CHAPTER IV

DISCUSSION AND CONCLUSIONS

Analytical procedure

Titration of vitamin C with 2,6-dichlorophenol indophenol (48) was used as analytical tool in this study. This method was recommended for its reliability, specificity and sensitive enough to differentiate and quantitate the intact vitamin C from its degradation products in the preparation (9, 49).

Order of reaction of vitamin C

From the plots of concentration-time profile (Figure 1) and logarithm concentration-time (Figure 2), it could be visuallized that the latter plot was more linear which indicated a first order degradation. When these data were statistically analyzed by the least squares method (53, 54), the slope, correlation coefficient (r), and F value were computed. It can be seen from Table 8 that the degradation has higher correlation (r) and F value in a first-order reaction than in a zero-order reaction. In all formulations, the degradation of vitamin C was a first-order reaction. The correlation coefficients (r) and F-test for a first order were all significant at 95 % confidence limits. This finding is in agreement with previous reports (12, 22).

Specific rate constant for degradation of vitamin C

The specific rate constant for degradation of vitamin C in liquid multivitamin preparation was obtained from the slope (k) of the linear regression line of logarithm concentration-time profile (50). The 95 % confidence interval of the slope ($t_{.05}Sk$) was also calculated as shown in Table 8. The unit of the specific rate constant was the reciprocal of day (day^{-1}). The specific rate constant (k) was used to indicate the stability of vitamin C in the investigated formulations. The formulation, whose specific rate constant was lower, was the more stable.

Effect of vehicles

The vehicle of organic polyhydric alcohols such as propylene glycol, glycerin and sorbitol were used in the formulation with the impression that they were miscible with water and might reduce dissolved oxygen thereby producing a stabilizing effect upon the oxidation of vitamin C in the preparation. The results of this study were in agreement with the previous reports (23 - 27) that polyhydric alcohols exhibited a marked stabilizing effect upon vitamin C. Increasing concentration of these compounds in the solutions would produce increasing stability of vitamin C. Propylene glycol appeared to poss the greater stabilizing effect than sorbitol and glycerin. However, propylene glycol can not be used as a single vehicle because of its unpleasant taste. The mixture of propylene glycol, sorbitol and glycerin in appropriate composition may be a good vehicle.

Corn syrup was used to increase the viscosity and palatability of multivitamin preparation. The viscous product might also hindered oxygen exchange. It was observed that corn syrup improved the products appearance and had stabilizing effect on vitamin C. Therefore, the viscosity of the solution is proprably an important factor on the stability of vitamin C.

Syrup USP is one of the most widely used vehicle in vitamin preparations. Because sucrose is made locally at lower price and there are few reports (23, 26) that syrup may help in vitamin stabilization to certain extents, it was hoped that syrup may be used as a major vehicle in the preparations. Unfortunately, the degradation rate of vitamin C in its presence was greater than in water. It was first suspected some impurities in commercial cane sugar may be responsible for this enhancing effect. Syrup prepared from sucrose A R. was used in the formulation. However, no significant difference ($P > 0.05$) was observed in the products prepared from either commercial cane sugar or sucrose A R. The increase in degradation rate was then caused by sucrose. When the content of syrup was increased, the degradation was also increased (see Table 9). Thus, it is suggested not to use syrup as a vehicle of multivitamin preparation containing vitamin C.

The color change from yellow to brown was also observed and corresponded to the extent of vitamin C degradation. The browning effect in polyhydric alcohol was less than in syrup USP (see Table 2).

This difference may due to degradation of sucrose and polymerization of furfuraldehyde.

Effect of antioxidants and chelating agent

Antioxidant was used in the preparations with the thought that it may stabilize vitamin C, which was usually degraded by oxidation. It has been reported that oxidation of vitamin C was accelerated by trace metal, which may be protected by using chelating agent (21, 27).

The antioxidant that commonly used in pharmaceutical preparations is sodium metabisulfite (NaMS) at 0.1 % concentration. In this study, cysteine hydrochloride was also used at the same concentration of 0.1 % and the chelating agent used was only sodium ethylenediamine tetraacetate (EDTA) at 0.02 % concentration.

It was observed that cysteine hydrochloride was significantly more effective stabilizer on vitamin C than sodium metabisulfite. Uprety and Revis (29) suggested that the protection mechanism of antioxidant to vitamin C depended upon the availability of the sulfur ion. This suggestion may be correct since the presence of cysteine hydrochloride resulted in strong sulfur smell during the degradation study, but not in the presence of sodium metabisulfite. Sodium metabisulfite was found not only no protective effect but also seemed to accelerate the destruction of vitamin C (see Table 10). This result was in agreement with the previous report (2). The reason why antioxidant

had no protective effect on the stability of vitamin C may be due to the degradation of vitamin C in the liquid multivitamin preparation followed largely the non-oxidative route (22).

EDTA in a concentration of 0.02 % gave some protection to vitamin C both in a single vehicle of 40 % syrup USP (F-19 and F-1), and in a mixture vehicle of 20 % sorbitol, 5 % propylene glycol and 40 % corn syrup (F-48 and F-47). This result was in agreement with the previous report (25).

The combination of antioxidant and chelating agent was found to have less stabilizing effect than using single agent. The following order of protective effect of antioxidant and chelating agent was observed that cysteine. HCl > cysteine. HCl + EDTA > EDTA > sodium metabisulfite > sodium metabisulfite + EDTA (see Table 10).

Although cysteine hydrochloride had stabilizing effect on vitamin C but the product was unacceptable because of strong sulfur smell produced, acid taste and rapid browning occured. Ultimately, only chelating agent EDTA is suggested in the multivitamin preparation of vitamin C.

Effect of suspending agent, preservative and flavoring agent

Sodium carboxymethylcellulose (CMC), the most common suspending agent, was used in liquid vitamin preparation to increase the viscosity and thus retard separation of immiscible drugs. The purpose of increasing

viscosity was to make the product better appearance and palatable and to hinder oxygen exchange by reducing diffusion of oxygen. The protective effect of the formulation containing CMC was found no significant difference ($P > 0.05$) with the control formulation (see Table 11). However, its presence had a tendency of protection, the physical appearance of formulation containing CMC was not appreciate because of cloudy, gritty and not palatable. So the use of CMC is not recommended in the formulation.

Preservative is needed to inhibit microbial growth in liquid formulations containing nutritive ingredients. Methylparaben and propylparaben are the most commonly used preservatives in many liquid formulations. They are effective at low concentration in a wide pH range. It is generally known that the parabens are solubilized in micellar solution of polysorbate which resulted in reduction of concentration of free parabens and their antimicrobial activities. This problem may be encountered in multivitamin preparations since solubilized forms of vitamin A and D usually contain some polysorbate. Therefore, sodium benzoate was also used in some preparations.

The effect of preservatives on the stability of vitamin C was investigated. Their antimicrobial activity was beyond the scope of this study. It was observed that methylparaben had some stabilizing effect on vitamin C but sodium benzoate enhanced vitamin C degradation (Table 12). This result may due to pH changes by sodium benzoate but not by methylparaben (Table 4).

Flavoring agent is also a pharmaceutical necessity commonly used to enhance product palatability. Trivedi and Patal (36) reported effects of some flavor on vitamin C stability. They found that banana was the most favorite flavor and vanillin was the worst in protection of vitamin C degradation. But the commercial product still use vanillin with strawberry flavor. In this study, the effect of vanillin with strawberry and banana flavor on vitamin C stability were compared. No significant effect of these flavors on vitamin C stability was observed (Table 13).

Effect of pH and buffer

pH is one of the most important factor that affect the stability of vitamins. The individual vitamin such as A, B_1, B_2, B_6, B_{12}, C, D and other is stable only in its appropriate pH range which is quite specific for each of them. It is difficult to find a pH that stabilize all vitamins. In general, the compromising pH should be selected with special considerations for the most labile vitamins such as vitamin B_1 and C. They were reported to be more stable in acid media not exceeding pH 4 (48).

In this study, acetate and citrate buffers were used in the preparations and their effects on vitamin C stability in the pHs 2.5, 3, 3.5 and 4 were investigated. In order to avoid the effect of ionic strength, it was kept constant at 0.5 by adjusting with sodium chloride. The results in Table 5 and Figure 5 show that there were no significant differences in pH effect on vitamin C stability in citrate buffer, but pH 3 seemed to be the best. In acetate buffer at pH 2.5 to 3.5

the stability of vitamin C was significantly pH dependent. Increasing pH would result in increasing degradation rate. At the same pH range 3.0 to 4.0 the degradation in acetate buffer and citrate buffer were about equal.

Color changes in both acetate and citrate buffers were also noted. Browning effect was more pronounced in citrate buffer. Lower pH caused more browning effect and presented undesirable taste. Form these results, the optimum pH range of 3 - 3.5 should be used in the preparation. This finding is in accordance with Uprety, et al. (28) who reported the most stable pH for vitamin C was approximately 3.

It should be noticed that vitamin C is a self buffering agent in the presence of its salt form. Preparations of multivitamin containing vitamin C usually had a pH in the range 3 - 3.5. Addition of external buffering agent is not neccessary in this preparation.

Formulation

In previous sections, individual effects of possible ingredients on the stability of vitamin C in multivitamin preparation were investigated. When these ingredients were combined, the preparations were evaluated for their physical appearance (acceptability) and chemical stability. From the previous studies, the vehicle was the most important atabilizer while the other pharmaceutical additives had a slight effect on the stability of vitamin C. In order to yield a stable multivitamin formula, many types of vehicle of polyhydric

alcohols mixture were considered in the preparation (Table 6) including EDTA, sodium benzoate and banana flavor. The results in Table 6 and Figure 6 show that all formulations containing the mixture of polyhydric alcohols (F-47, F-48, F-49, F-51) had more stabilizing effect than a single vehicle of sorbitol and glycerin. (F-45, F-50), while syrup USP (F-46) had a deterioration effect on vitamin C. Propylene glycol, a bitter taste vehicle, was used at 5 % concentration to enhance the stabilizing effect and the taste still to be pleasant (F-47 to F-49).

All formulations containing polyhydric alcohols and corn syrup (F-47 to F-51) enhanced not only chemical stability of vitamin C but also physical appearances of palatability, clarity and viscosity of products which were acceptable.

Kinetic studies on the stability of vitamin C in liquid multivitamin formulations

Arrhenius Relationship

The stability testing of a product under normal storage conditions is usually a time consuming. The accelerated stability testing method has been introduced to shorten the duration of product development. This technique is based on Arrhenius relationship (Equation 4) where the degradation rate is dependent on temperature. The method provides a mean for prediction of product shelf-life with very good accuracy and reliability for many products (40 - 43).

The Arrhenius relationship has been recommended (57) for prediction of product stability when the following assumptions are valid : (1) the heat of activation was temperature independent, (2) the reaction mechanism was the same at all temperature studied, and (3) the system did not change physically. However, only stability testing under normal storage conditions is accepted by official regulations.

Five formulations developed and a commercial product were used in this study. Their stability were studied at air-conditioned room (20°C), normal room (30°C), 40°, 50°, 60° and 70°C. The accelerated stability testing method requires a minimum of four temperature studies, so that the degradation rate at lower temperature could be accurately predicted. The specific rate constant obtained from temperatures 40°, 50°, 60° and 70°C were plotted according to Arrhenius relationship. The predicted degradation rate at lower temperatures (20° and 30°C) were obtained from extrapolation of Arrhenius plot and compared to the actual storage values.

Arrhenius plot of natural logarithm of the rate constant (ln k) at four elevated temperatures 40°, 50°, 60° and 70°C, against the corresponding reciprocal degree kelvin $(\frac{1}{T})$ of all formulations studied were all linear (Table 15). A typical Arrhenius plot was shown in Figure 8. The linearity of Arrhenius plot indicated proper selection of temperature range studied and possible prediction of degradation rate at lower temperature could be obtained by extrapolation.

The predicted rates at temperature 30°C and 20°C were compared to the actual normal storage rate at room temperature (30°C) and at air-conditioned room (20°C) using t-test. The results were shown in Table 18, 19 and Figure 12 that the predicted rate and the actual normal rate of all formulations at 30°C and at 20°C were not significant differences ($P > 0.05$). It was proved that the accelerated stability testing program was valid and reliable as a simple method for stability prediction of vitamin C in liquid multivitamin preparations. This finding was in agreement with the previous reports of Garrett (55) and Tingstad, et al. (2).

It should be noted that the standard error for prediction of rate constants from Arrhenius plot is inversely proportion to the number of temperatures studied, the confidence of predicted value may be increased by increasing the number of temperatures studied. And the longer extrapolation to lower temperature will be less reliable (51, 52). In general, four temperature studies are considered the best because of the economic aspect (51).

In selection of the best formulation, the average degradation rate was considered, the lower value was the more stable. The results in Table 22 indicated the stable formulation decreased as following $54 > 57 > 55 > 56 > 53 > 52$. The best formulation (F-54), in each 5 ml, contains vitamin A 5000 I.U. , vitamin D 1000 I.U. , thiamine hydrochloride 2 mg, riboflavin 2 mg, pyridoxine hydrochloride 2 mg, vitamin C 75 mg, vitamin B_{12} 3 mcg, nicotinamide 20 mg, saccharin

sodium 0.1 %, sorbitol 40 %, propylene glycol 5 %, corn syrup 40 %, sodium edetate 0.02 %, methylparaben 0.1 %, vanillin and strawberry flavor 0.1 %. It was the most stable product for vitamin C, good appearance and palatability.

