in these preparations during storage and of methods to evaluate such changes.

In 1955, Campbell and McLeod reported that many market samples of oral multivitamin preparations, particularly those over one year old, did not meet the label claim for one or more vitamins. They suggested that the situation could be improved by the use of expiration dates based on actual shelf life. Since that time legislation has been enacted (F.D.A.R., 1954) requiring manufacturers of vitamin preparations to determine the period during which the drug will maintain its labelled potency and to indicate on the label the coded date of manufacture or an expiration date after which the drug is not recommended for use. Although these regulations afford the consumer some protection against purchasing products which have passed their normal shelf life the possibility exists that a product may meet labelled claim when purchased but may fall in potency during normal use. There appears to be no published date on stability during this period.

This report concerns the stability of representative vitamin products during the time and under conditions encountered in normal use in the home. Liquid preparations were used because they were the most likely preparations to be adversely affected by the conditions of the experiment.

Experimental

Three bottles each of the largest available size of six liquid multivitamin preparations were purchased from a local wholesale outlet. The three bottles of each product were of the same batch (lot) number but no attempt was made to choose products of a particular age. Two bottles of each product were opened and assayed for vitamin A, vitamin C and thiamine, while the unopened bottles were refrigerated at about 4° until the end of the experiment. One of the opened bottles was refrigerated,

the other kept at room temperature, and from both a recommended daily dose was removed each day except Saturday and Sunday. Vitamin A, vitamin C and thiamine were determined at intervals until the bottles were emptied. Vitamin A was determined by the U.S.P. XVI method (1960) where possibly, by the antimony trichloride method, by a chromatographic method (Murray, 1962) and, biologically by the liver storage assay (Ames and Harris, 1956). Vitamin C was determined by 2,6-dichlorophenolindophenol titration and thiamine by conversion to thiachrome (Methods of Vitamin Assay, 1951).

Results and Discussion

The initial and final vitamin contents of the samples are shown in Table I and all analyses are plotted in Fig. 1. Samples containing less

TABLE I

POTENCY OF LIQUID MULTIVITAMIN PREPARATIONS DURING USE (AS PER CENT OF LABEL CLAIM)

Product	Vitamin	Refrigerated			Room temperature	
		Initial	Final		Initial	Final
			Opened	Unopened		
1	A	84	103	84	104	98
	C	100	92	98	100	69
	B_1	104	100	106	106	79
2	A	111	107	111	107	95
	C	97	97	99	96	89
	B_1	130	137	135	133	118
3	A	90	85	93	93	94
	C	124	114	117	126	88
	B_1	111	110	114	116	90
4	A	90	89	92	92	77
	C	93	93	93	94	86
	B_1	103	101	103	107	91
5	A	108	116	135	154	98
	C	109	82	110	108	67
	B_1	124	97	126	127	75
6	A	111	103	103	105	95
	C	85	64	86	86	27
	B_1	100	88	98	104	69

than 95 per cent of the labelled amount of the vitamins were arbitrarily considered not to meet the label claim. Initially, one product (No. 4) contained less than the labelled amount of vitamins A and C, one, less than the labelled amount of vitamin A (No. 3) and one was deficient in vitamin C alone (No. 6). In addition, one of two bottles of another product (No. 1) did not meet label claim for vitamin A but this might be because of inadequate mixing. The very high vitamin A content of product 5 was verified by repeated analyses. At least half of the products, therefore, did not meet label claim initially for one or more of the vitamins.

All products exhibited good stability, as they should, when stored unopened in the refrigerator for periods of from 8 to 24 weeks. When, under the same storage conditions, daily doses were removed, two

