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ACCELERATED TESTS IN RELATION TO SHELF-LIFE OF MULTIVITAMIN LIQUID PREPARATIONS

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ABSTRACT

Chemical kinetics for the decomposition of vitamin A, vitamin B_1, sodium pantothenate, folic acid and vitamin B_{12} were studied at higher temperatures in the case of two multivitamin preparations. Vitamin A, vitamin B_1 and sodium pantothenate were found to decompose in accordance with the first order reaction at higher temperatures, whereas folic acid and vitamin B_{12} did not follow first order kinetics. It was concluded that, in the cases of multivitamin preparations, accelerated study at higher temperatures was feasible only in the case of vitamin A, vitamin B_1 and sodium pantothenate.

INTRODUCTION

Multivitamin preparations have been criticised for inadequate control, stability and potency, hence the evaluation of shelf-life period is necessary before marketing them. In order to avoid undesirable delay in evaluating potential formulations at shelf-life temperatures, the manufacturer attempts to predict stability under conditions of room temperature or actual storage conditions, through the use of data for rates of decomposition obtained at elevated temperatures. Two techniques are employed for such accelerated tests--non-isothermal tests and isothermal tests. An accelerated non-isothermal test, which enables determination of the rate constant of decomposition at storage temperature, is the technique (1) in which the temperature of the preparation is steadily raised in accordance with a predetermined programme and the samples are withdrawn at intervals and analysed for active ingredients. Though the data required to calculate the stability of the product are obtained in a single experiment lasting for one day, the test requires a strict schedule for temperature programming and use of high temperatures at which there is every likelihood of changes in mechanism of degradation. Besides the test will only be useful for studying the empirical stability of mono-

component systems usually having high activation energies. The iso-thermal procedure, though more elaborate, is accurate for multicomponent systems having both low and high activation energies. This procedure is based on heating the product at various (minimum three) fixed elevated temperatures for a fixed period of time and determining degradation rate constants from the data on the basis of first order reaction by using various kinetic equations. The rate constant at marketing or storage temperature is also determined graphically by plotting and extrapolating the Arrhenius relationship between rate constant and absolute temperature. The linearity of the plot confirms that the correct order of reaction for decomposition has been assumed. Deviations from linearity indicate that the wrong order of reaction has been chosen or that the mechanism of the reaction changes as the temperature is raised (2).

The feasibility of employing chemical kinetic principles to predict stability at shelf conditions from accelerated data on vitamin solid dosage forms was examined by Katz (3), Garrett (4) and Lachman (5). Accelerated aging test on liquid vitamin combinations have been conducted by Garrett (6) and Gambier (7).

Almost all the investigators obtained linear relationships with respect to Arrhenius plot for vitamin A, vitamin B_1,

sodium pantothenate, folic acid and vitamin B_{12} in multivitamin preparations on the basis of first order reaction and employed the results to predict the stability of these vitamins by extrapolation. We studied the decomposition kinetics of these vitamins in two multivitamin preparations and confirmed linear relationship with respect to vitamin A, vitamin B_1 and sodium pantothenate, but found that in the cases of folic acid and vitamin B_{12} the Arrhenius plots were non-linear. Hence the stability of these vitamins could not be predicted by extrapolation of the plot. The validity of the predicted rate constant from accelerated studies has been demonstrated by its close agreement with the rate constant determined from shelved preparations.

EXPERIMENTAL

Materials

The following two preparations were studied:

(1) Multivitamin drops containing vitamin A (6500 units), vitamin D_2 (1000 units), vitamin B_1 (2.5 mg), vitamin B_2 (0.4 mg), sodium pantothenate (2 mg), vitamin B_6 (1 mg), niacinamide (5 mg), vitamin C (50 mg) and vitamin E (1 mg) per 0.6 ml.

(2) Iron Vitamin-syrup containing ferrous gluconate (0.33 gm), vitamin B_1 (5 mg), vitamin B_2 (1 mg), niacinamide (12.5 mg), folic acid (0.6 mg) and vitamin B_{12} (3.33 mcg) per 15 ml.