Heat of Activation

The Heat of activation has been used in identification of reaction mechanisms. Although this study was not intended to involve detailed reaction mechanism because of complexity of the formulated products and it was unnessary for the purpose of stability prediction. The magnitude of heat of activation is a valuable information, since the Arrhenius equation would have practical application when the heat of activation falls in the range 10 to 30 kcal/mol (50, 51). If diffusion or photolysis were the rate determining steps of the reaction, the heat of activation would be in the order of 2 to 3 kcal/mol. Little advantage was gained by accelerated temperature studies in prediction, since the temperature effect on rate was small. For reactions such as pyrolysis, the heat of activation was in the magnitude of 50 to 70 kcal/mol, the rate of degradation which might be great at elevated temperatures and might not be of any practical important at the temperature of marketing and storage of preparations.

The heat of activation was calculated from the slope of a linear regression line obtained from Arrhenius plot (Equation 5). The heat of activation of five formulas developed were not significant differences from each other (Table 17, Figure 10) and all values are in the range 13 - 15 kcal/mol.

It is obvious that slight modification of the composition did not alter the heat of activation. This finding was in agreement with Garrett's report (46).

In the previous reports, it was found that activation energies for aerobic and anaerobic decomposition of vitamin C was approximately in the range 10-15 kcal/mol and 19-25 kcal/mol respectively (11-13).

The commercial product studied had the heat of activation of 18 kcal/mol. This difference of heat of activation for commercial product from five formulations studied, would suggest a prevalence of anaerobic pathway in the commercial product (11 - 13). However, these values were fall within acceptable limit for Arrhenius equation which indicated that the degradation of vitamin C in multivitamin preparation was through solvolytic process (50, 51).

Once the heat of activation is known, it is possible to estimate the reaction rate constant at any temperature from rate obtained at one elevated temperature (Equation 6). This method provides some advantage in reducing the number of experiments required for prediction of product stability. It is also useful in routine quality control to assure constant batch-to-batch products.

Shelf-Life

The shelf-life of vitamin C in liquid multivitamin is defined as the time for potency drop to 90 % of the label claimed at room temperature. Shelf-life (t_{90}), the time for potency loss 10 % from

original concentration 100 % reach to 90 %, was calculated from the first-order reaction rate (Equation 7) by using predicted rate and actual normal rate. It was also shown no significant differences from both calculations ($P > 0.05$) (see Table 20, Fiqure 13). Finally, the scientific approach of prediction shelf-life by accelerated testing program was proved to be valid and reliable method.

Simplified technique of stability prediction

A more simplified technique of graphical method for prediction of shelf-life was demonstrated using the temperature dependency of shelf-life (t_{90}) at elevated temperature. The Arrhenius equation (Equation 4) may be modified as follows :

$$\ln k = \ln A - \frac{\Delta Ha}{RT}$$

$$\ln \left[\frac{0.1054}{t_{90}}\right] = \ln A - \frac{\Delta Ha}{RT}$$

$$\ln t_{90} = \ln \left[\frac{0.1054}{A}\right] + \frac{\Delta Ha}{RT}$$

Plot $\ln t_{90}$ at four elevated temperatures of 40°, 50°, 60° and 70°C versus the corresponding reciprocal degree kelvin $(\frac{1}{T})$ was a straight line. The typical plot of shelf-life (t_{90}) was shown in Figure 14. The predicted t_{90} at room temperature (30°C), or at any other desirable temperature such as at air-conditioned store room (20°C) and at refrigerator (5°C) could be read out directly from the extrapolated line. Figure 14 shows the t_{90} of F-53 was observed 32

days at 30°C and 72 days at 20°C, while t_{90} from calculation was 30 and 65 days at 30° and 20° C respectively. Shelf-life (t_{90}) obtained from simplified technique and from calculation was no significant difference.

The overage

Although the shelf-life (t_{90}) of the developed formulations were improved, the time was too short to provide adequate shelf-life for the product. The overage, the addition of an excess of vitamin C in initial concentration, was used to prolong the shelf-life and assure the potency not to be less than 90 % of the labeled amount until its expired date.

The amount of overage had to be very high but within the limits of maximum not more than 30 % over the labeled amount as recommended by The International Pharmaceutical Federation (15).

The shelf-life of 30 % overage was calculated from the first-order kinetic equation (equation 8). When the initial concentration of vitamin C at 130 % labeled amount, the shelf-life of decomposition to 90 % was longer than the normal shelf-life (t_{90}) approximately from 44 days to be 153 days in F-54. The shelf-life of 30 % overage of all formulations were reported in Table 21.

In addition, the shelf-life of 30 % overage can be determined from the overage curve (51). Typical plot of Figure 15 shows the logarithm concentration versus time plot. The dashed line represents

the overage curve which is parallel to the solid line of normal loss curve. The horizental line is the 90 % labeled amount at room temperature and the arrows point the shelf-life of the overage. The shelf-life of 30 % overage of F-53 obtained from overage curve (Figure 15) and from calculation (Table 21) were 100 days and 105 days, respectively and they were not significantly different.

Once the normal loss curve is known, it is possible to estimate the amount of overage from the intercept of the overage curve which is obtained at a desired shelf-life. This method provides some advantage in adjusting an appropriate amount of initial concentration of drug in preparation for the desired shelf-life.

Vitamin C was previously reported to be the least stable drug in liquid multivitamin (2). Therefore, its shelf-life should be taken as the shelf-life of the preparation. In the purpose of study the expiratory date of preparation, the final formulations developed should further study for its stability in the containers, closures and packaging in same manner as the marketted products. The appropriate expiration dating should be placed in order to assure a drug product to meet the standards of identity, strength, qualitg and purity at the time of use.

Conclusions

Vitamin C in oral liquid multivitamin preparation has been intended to prolong its shelf-life by formulation development. In

this field study, a systemic kinetics was approached to investigate the effects of many pharmaceutical necessities, such as vehicles, antioxidants, chelating agents, suspending agents, flavors, preservatives and pH on both chemical stability and physical appearance. The value of degradation rate was used as an indicator for the comparison of vitamin C stability, the lower the more stable. The degradation of vitamin C was found to be a first-order reaction. By means of preformulation studies, it was observed that polyhydric alcohols vehicle such as sorbitol, glycerin and propylene glycol had the most stabilizing effect, while the other ingredients of corn syrup, sodium edetate, methylparaben, sodium carboxymethylcellulose and flavors showed no signigicant effect on vitamin C degradation.

It was surprising that sodium metabisulfite and syrup USP the most widely used antioxidant and vehicle in liquid preparations were found to accelerate the degradation of vitamin C, so that it is suggested not to use them in the liquid multivitamin containing vitamin C. Multivitamin formulation at pH 3, adjusting by acetate and by citrate buffer was shown the best stable of vitamin C but the browning effect and taste were unacceptable. In the fact that general multivitamin preparation has pH range 3 - 3.5 which is the optimum pH for vitamin C stability. Therefore, all buffers are not necessary in liquid multivitamin preparation. Ultimately, the best formula of good appearance, and the most stable of vitamin C is yielded. The formula of each 5 ml contains : vitamin A 5000 I.U. , vitamin D 1000 I.U. , thiamin hydrochloride 2 mg, riboflavin 2 mg, pyridoxine

hydrochloride 2 mg, vitamin C 75 mg, vitamin B_{12} 3 mcg, nicotinamide 20 mg, saccharin sodium 0.1 %, sorbitol 40 %,propylene glycol 5 %, corn syrup 40 %, sodium edetate 0.02 %, methylparaben 0.1 % , vanillin and strawberry flavor 0.1 % showed the best result.

In determination of shelf-life, five formulations (F-53 to F-57) were developed and evaluated the stability by using accelerated thermodegradation method at 40°, 50°, 60° and $70^{\circ}C$ and by actual condition at 30° and $20^{\circ}C$. The predicted rate and actual normal rate were not significant differences ($P > 0.05$). Therefore, it is proved that the accelerated stability testing method is valid and reliable for shelf-life prediction of vitamin C in liquid multivitamin formulations. The Arrhenius plots of all formulations studied were straight line with the heat of activation in range 13 - 18 kcal/mol which indicated a solvolytic reaction. The normal shelf-life (t_{90}) of the best formula obtained from predicted rate was 44 days, which was about 2 times longer than the commercial product and the shelf-life of 30 % overage was about 150 days. The simplified technique to evaluate the shelf-life and the overageare also suggested by graphical method. This technique is useful and rapid for routine work.

It is hoped that this stability data would be useful and provide pharmacists the applications of chemical kinetics to design and assess formulation development and also control drug and dosage form stability.

Table 2. Effect of Various Vehicles on the Specific Rate Constants of Vitamin C in Liquid Multivitamin Preparations[a].

F	Percent Vehicle							Specific Rate Constant at 60°C $(k \pm t_{.05}\ Sk) \times 10^2$ (day^{-1})	Physical Changes	
	Syrup USP	Syrup Sucrose AR	Glycerin	Sorbitol	Propylene Glycol	Corn Syrup	Distilled Water		pH	Color
1	40	-	-	-	-	-	-	5.994 ± 0.523	3.57	++++
2	-	40	-	-	-	-	-	5.859 ± 0.354	3.61	++++
3	20	-	-	-	-	-	-	4.836 ± 0.717	3.65	+++
4	-	-	40	-	-	-	-	3.856 ± 0.648	3.61	++
5	-	-	-	-	-	-	100	3.574 ± 0.304	3.56	++
6	-	-	-	-	-	60	-	3.011 ± 0.196	3.34	+
7	-	-	-	40	-	-	-	2.948 ± 0.461	3.51	+
8	-	-	-	-	40	-	-	2.044 ± 0.617	3.77	+

[a] Preparation contains core formula, vehicle as stated and distilled water to 100 ml.

Table 2. (continue)

F	Percent Vehicle						Specific Rate Constant at 60°C $(k \pm t_{.05} Sk) \times 10^2$ (day^{-1})	Physical Changes	
	Syrup USP	Glycerin	Sorbitol	Propylene Glycol	Corn Syrup	Alcohol		pH	Color
9	40	-	-	-	20	-	5.752 ± 0.442	3.48	++++
10	40	-	20	-	-	-	5.566 ± 0.389	3.52	++++
11	40	20	-	-	-	-	4.524 ± 0.481	3.53	+++
12	40	-	-	-	-	10	4.250 ± 0.604	3.58	++++
13	40	-	-	20	-	-	3.974 ± 0.331	3.59	+++
14	20	20	-	-	-	-	4.310 ± 0.474	3.55	++
15	20	-	20	-	-	-	4.133 ± 0.198	3.53	++
16	20	-	-	20	-	-	3.066 ± 0.409	3.60	++

Table 3 Effect of Antioxidants and Chelating Agent on the Specific Rate Constants of Vitamin C in Liquid Multivitamin Preparations[a].

F	Percent Vehicle				Percent Antioxidant		Percent EDTA	Specific Rate Constant at 60°C ($k \pm t_{.05}Sk$) x 10^2 (day^{-1})	Physical Changes	
	Syrup USP	Glycerin	Sorbitol	Propylene Glycol	NaMS[b]	Cys. HCl[c]			pH	Color
17	40	-	-	-	0.1	-	-	5.858 ± 0.447	3.49	++++
18	40	-	-	-	-	0.1	-	4.762 ± 0.297	3.31	++++
19	40	-	-	-	-	-	0.02	5.550 ± 0.329	3.43	++++
20	40	-	-	-	0.1	-	0.02	5.913 ± 0.351	3.45	++++
21	40	-	-	-	-	0.1	0.02	5.007 ± 0.639	3.41	++++
22	40	20	-	-	0.1	-	0.02	4.845 ± 0.551	3.52	++++
23	40	-	20	-	0.1	-	0.02	5.821 ± 0.295	3.49	++++
24	40	-	-	20	0.1	-	0.02	4.001 ± 0.362	3.56	++++
25	40	20	-	-	-	0.1	0.02	4.149 ± 0.310	3.35	++++

[a] Preparation contains core formula, vehicle, antioxidant, chelating agent as stated and distilled water to 100 ml.

[b] Sodium Metabisulfite

[c] Cysteine hydrochloride

Table 4 Effect of Suspending Agent, Preservatives and Flavoring Agents on the Specific Rate Constants of Vitamin C in Liquid Multivitamin Preparations[a].

F	Percent Vehicle			Percent CMC	Percent Preservative		Percent Flavors		Specific Rate Constant at 60°C	Physical Changes	
	Syrup USP	Syrup SucroseAR	Sorbitol		M.P	NaBz[b]	Vanillin Strawbery	Banana	$(k \pm t_{.05}Sk) \times 10^2$ (day^{-1})	pH	color
26	-	-	-	-	0.1	-	0.1	-	4.781 ± 0.955	3.45	++++
27	40	-	-	-	0.1	-	0.1	-	5.682 ± 0.605	3.38	++++
28	-	40	-	-	0.1	-	0.1	-	5.957 ± 0.484	3.37	++++
29	-	40	-	-	-	0.1	0.1	-	5.736 ± 0.287	3.48	++++
30	-	40	-	-	-	0.1	-	0.1	5.580 ± 0.217	3.43	++++
31	-	-	40	-	-	0.1	-	0.1	3.774 ± 0.447	3.53	++++
32	-	-	40	-	0.1	-	0.1	-	3.419 ± 0.459	3.58	+++
33	-	-	40	-	0.1	-	-	0.1	2.893 ± 0.350	3.67	++
34	-	-	40	0.6	-	0.1	0.1	-	3.175 ± 0.311	3.69	++
35	-	-	40	0.6	-	0.1	-	0.1	3.555 ± 0.489	3.73	++

[a] Preparation contains core formula, vehicle, Suspending agent, sodium carboxy methylcellulose (C.M.C.) Preservative, Flavor as stated and distilled water to 100 ml.