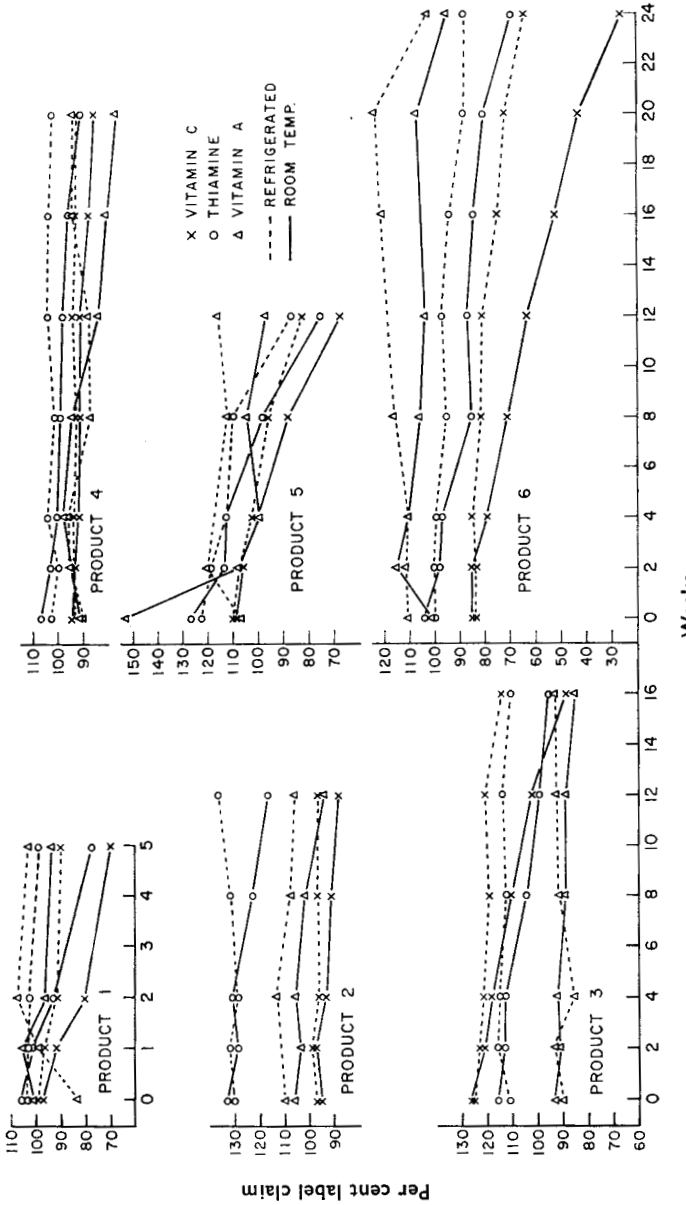

FIG. 1. Changes in potency of vitamin A, vitamin C and thiamine during storage of liquid multivitamin preparations.

products (Nos. 5 and 6) lost more than 10 per cent of vitamin C and thiamine but vitamin A proved relatively stable under these conditions. At the end of this storage period only one product met the label claim for all three vitamins.

The decrease in potency was more marked in samples held at room temperature. Losses of more than 10 per cent were found in all samples

for thiamine, in samples 1, 3, 5 and 6 for vitamin C, and in samples 2, 4 and 5 for vitamin A. Under these conditions no product met the label claim for the three vitamins at the end of the test period.

The least satisfactory aspect of these products was in their low potency when purchased. Had the products as purchased contained the amount indicated on the label plus a 10 per cent overage, all but two of the refrigerated samples (Products 5 and 6) would have met the label claim at the end of the experiment. Vitamin C and thiamine were markedly unstable in products 5 and 6. Samples held at room temperature, on the other hand, lost up to 59 per cent of their vitamin content and a 10 per cent overage would not have permitted any to meet the label claim at the end of the experiment. A 15 per cent overage would have permitted two products to do so. Although refrigeration was very important in the stability of these products only one product's label had a statement to this effect.

Most of the products examined were available in smaller sizes in which stability could have been studied over a shorter period. Had the samples been half the size used, and had all met claim initially, three would have been deficient at the end of the experiment. Obviously, the stability of liquid multivitamin preparations during use requires further study.

It is obvious that the use of expiration dates is much more valuable to the consumer than is the coded date of manufacture and such dates should allow for losses incurred during normal use.

An interesting analytical problem arose in these studies. The U.S.P. XVI method for vitamin A could not be applied to Product 6 since the absorbance curve was distorted. The values shown in Table I were obtained by the antimony trichloride method because it was thought this would measure any change in potency. At the beginning and end of the experiment, Product 6 (unrefrigerated sample) was assayed by the U.S.P. spectrophotometric procedure after purification by chromatography (Murray, 1962) and by the liver storage assay. The results as per cent of label claim are:

	Method		
Week	$SbCl_3$	Chromatographic	Biological
0	105	58	67
24	95	10	43

The values found by the antimony trichloride method greatly overestimated biological potency and did not measure the decrease in potency which occurred during the experiment. It is obvious that this method is inadequate for estimating the potency of certain samples. Chromatographic purification gave a fair estimate of the initial potency but grossly underestimated it at the end.

The absorbance curve of the interfering substance removed by chromatography at the end of the experiment is shown in Fig. 2. The peaks at 330 350 and 370 mμ identify it as retrovitamin A (Beutel, Hinkley and Pollak,

1955), a compound which produces a blue colour with antimony trichloride but which has been reported to have a low biological potency (Shantz, 1950). It has not been previously reported to occur in pharmaceuticals although it is recognised (Miguchi and Reinstein 1959) that anhydrovitamin may do so on occasion. Since both retro and anhydrovitamin A interfere with the estimation of vitamin A activity, their occurrence in pharmaceuticals is being further investigated.

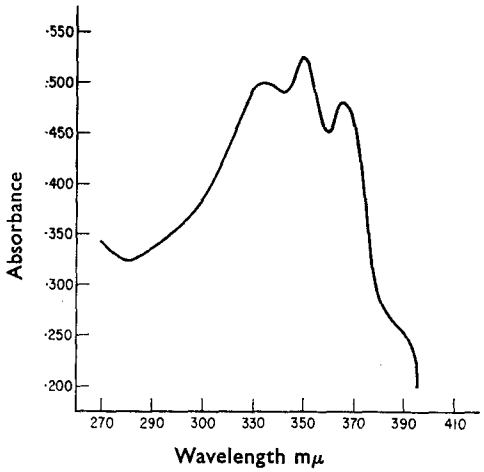

FIG. 2. Absorbance curve of retrovitamin A isolated from a liquid multivitamin preparation.

It may be concluded that both overages and adjustment of formulation are necessary to ensure that some liquid multivitamin preparations meet the label claim when purchased and maintain it during normal use. The stability of all the products examined was improved by refrigeration.

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