Methods

100 ml of preparations were filled in 110 ml round amber glass bottles with pilfer-proof caps and were heated at 45°, 55° and 65° for 15 to 30 days in an air oven thermostatically regulated to maintain the temperature within $\pm$ 1°. The same samples were preserved at refrigeration temperature (4°C) to serve as standards. The thermal degradation of vitamin A, vitamin B_1, sodium pantothenate, folic acid and vitamin B_{12} were studied by assaying the components after various times of maintenance at elevated temperatures. Folic Acid, vitamin B_{12} and sodium pantothenate were assayed by microbiological technique and vitamin A and vitamin B_1 were assayed by the official spectrophotometric methods. Refrigerated samples were checked bi-weekly and no significant changes were noted for the duration of the study. The remaining vitamins being highly stable were not studied. Decomposition rate constants were determined from the following equation:

$$k = \frac{2.303}{t} \quad \log \quad \frac{Co}{C}$$

where t is the time in days, Co is initial concentration and C is the final concentration. The following equation (8)

$$\log \frac{k2}{k1} = \frac{Ea}{2.303\ R} \times \frac{T_2 - T_1}{T_1 T_2}$$

where k_2 and k_1 are decomposition rate constants at absolute temperatures T_2 and T_1 respectively and Ea is activation energy was used to evaluate $\frac{Ea}{2.303\ R}$.

$\frac{Ea}{2.303\ R}$ was determined thrice from the three ratios of decomposition rate constants namely $\frac{k_{65}}{K_{45}}$, $\frac{k_{55}}{K_{45}}$ and $\frac{k_{65}}{K_{55}}$.

The mechanism of decomposition and the linearity or non-linearity of the Arrhenius plot could be predicted from these three values. In the cases where these values did not differ significantly from one another, the value for decomposition rate constant at virtual temperature (taking it as 30° for India) was determined after taking the average value of $\frac{Ea}{2.303\ R}$. Linearity or non-linearity of the Arrhenous plot was confirmed by plotting log k against the reciprocal of absolute temperature. In the case of linear relationship the plot was extrapolated to virtual temperature (30°) and k_{30} was determined. Finally the decomposition

rate constants at ambient temperature for various vitamins were determined from the shelf-life data for 15 to 18 months.

RESULTS AND DISCUSSION

All the results are given in table I. In the case of vitamin B_1 in both the preparations, the three values of $\frac{Ea}{2.303\,R}$ did not differ significantly. Hence the three values for degradation rate constant (k_{30}) calculated from kinetic equation taking virtual temperature as 30° were in agreement. k_{30} value derived from shelf-life study of 15 to 18 months and that derived from extrapolation of the linear Arrhenius plots (figures 1 and 2) were also tallying. The same held true in the cases of vitamin A and sodium pantothenate in multivitamin drops. However, in the cases of folic acid and vitamin B_{12} the three values of $\frac{Ea}{2.303\,R}$ differed significantly. Hence the values for k_{30} could not be determined from kinetic equations. Arrhenius plots (figure 2) were not linear and hence it was not possible to determine decomposition rate constants at virtual temperature by extrapolation. The k (ambient) values for folic acid and vitamin B_{12} are opposite. From the concave nature of the Arrhenius plot for folic acid we can deduce that as the temperature is raised additional factors come into play which accelerate the decomposition rate. In the same way from the convex nature of the

TABLE I

Degradation Constant (k 30) at virtual temperature (30°) from kinetic equations and from extrapolations of Arrhenius plot and k (ambient) from Shelf-life study.

Preparation	Vitamin	$\frac{Ea}{2.303\ R}$ from ratio.			$K_{30} \times 10^{-4}$ from ratio (Taking virtual temp. as 30°)			$K_{30} \times 10^{-4}$ from extrapolation of Arrhenius Plot for log k and $\frac{1}{T}$	k (ambient) from Shelf-life study $\times 10^{-4}$
		$\frac{k65}{k45}$	$\frac{k55}{k45}$	$\frac{k65}{k55}$	$\frac{k65}{k30}$	$\frac{k55}{k30}$	$\frac{k45}{k30}$		
Multivitamin Drops	A	4898	4656	5258	6.9	6.5	6.9	7.9	6.4
"	B_1	3878	3600	4160	28.9	27	29	33	35
"	Sodium Panto-thenate	3843	3889	3800	11.5	11.7	11.6	12.9	10.5
Iron-Vit. Syrup	B_1	2552	2686	2409	11	11	11	11	13
"	Folic Acid	2342	3221	1408	-	-	-	-	15.4
"	B_{12}	2486	1430	3601	-	-	-	-	33.5