[b] Sodium benzoate

Table 5. Effect of Buffer and pH on the Specific Rate Constants of Vitamin C in Liquid Multivitamin Preparations[a]

F	Percent Sorbitol	Percent Banana Flavor	Buffer System		pH	Specific Rate Constant at 60°C ($k \pm t_{.05}\ Sk$) x 10^2 (day^{-1})	Color change
			Acetate	Citrate			
36	40	0.1	-	-	3.30	3.957 ± 0.274	+
37	40	0.1	Acetate	-	2.58	2.598 ± 0.409	+++
38	40	0.1	Acetate	-	2.98	3.307 ± 0.289	+++
39	40	0.1	Acetate	-	3.41	3.955 ± 0.436	++
40	40	0.1	Acetate	-	3.90	3.914 ± 0.423	+
41	40	0.1	-	Citrate	2.54	3.472 ± 0.397	++++
42	40	0.1	-	Citrate	3.01	3.286 ± 0.446	++++
43	40	0.1	-	Citrate	3.44	3.576 ± 0.556	++
44	40	0.1	-	Citrate	3.92	3.886 ± 0.464	+

[a] Preparation contains core formula, vehicle, flavor, 0.2M buffer ionic strength 0.5 M, pH as stated and distilled water to 100 ml.

Table 6 Effect of Formulation on the Specific Rate Constants of Vitamin C in Liquid Multivitamin Preparations[a]

F	Percent Vehicle					Prscent NaMS[b]	Percent EDTA	Percent $NaBz^c$	Percent Banana	Specific Rate Constant at 60°C ($k \pm t_{.05}Sk$) x 10^2 (day^{-1})	Physical Changes	
	Syrup USP	Glycerin	Sorbitol	Propylene Glycol	Corn Syrup						pH	color
45	-	-	40	-	-	0.1	0.02	0.1	0.1	3.676 ± 0.656	3.52	+++
46	30	-	30	-	-	-	0.02	0.1	0.1	5.041 ± 0.402	3.50	++++
47	-	-	20	5	40	-	-	0.1	0.1	3.206 ± 0.218	3.52	++
48	-	-	20	5	40	-	0.02	0.1	0.1	3.151 ± 0.221	3.55	++
49	-	20	-	5	40	--	0.02	0.1	0.1	3.377 ± 0.606	3.55	++
50	-	20	-	-	40	-	0.02	0.1	0.1	3.773 ± 0.219	3.56	+++
51	-	20	20	-	20	-	0.02	0.1	0.1	2.899 ± 0.455	3.58	++

[a] Preparation contains core formula, Vehicle, Preservative, Chelating agent, flavor as stated and distilled water to 100 ml.

[b] Sodium metabisulfite

[c] Sodium benzoate

Table 7 Preparation of Various liquid Multivitamin Formulations[a]

F	Percent Vehicle					Percent C.M.C.	Percent NaMS[b]	Percent EDTA	Percent Vanillin and Strawbery	Percent Preservative	
	Syrup USP	Glycerin	Sorbitol	Propylene Glycol	Corn Syrup					MP	NaBz[c]
52	53	3.3	-	-	-	0.06	0.1	-	0.1	0.1	-
53	-	-	40	5	20	-	-	0.02	0.1	0.1	-
54	-	-	40	5	40	-	-	0.02	0.1	0.1	-
55	-	20	40	-	20	-	-	0.02	0.1	0.1	-
56	-	-	40	5	40	-	-	0.02	0.1	-	0.1
57	-	20	40	5	20	-	-	0.02	0.1	-	0.1

[a] Preparation contains core formula, pharmaceutical necessities as stated and distilled water to 100 ml.

[b] Sodium metabisulfite

[c] Sodium benzoate

Table 8 Stability of Vitamin C in Liquid Multivitamin Formulation Number 1[a](F-1)

Time (days)	Concentration remaining of vitamin C at 60°C			Physical Change (color intensity)
	mg/ml	Percent	Natural logarithm	
0	14.770	100.0	4.6052	-
1	14.690	99.45	4.5997	+
2	13.565	91.84	4.5200	+
4	12.305	83.32	4.4227	+
7	10.105	68.42	4.2257	+
10	7.720	52.28	3.9566	++
13	7.481	50.65	3.9249	++
17	5.728	38.78	3.6579	+++
22	3.938	26.66	3.2832	++++

Zero - Order Reaction : Correlation Coefficient (r)	- 0.9827
F - Test	196.73 ($P < 0.05$)
First - Order Reaction : Correlation Coefficient (r)	- 0.9953
F - Test	734.16 ($P < 0.05$)
The Specific Rate Constant, k (day^{-1}) $(k \pm t_{.05}Sk) \times 10^2$	5.994 ± 0.523

[a] Composition of Formulation Number 1 see Table 2

Table 9 Effect of Polyhydric Alcohol Vehicles on the Stability of Vitamin C in Various Liquid Multivitamin Formulations.

Vehicle / Polyhydric Alcohol Vehicle	water		20 % Syrup USP		40 % Syrup USP		Sum $k \times 10^2$	$\bar{X}i$ $k \times 10^2$ (day^{-1})
	F	$k \times 10^2$ (day^{-1})	F	$k \times 10^2$ (day^{-1})	F	$k \times 10^2$ (day^{-1})		
40 % Glycerin	4	3.856	14	4.310	11	4.524	12.690	4.230
40 % Sorbitol	7	2.948	15	4.133	10	5.566	12.647	4.216
40 % Propylene Glycol	8	2.044	16	3.066	13	3.974	9.084	3.028
Corn Syrup	6	3.011			19	5.752	8.763	4.382
Sum $(k \times 10^2)$	11.859		11.509		19.816			
$\bar{X}j$ $(k \times 10^2)$ (day^{-1})	2.965		3.836		4.954			

Table 10. Effect of Antioxidants and Chelating Agent on the Stability of Vitamin C in Various Liquid Multivitamin Formulations.

Vehicle	40 % Syrup USP.				
Formulation NO	18	21	19	17	20
Antioxidant	Cysteine. HCl	Cysteine. HCl	-	Sodium metabisulfite	Sodium metabisulfite
Chelating Agent	-	EDTA	EDTA	-	EDTA
$k \times 10^{2}(day^{-1})$	4.762	5.007	5.550	5.858	5.913

Table 11 Effect of Suspending Agent on the Stability of Vitamin C in Liquid Multivitamin Formulations.

Vehicle	Preservative	Flavoring Agent	Suspending Agent			
			⊕ CMC [a]		⊖ CMC [b]	
			F	k x 10^2(day^{-1})	F	k x 10^2(day^{-1})
40 % Sorbitol	Sodium benzoate	Banana	35	3.555	31	3.774

[a] Added sodium carboxymethylcellulose in formulations.

[b] No sodium carboxymethylcellulose in formulations

Table 12 Effect of Preservatives on the stability of vitamin C in Liquid Multivitamin Formulations.

Vehicle	Flavoring Agent	CMC	Preservative			
			Methyl paraben		Sodium benzoate	
			F	$k \times 10^2 (day^{-1})$	F	$k \times 10^2 (day^{-1})$
40 % Syrup USP from cane sugar	Vanillin + Strawberry	-	28	5.957	29	5.736
40 % Sorbitol	Banana	-	33	2.893	31	3.774
Sum $(k \times 10^2)$				8.850		9.510
$\bar{X}_j$ $(k \times 10^2)$ (day^{-1})				4.425		4.755

Table 13. Effect of Flavoring Agents on the Stability of vitamin C in Various Liquid Multivitamin Formulations

Flavoring Agent	Preservatives	40 % Sorbitol				40% Syrup USP		Sum $k \times 10^2$	$\bar{X}_j$ $k \times 10^2$ (day^{-1})
		⊕ CMC[a]		⊖ CMC[b]		⊖ CMC			
		F.	$k \times 10^2$	F.	$k \times 10^2$	F.	$k \times 10^2$		
Vanillin	MP			32	3.419			12.330	4.110
	NaBz	34	3.175			29	5.736		
Banana	MP			33	2.893			12.028	4.009
	NaBz[c]	35	3.555			30	5.580		

a Added Sodium carboxymethylcellulose in Formulations

b No. Sodium carboxymethylcellulose in Formulations

c Sodium benzoate

Table 14 Kinetic Study on the Stability of Vitamin C in Formulation 53 (F - 53)

Formulation	Concentration remaining of vitamin C after incubated											
	20°C		30°C		40°C		50°C		60°C		70°C	
	t[a]	Percent	t	Percent	t	Percent	t	Percent	t	Percent	t	Percent
53	0	100.0	0	100.0	0	100.0	0	100.0	0	100.0	0	100.0
	9	96.45	9	94.57	4	93.55	3	93.43	2	92.06	2	87.72
	19	91.96	19	87.08	8	94.17	6	86.20	4	85.32	4	80.32
	29	89.97	29	85.97	13	85.39	10	82.09	6	81.22	6	74.65
	39	88.43	39	84.47	18	85.35	14	78.93	9	73.49	9	63.48
	49	87.24	49	82.13	24	80.16	19	73.81	12	68.42	12	53.00
	59	86.20	59	79.13	30	77.83	25	66.80	15	59.62	15	43.94
	69	83.36	69	77.03	36	76.16	32	64.07	20	57.98	20	37.18
	79	83.18	79	75.86	48	67.33	39	52.17	24	51.76	24	30.44
$(k \pm t_{.05}Sk)$,[b] $\times 10^2$ (day^{-1})	0.222±0.050		0.328±0.072		0.705±0.141		1.496±0.205		2.686±0.315		4.925±0.181	
t_{90} (day)[c]	47.46		32.13		14.95		7.04		3.92		2.14	

[a] Time in days

[b] The Specific Rate Constant of first order Reaction with 95 % Confidence Limit.

[c] The shelf-life of vitamin C 10 % concentration loss.

Table 15 Kinetic Study on the Stability of Vitamin C in Various Liquid Multivitamin Formulations.

Formulation / Temperature °C	Specific rate constant, $(k \pm t_{.05} Sk) \times 10^2$ (day^{-1})					
	52	53	54	55	56	57
20	0.403 ± .068	0.222 ± 0.049	0.121 ± 0.022	0.117 ± 0.019	0.155 ± 0.048	0.163 ± 0.041
30	0.543 ± 0.158	0.328 ± 0.072	0.245 ± 0.063	0.232 ± 0.029	0.290 ± 0.058	0.196 ± 0.058
40	1.263 ± 0.161	0.705 ± 0.141	0.562 ± 0.045	0.583 ± 0.116	0.664 ± 0.074	0.549 ± 0.097
50	2.553 ± 0.154	1.496 ± 0.205	1.109 ± 0.110	1.458 ± 0.197	1.363 ± 0.112	1.008 ± 0.177
60	6.852 ± 0.343	2.686 ± 0.315	2.830 ± 0.119	2.584 ± 0.359	2.902 ± 0.169	2.406 ± 0.273
70	17.700 ± 1.082	4.925 ± 0.182	4.790 ± 0.205	4.234 ± 0.211	5.513 ± 0.475	4.479 ± 0.264
The correlation coefficient (r) of Arrhenius plot (40°, 50°, 60°, 70°C)	.9955	.9993	.9956	.9923	.9998	.9969

Table 16 Arrhenius Relation of Vitamin C in Formulation 53

Temperature		Specific rate constant (day^{-1})				
°C	$\frac{1}{T} \times 10^3$ K	$(k \pm t_{.05}Sk) \times 10^2$	ln k	ln $(k + t_{.05}Sk)$	to ln	$(k - t_{.05}Sk)$
40	3.195	0.705 ± 0.140	- 4.9553	- 4.773	to	- 5.178
50	3.096	1.496 ± 0.204	- 4.2024	- 4.074	to	- 4.349
60	3.003	2.686 ± 0.315	- 3.6171	- 3.506	to	- 3.742
70	2.915	4.925 ± 0.181	- 3.0108	- 2.975	to	- 3.048
Arrhenius Equation		$\ln k = 17.0659 - 6884 \frac{(1)}{T}$				
Correlation coefficient (r)		0.9993				
Standard error of estimation (Sy.x)		3.815×10^{-2}				
Heat of activation (kcal/mol)		13.68 ± 1.63				
Extrapolated rate at temperature		30°C		20°C		
Predicted rate (k)		3.511×10^{-3}		1.613×10^{-3}		
95 % confidence limit of prediction $k \pm t_{.05} S\hat{y}$		$2.842 \times 10^{-3} - 4.335 \times 10^{-3}$		$1.205 \times 10^{-3} - 2.167 \times 10^{-3}$		

Table 17 Arrhenius Relation of Vitamin C in Various Liquid Multivitamin Formulations.

F	Arrhenius Equation $\ln k = \ln A - \frac{Ea}{R}\left(\frac{1}{T}\right)$	Heat of Activation $\Delta Ha \pm t_{.05}S_{\Delta Ha}$ (kcal/mol)	Predicted rate at 30°C		Predicted rate at 20°C	
			$k \times 10^3$	$(k \pm t_{.05}S_{\hat{y}}) \times 10^3$ *	$k \times 10^3$	$(k \pm t_{.05}S_{\hat{y}}) \times 10^3$
52	$25.9586 - 9524\left(\frac{1}{T}\right)$	18.93 ± 5.51	4.199	1.999 - 8.843	1.432	0.506 - 4.053
53	$17.0659 - 6884\left(\frac{1}{T}\right)$	13.68 ± 1.63	3.511	2.842 - 4.335	1.613	1.205 - 2.163
54	$20.0291 - 7896\left(\frac{1}{T}\right)$	15.69 ± 4.47	2.411	1.317 - 4.412	0.988	0.425 - 2.297
55	$17.3477 - 7009\left(\frac{1}{T}\right)$	13.93 ± 5.28	3.076	1.506 - 6.282	1.393	0.514 - 3.776
56	$19.3105 - 7616\left(\frac{1}{T}\right)$	15.13 ± 1.03	2.955	2.572 - 3.393	1.250	1.030 - 1.521
57	$19.2635 - 7673\left(\frac{1}{T}\right)$	15.25 ± 3.65	2.335	1.424 - 3.826	0.981	0.492 - 1.956

* The 95 % confidence limit of prediction

Table 18 Verification of Predicted Degradation Rate of Vitamin C at Room Temperature ($30^{\circ}C$) in Various Liquid Multivitamin Formulations.

F	Predicted rate from Arrhenius plot		Actual normal storage rate	
	$k \times 10^3$	$(k \pm t_{.05}S\hat{y})^a \times 10^3$	$k \times 10^3$	$(k \pm t_{.05}Sk)^b \times 10^3$
52	4.199	1.999 - 8.843	5.426	3.842 - 7.010
53	3.511	2.842 - 4.335	3.279	2.563 - 3.994
54	2.411	1.317 - 4.412	2.451	1.819 - 3.082
55	3.076	1.506 - 6.282	2.321	2.031 - 2.611
56	2.955	2.572 - 3.393	2.899	2.314 - 3.485
57	2.335	1.424 - 3.826	1.961	1.376 - 2.545

[a] the 95 % confidence limit of prediction.

[b] the 95 % confidence limit of standard error of slope (k)

Table 19 Verification of Predicted Degradation Rate of Vitamin C at 20°C in Various Liquid Multivitamin Formulations.

F	Predicted rate from Arrhenius plot		Actual normal storage rate	
	$k \times 10^3$	$(k \pm t_{.05}\hat{Sy})^a \times 10^3$	$k \times 10^3$	$(k \pm t_{.05}Sk)^b \times 10^3$
52	1.432	0.506 - 4.053	4.032	3.354 - 4.710
53	1.613	1.205 - 2.163	2.216	1.720 - 2.711
54	0.988	0.425 - 2.297	1.211	0.682 - 1.741
55	1.393	0.514 - 3.776	1.173	0.715 - 1.632
56	1.250	1.030 - 1.521	1.546	1.070 - 2.022
57	0.981	0.492 - 1.956	1.632	1.227 - 2.037

[a] the 95 % confidence limit of prediction

[b] the 95 % confidence limit of standard error of slope (k)

Table 20 Shelf-life of 10 % Concentration loss (t_{90}) of Vitamin C in Various Liquid Multivitamin Formulations.

F	Predicted shelf-life from Arrhenius Plot (days)				Actual shelf-life (days)			
	at 30°C		at 20°C		at room Temperature		at 20°C	
	t_{90}	$(t_{90} \pm t_{.05}S_p)^a$	t_{90}	$(t_{90} \pm t_{.05}S_p)^a$	t_{90}	$(t_{90} \pm t_{.05}S_A)^b$	t_{90}	$(t_{90} \pm t_{.05}S_A)^b$
52	25.1	11.9 - 52.7	73.6	25.9 - 208.3	19.4	15.0 - 27.4	26.1	22.4 - 31.4
53	30.0	24.3 - 37.1	65.3	48.6 - 87.4	32.1	26.4 - 41.1	47.4	38.9 - 61.3
54	43.7	23.9 - 80.0	106.7	45.9 - 248.1	43.0	34.2 - 57.9	87.0	60.5 -154.5
55	34.3	16.8 - 69.9	75.6	27.9 - 205	45.4	40.4 - 51.9	89.8	64.6 -147.4
56	35.7	31.1 - 40.9	84.3	69.3 - 102.3	36.4	30.2 - 45.5	68.2	52.1 - 98.5
57	45.1	27.5 - 73.9	107.4	53.9 - 214.2	53.7	41.4 - 76.6	64.6	51.7 - 85.7

[a] the 95 % confidence limit of predicted shelf-life

[b] the 95 % confidence limit of actual normal shelf-life

Table 21. Shelf-life of Vitamin C Overage in Various Liquid Multivitamin Formulations.

F	Predicted shelf-life[a] (days)	
	Normal initial concentration 100 %	30 % Overage[b]
52	25.09	87.6
53	30.01	104.7
54	43.7	152.5
55	34.3	119.5
56	35.7	124.4
57	45.1	157.5

[a] Time for vitamin C decomposition to reach 90 % labeled amount, was calculated from first order reaction by using predicted rate at 30°C.

[b] Initial concentration of vitamin C added, 130 % labeled amount.

Table 22. The Degradation Rate of Vitamin C in Various Liquid Multivitamin Formulations.

Formulation NO	Degradation Rate ($k \times 10^3$) (day^{-1})					
	$30^{\circ}C$		$20^{\circ}C$		Sum	Average
	Predicted	Observed	Predicted	Observed		
52	4.199	5.426	1.432	4.302	15.359	3.840
53	3.511	3.279	1.613	2.216	10.619	2.655
54	2.335	2.321	0.988	1.211	6.854	1.714
55	2.411	2.899	1.393	1.173	7.876	1.969
56	3.076	2.451	1.250	1.546	8.323	2.081
57	2.955	1.961	0.981	1.632	7.529	1.882
Stability of Formulation	54 > 57 > 55 > 56 > 53 > 52					

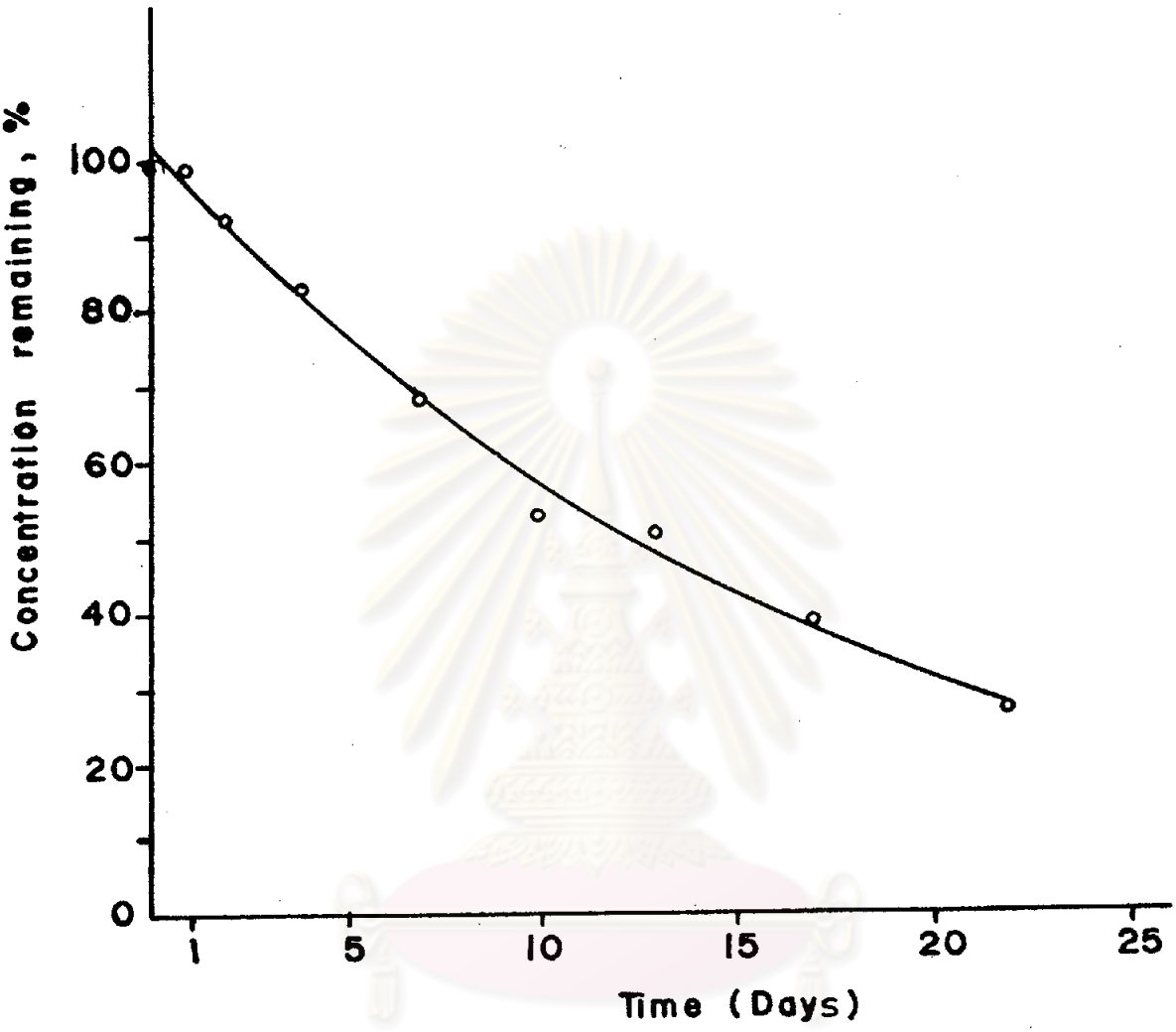

Figure 1 Concentration remaining versus time plot for zero-order degradation reaction of vitamin C in liquid multivitamin formulation number 1 at 60°C.

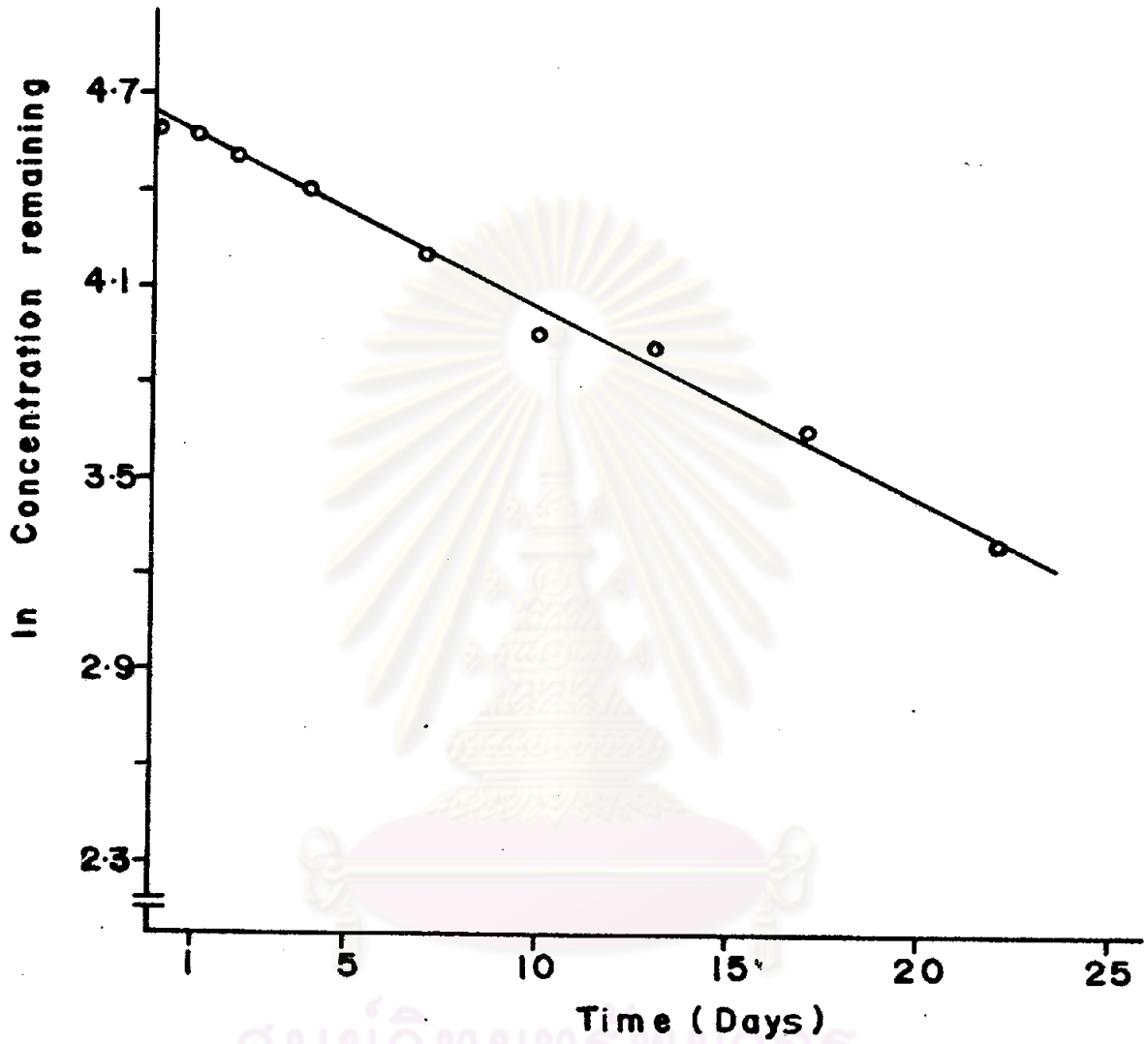

Figure 2 Natural logarithm of concentration remaining versus time plot for first-order degradation reaction of vitamin C in liquid multivitamin formulation number 1 at 60°C.