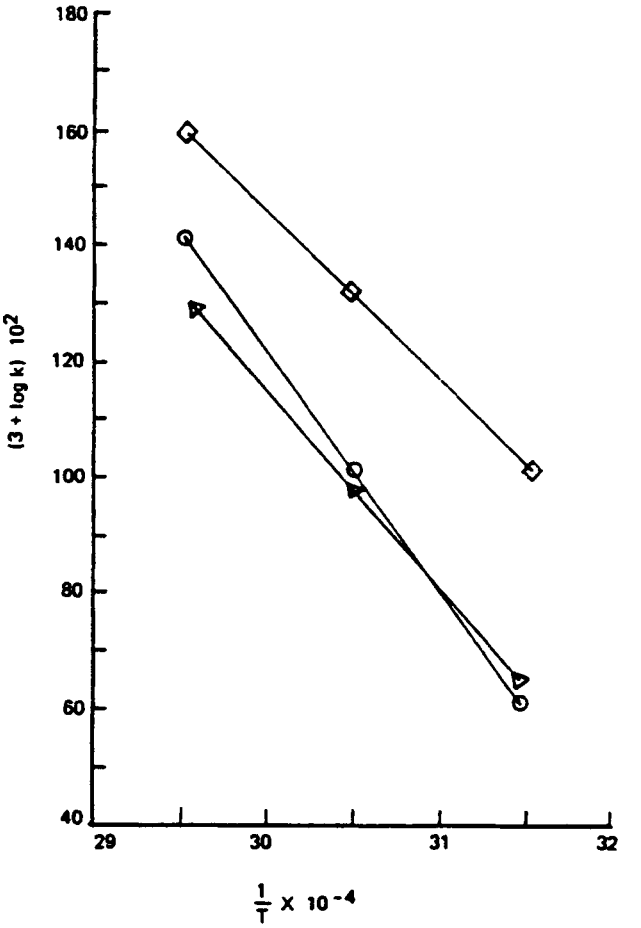

FIGURE 1

Arrhenius plots for (O) vitamin A, (Δ) sodium pantothenate, and (□) vitamin B_1 in multivitamin drops.

Arrhenius plot for vitamin B_{12} we can deduce that as the temperature is raised additional factors come into play which inhibit the decomposition rate. More detailed studies, at a

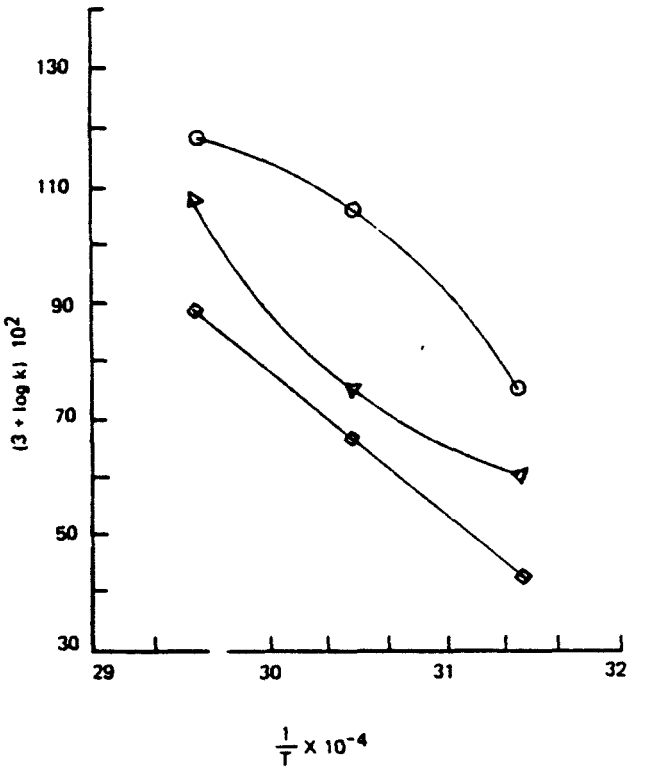

FIGURE 2

Arrhenius plots for (O) folic acid, (△) vitamin B_{12}, and (□) vitamin B_1 in iron vitamin syrup.

number of temperatures, are needed to fully define the kinetics of these systems.

CONCLUSIONS

In the case of multivitamin preparations, vitamins A, vitamin B_1 and sodium pantothenate decompose in accordance with first order reaction at high temperatures as well as at

ambient temperature. Hence shelf-life can safely be predicted from kinetic data at higher temperature. The same cannot be assumed to be true in the case of folic acid and vitamin B_{12}, where the order of reaction at higher temperature differ significantly from that at ambient temperature.

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