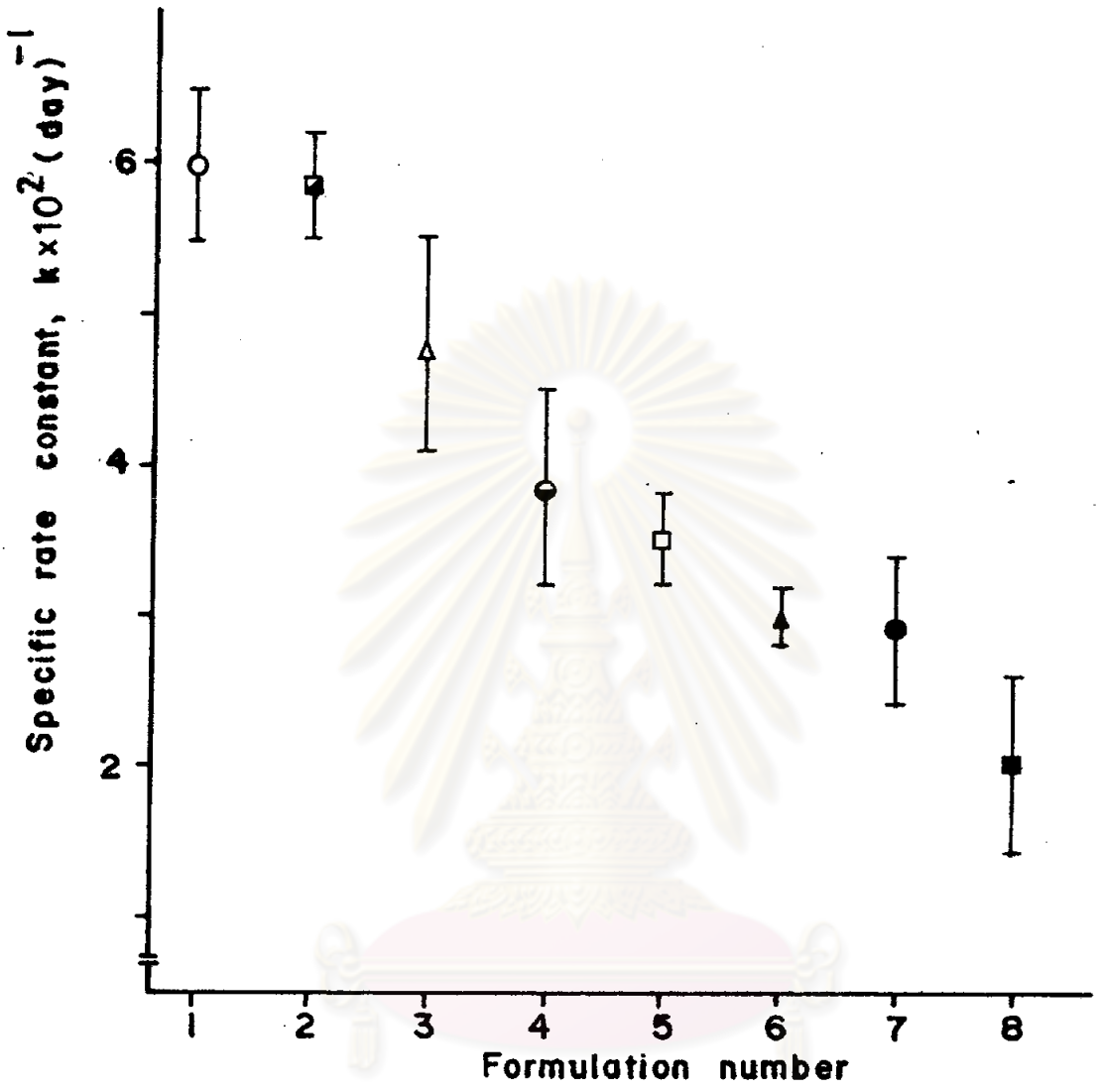

Figure 3 The specific rate constant (k)of vitamin C at 60°C in liquid multivitamin formulations of various vehicles; (O) 40 % syrup USP from cane sugar; (◪) 40 % syrup USP from sucrose AR. ; (Δ) 20 % syrup USP from cane sugar; (◒) glycerin; (□) distilled water; (▲) corn syrup; (●) sorbitol; (■) propylene glycol; the bars represent the 95 % confidence limits.

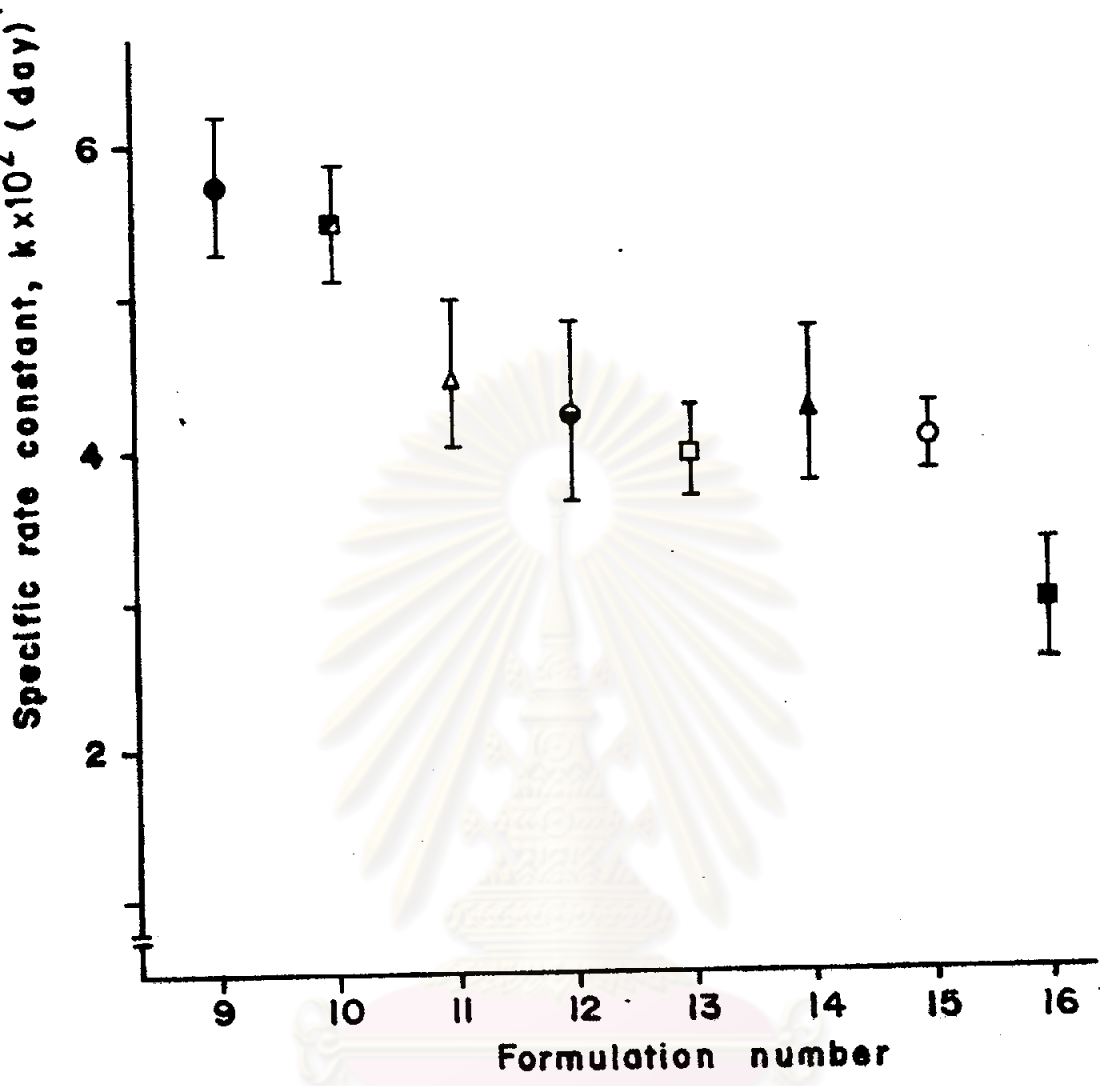

Figure 4 The specific rate constant (k)of vitamin C at 60°C in liquid multivitamin formulations of various mixed vehicles; (●) 20 % corn syrup and 40 % syrup USP; (◪) 20 % sorbitol and 40 % syrup USP; (Δ) 20 % glycerin and 40 % syrup USP; (◒) 10 % alcohol and 40 % syrup USP; (□) 20 % propylene glycol and 40 % syrup USP; (▲) 20 % glycerin and 20 % syrup USP; (○) 20 % sorbitol and 20 % syrup USP; (■) 20 % propylene glycol and 20 % syrup USP; the bars represent the 95 % confidence limits.

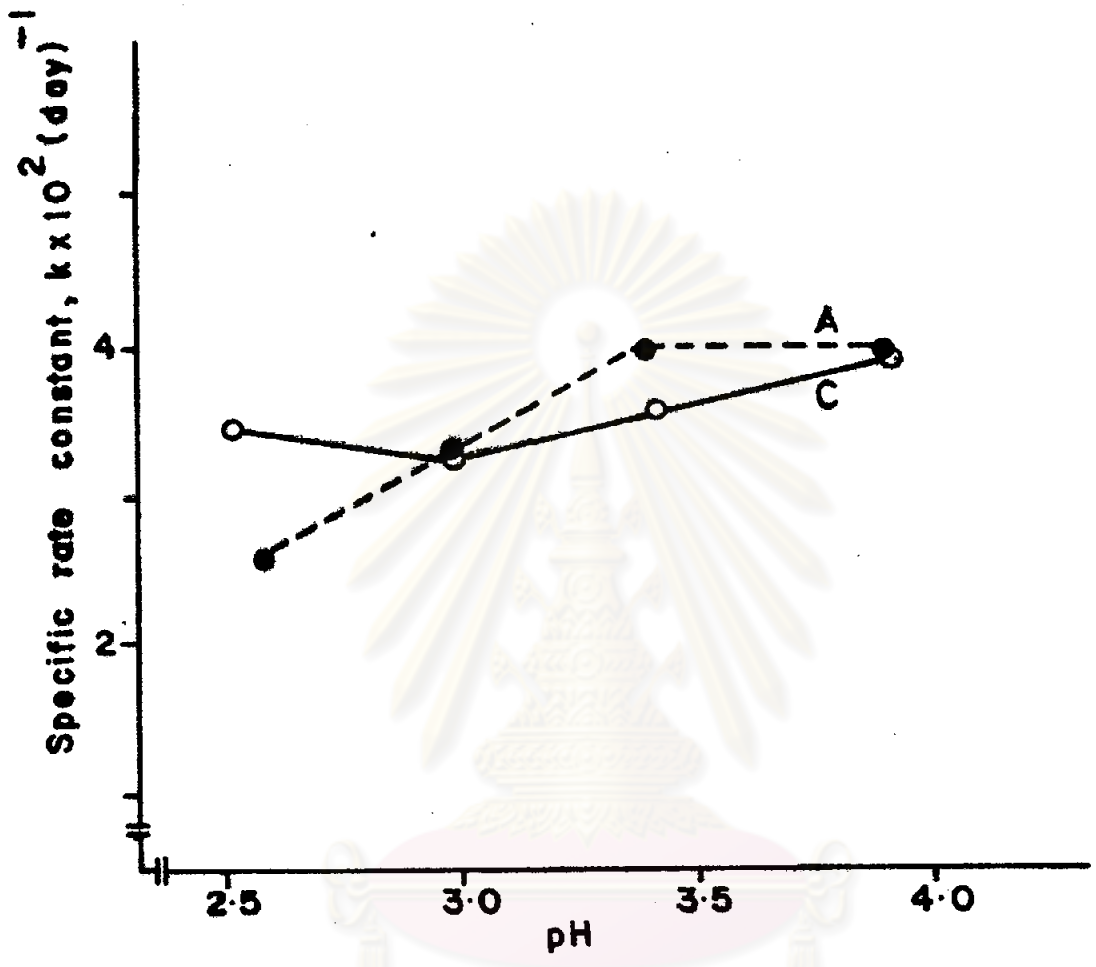

Figure 5 The specific rate constant (k) at 60°C versus pH plot of vitamin C in liquid multivitamin formulation; (A) Acetate buffer; (C) Citrate buffer.

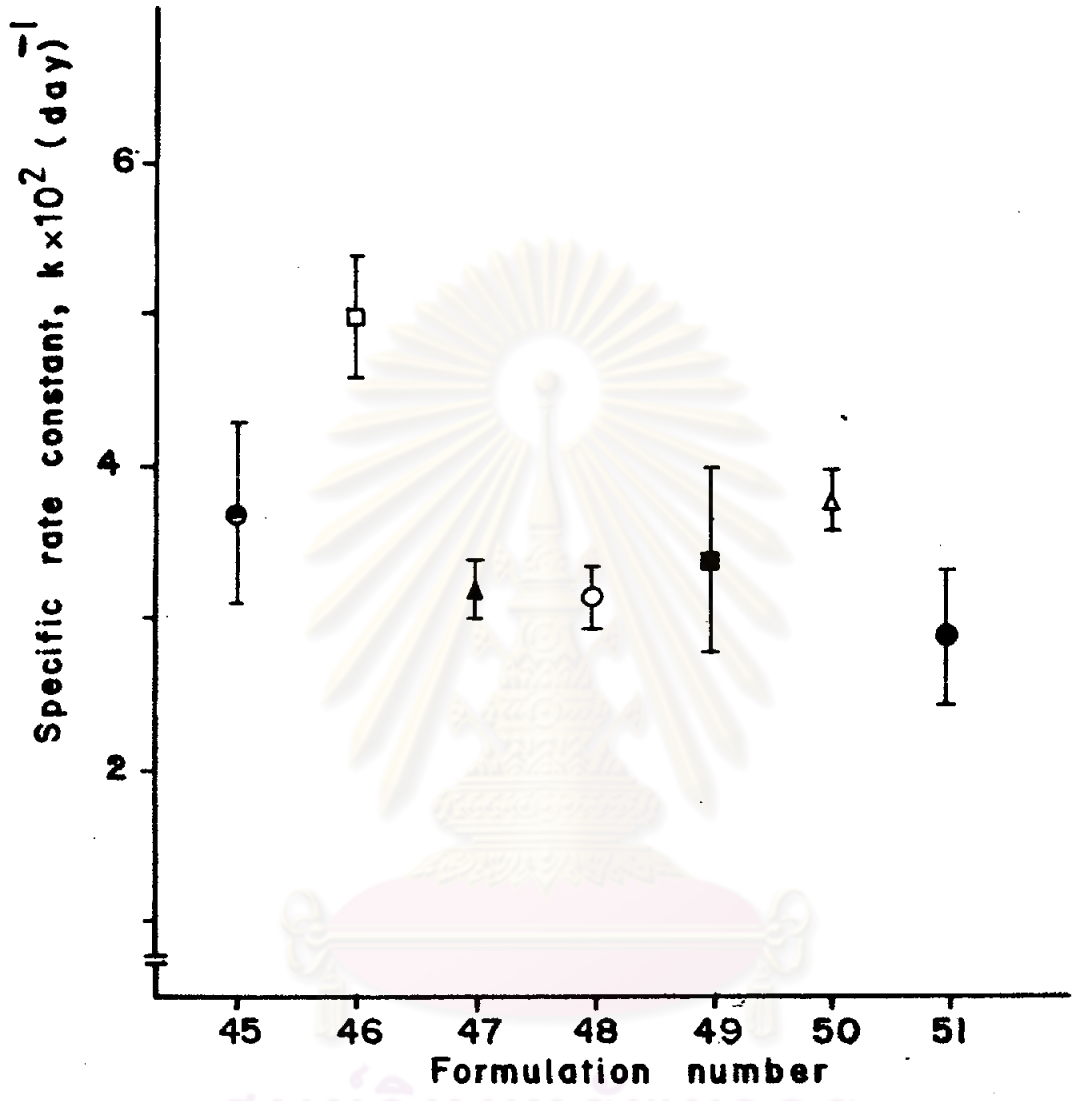

Figure 6 The specific rate constant (k)of vitamin C at 60°C in various liquid multivitamin formulations; (◓) no 45; (□) no 46; (▲) no 47; (O) no 48; (■) no 49; (Δ) no 50; (●) no 51; the bars represent the 95 % confidence limits.

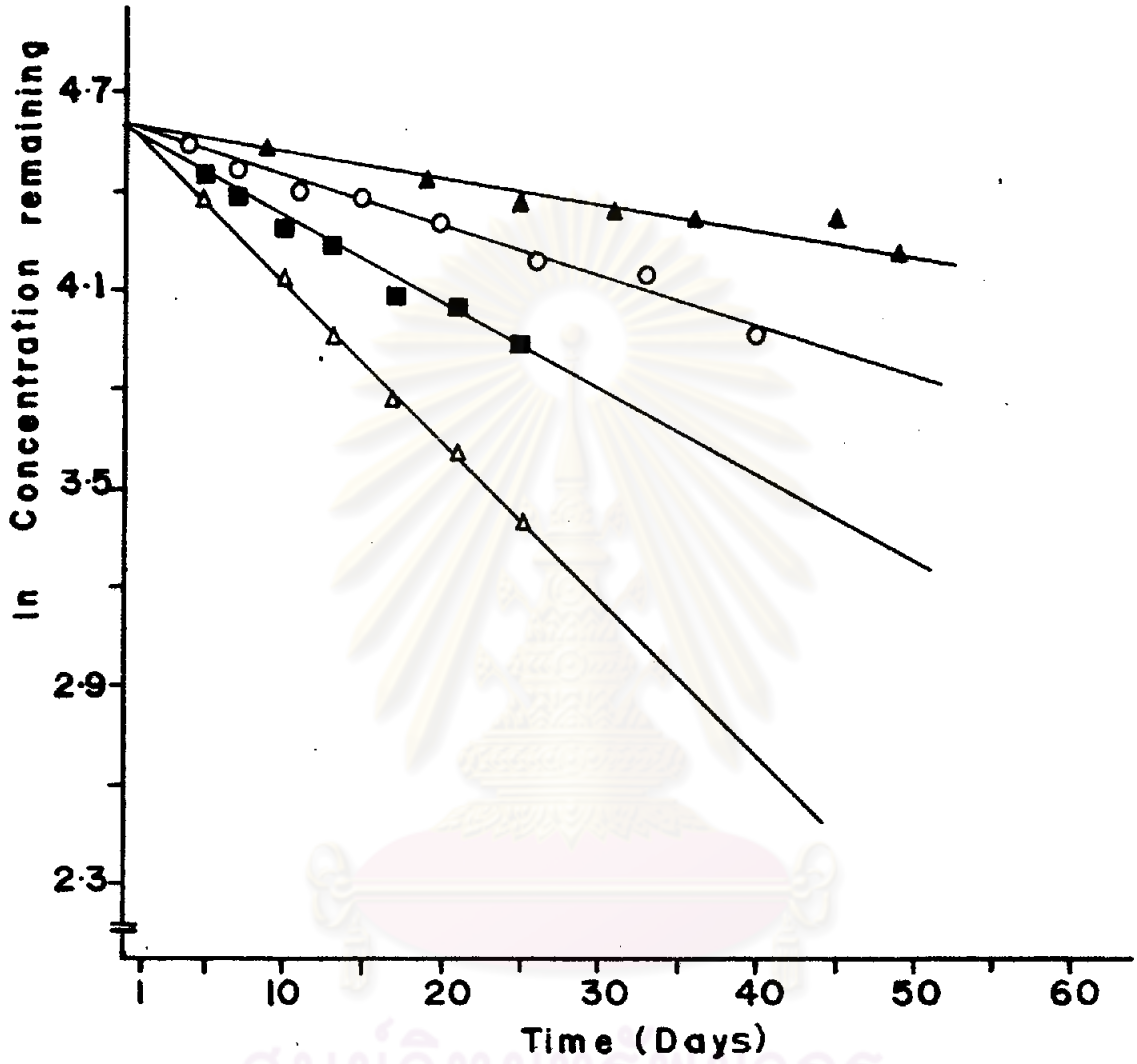

Figure 7 Natural logarithm of concentration remaining versus time plot for first-order degradation reaction of vitamin C in liquid multivitamin formulation number 53; (▲) 40°C; (○) 50°C; (■) 60°C; (△) 70°C.

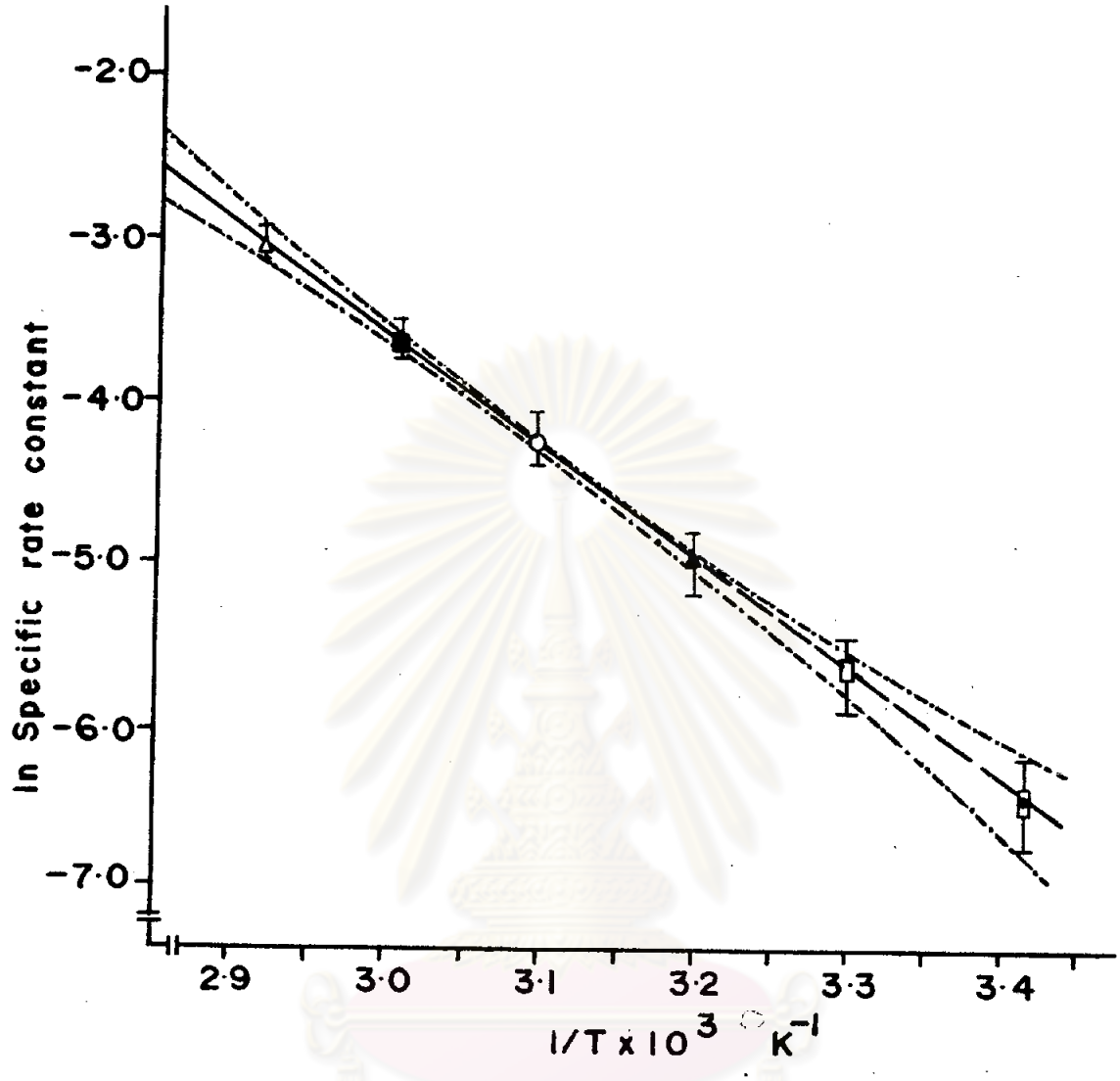

Figure 8 Arrhenius plots of the natural logarithm of specific rate constant versus the reciprocal of ($\frac{\text{degree kelvin}}{}$) (1/T) of vitamin C in liquid multivitamin formulation number 53; (——) represent experimental thermal degradation, (Δ) 70°C; (■) 60°C; (○) 50°C; (▲) 40°C; (– – –) represent extrapolated degradation (□) 30°C; (▣) 20°C; The height of rectangles at 30° and 20°C represent the standard error of prediction; the bars and (-·-·-·-) represent 95 % confidence limits of prediction.

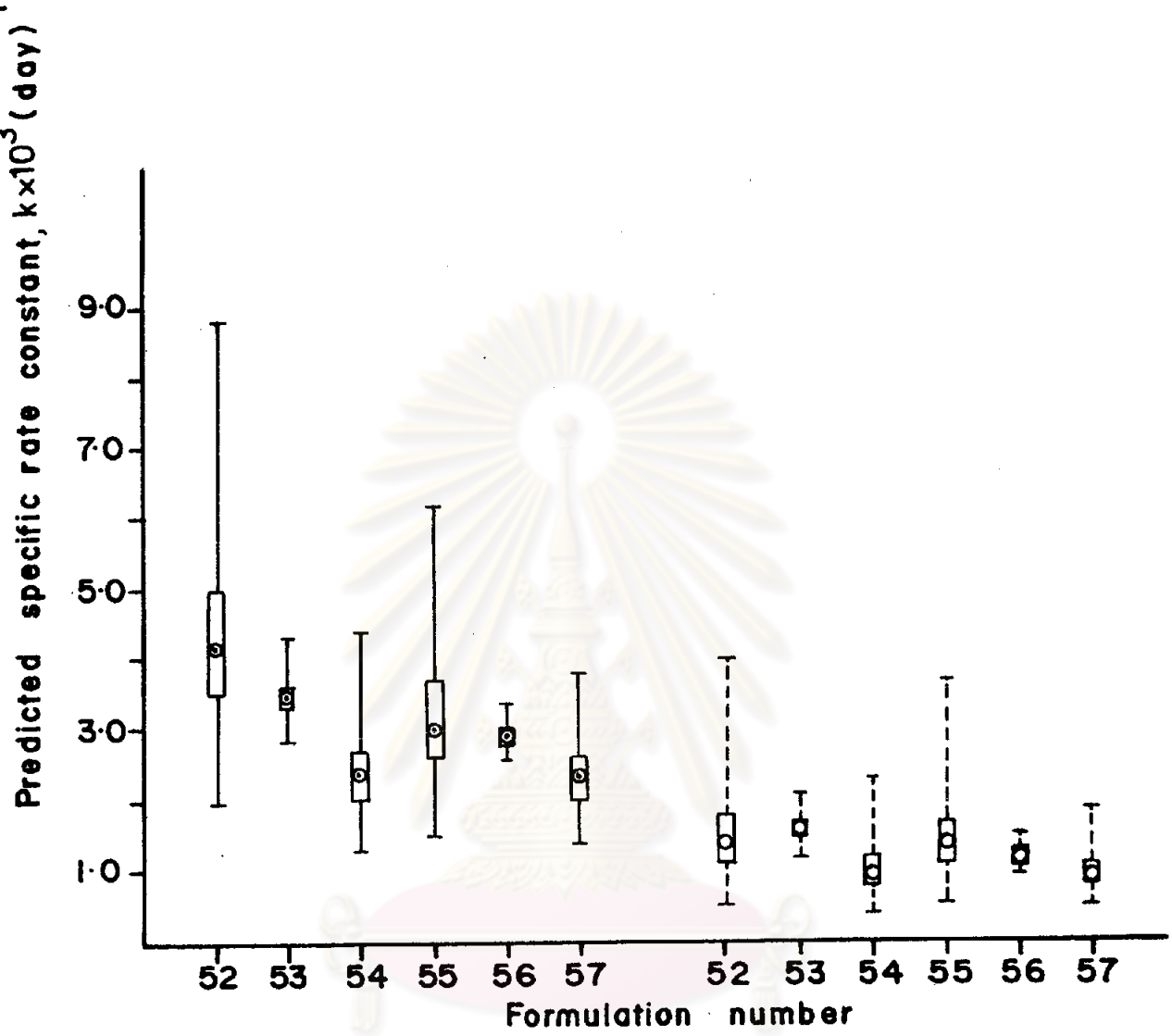

Figure 9 Predicted specific rate constant of vitamin C in liquid multivitamin various formulations at 30°C (⊢⊙⊣), and 20°C (⊢-○-⊣); the height of rectangles represent the standard error; the bars represent the 95 % confidence limits of prediction.

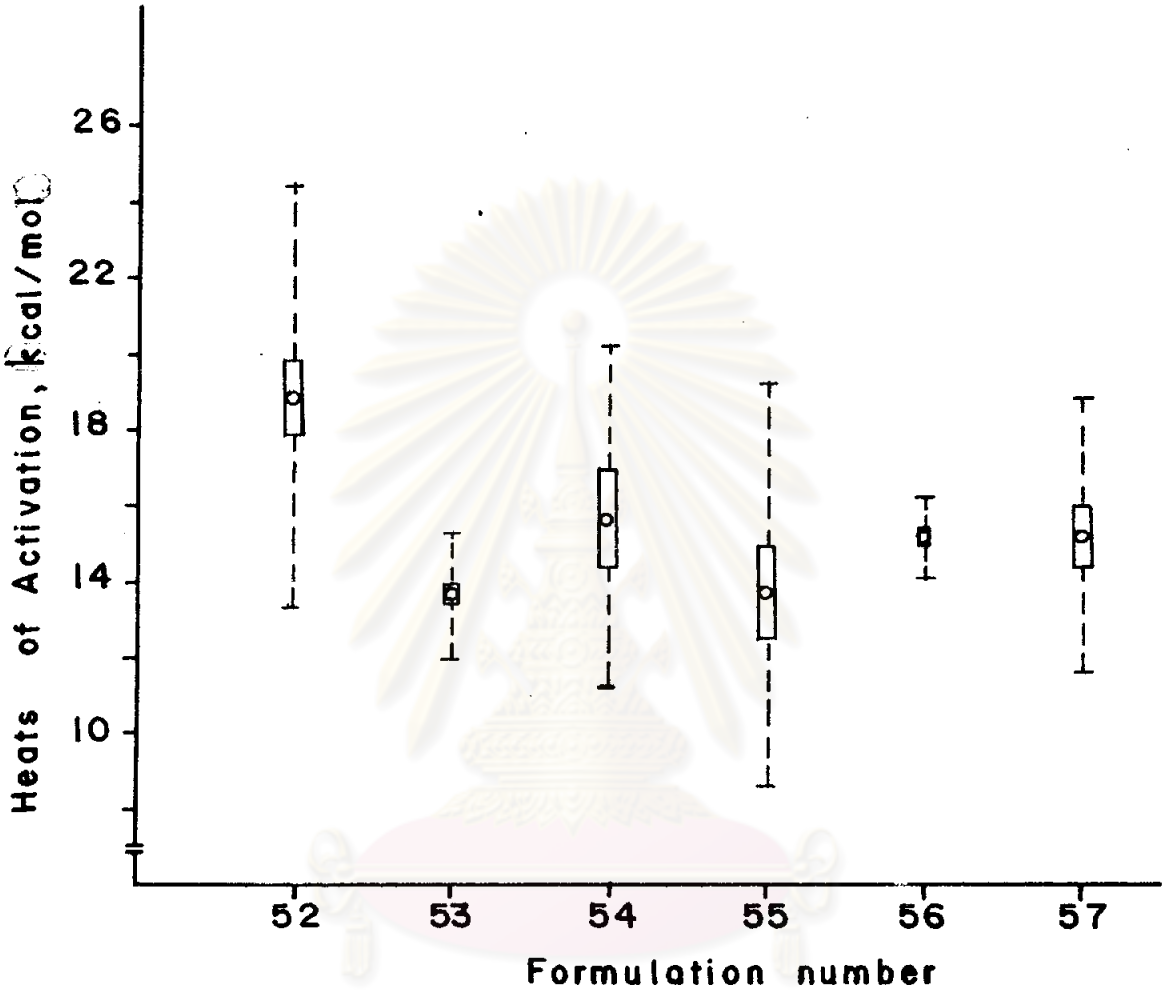

Figure 10 The Heats of activation (kcal/mol) of vitamin C in various liquid multivitamin formulations; the height of rectangles represent the standard error; the bars represent the 95 % confidence limits.

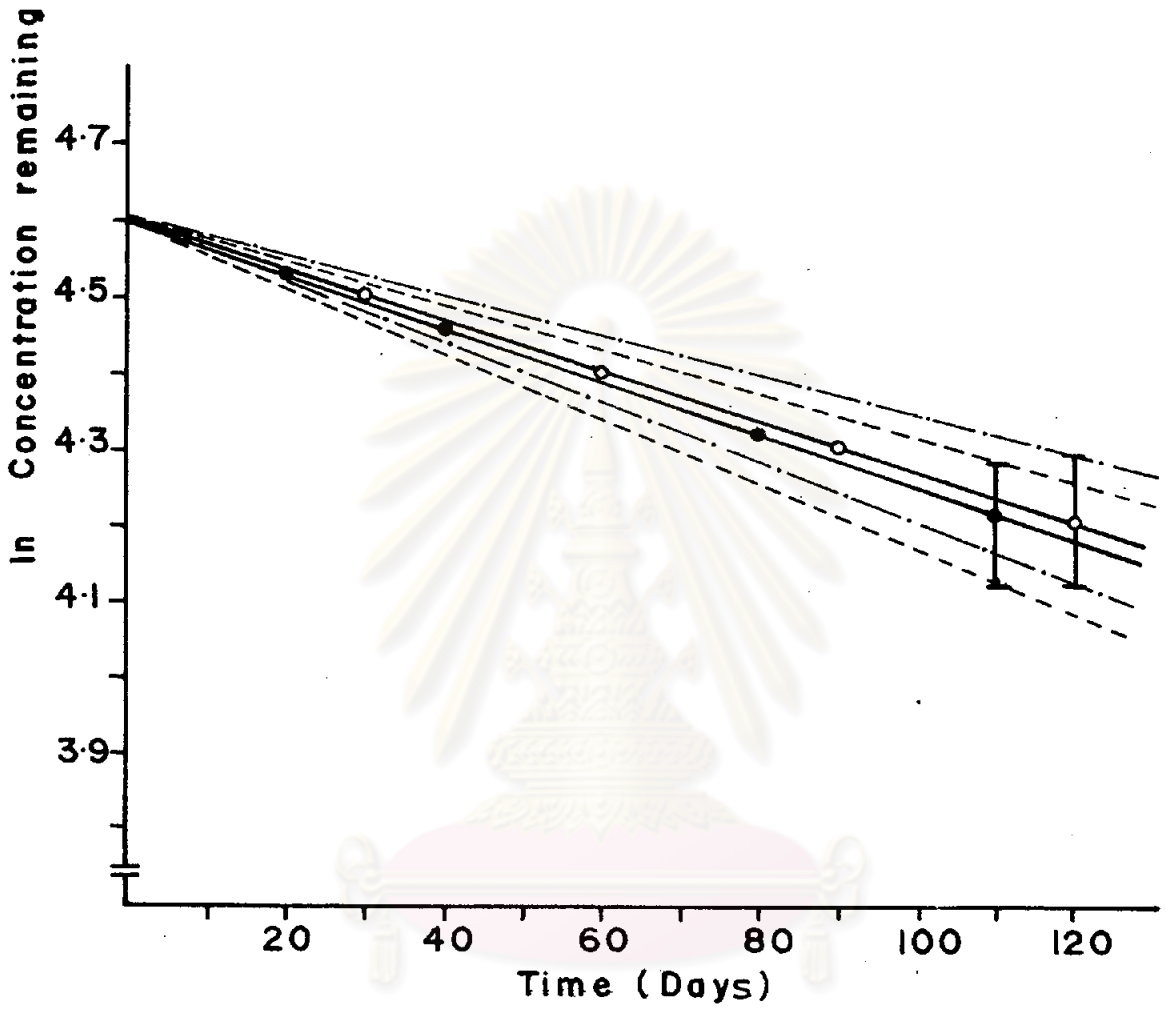

Figure 11 Verification of the stability prediction of vitamin C in liquid multivitamin formulation number 53, at room temperature (30°C); (——) represent the degradation rate; (– – –); (–·–·–) represent 95 % confidence limits of standard error; (●) predicted degradation rate obtained from Arrhenins plot; (O) Apparent degradation rate obtained from actual normal storage conditions.

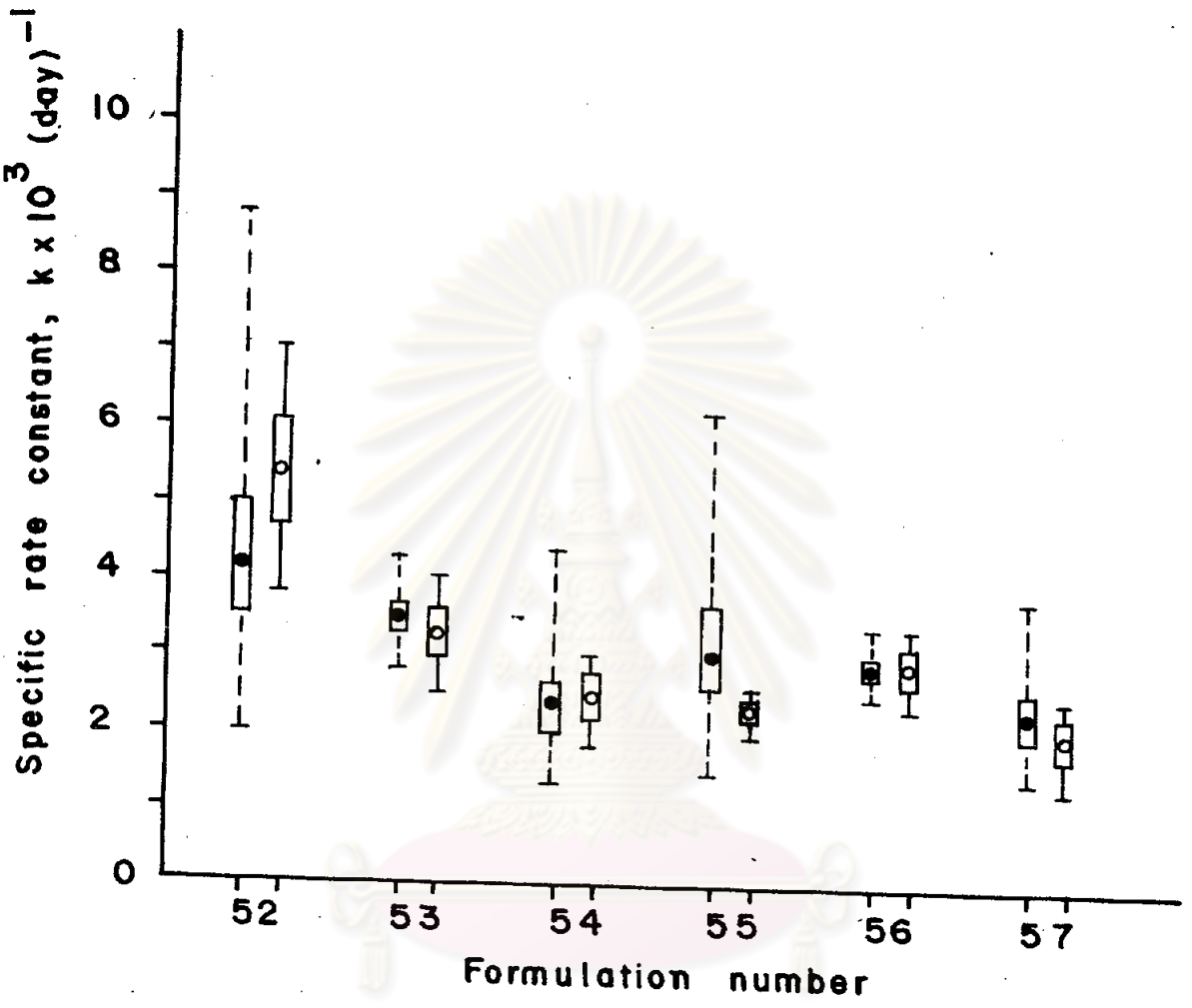

Figure 12 The specific rate constants(k) of vitamin C at room temperature (30°C) in various liquid multivitamin formulations; (--●--) Predicted rate obtained from Arrhenius plot; (—o—) Apparent rate obtained from actual normal storage conditions; the height of rectangles represent the standard error; the bars represent the 95 % confidence limits.

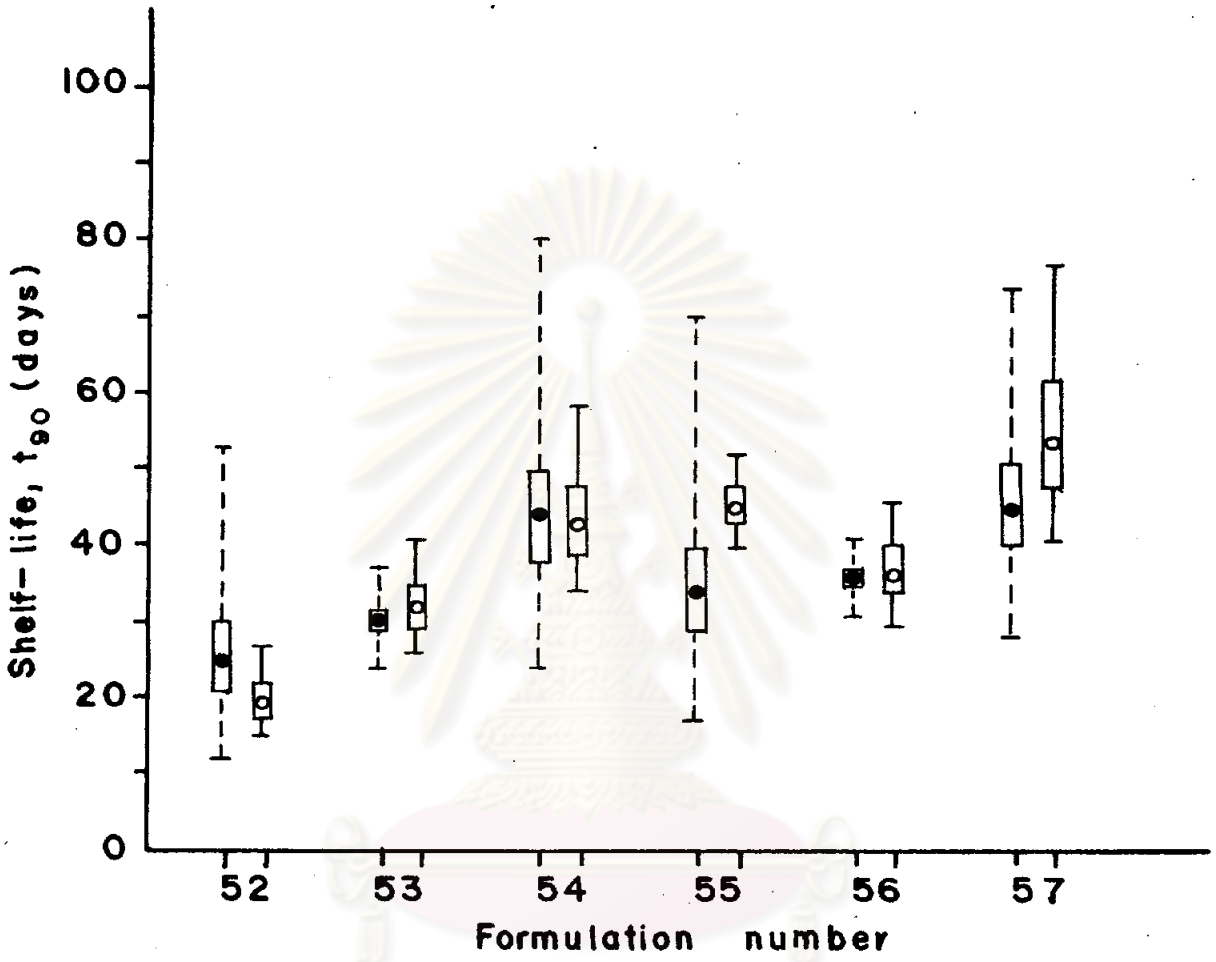

Figure 13 The shelf-life (t_{90}) of vitamin C at room temperature (30°C) in various liquid multivitamin formulations; (--●--) Predicted shelf-life; (—○—) shelf-life at actual normal storage conditions; the height of rectangles represent the standard error; the bars represent the 95 % confidence limits.

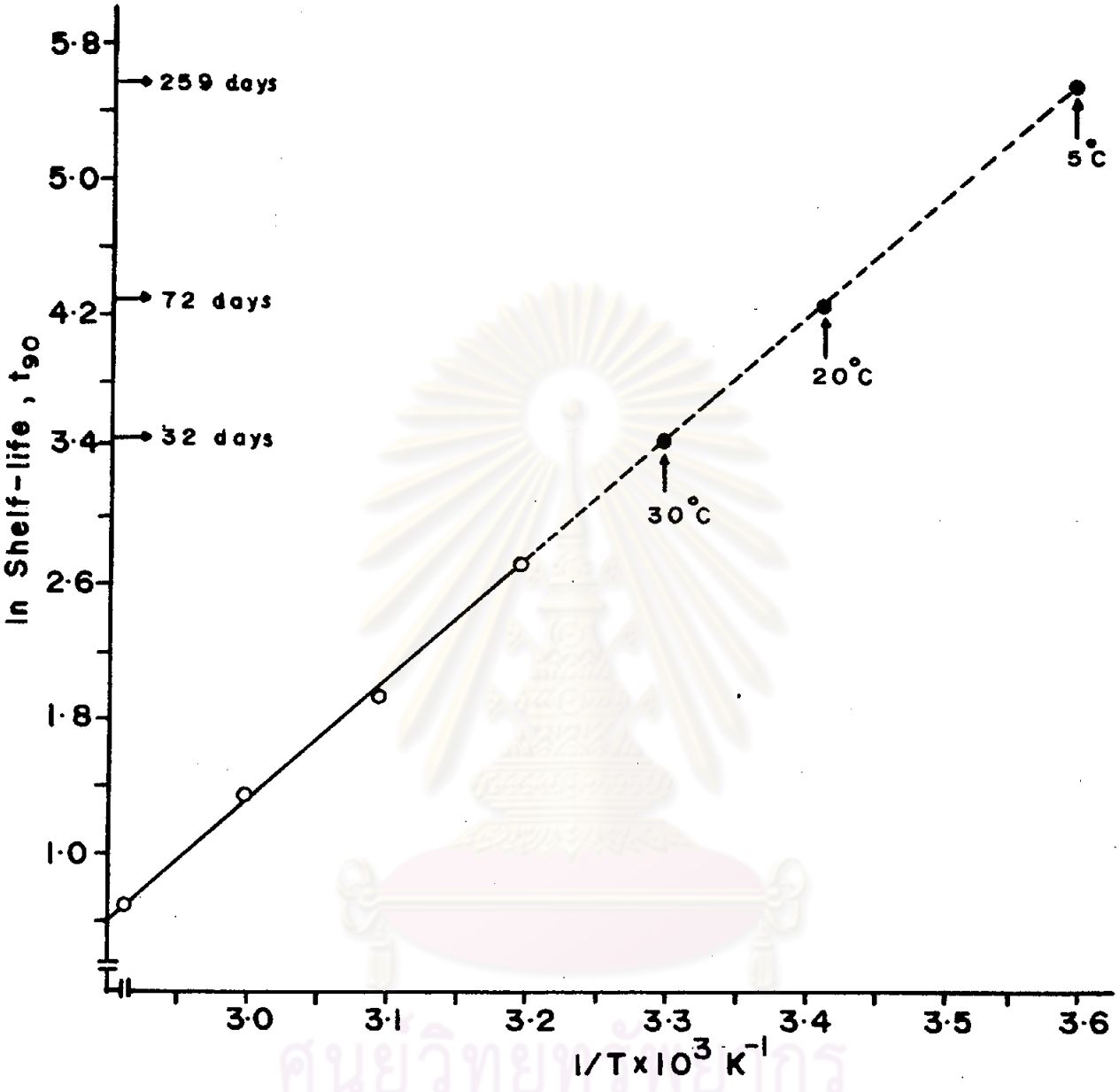

Figure 14 Natural logarithm of shelf-life of 10 % potency loss (t_{90}) versus the reciprocal of degree kelvin (1/T) plot of vitamin C in liquid multivitamin formulation number 53; (———) represent experimental thermal shelf-life; (----) represent extrapolated shelf-life at 30°, 20° and 5°C.

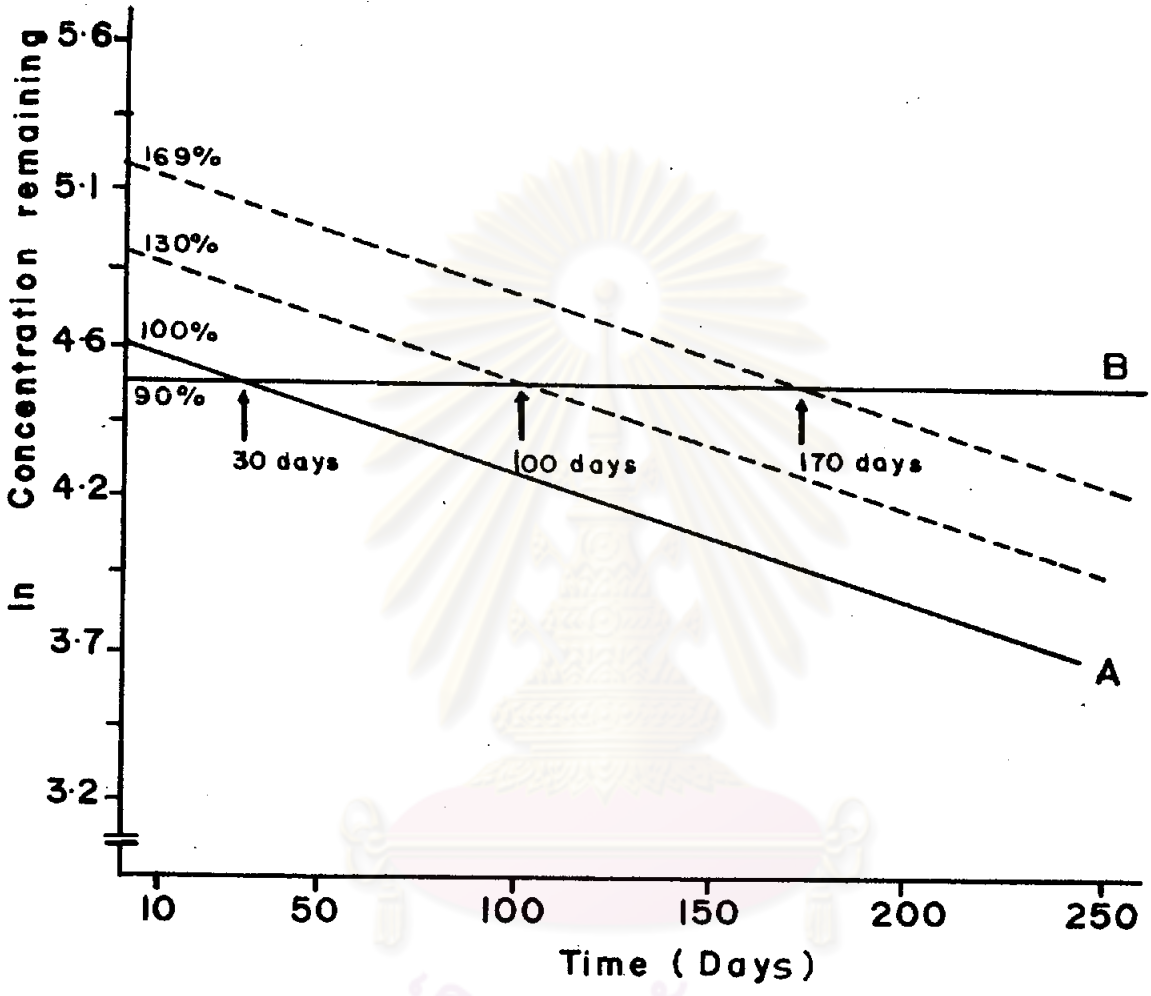

Figure 15 Natural logarithm of concentration remaining versus time plot of vitamin C in liquid multivitamin formulation number 53; (A) the normal loss curve; (B) the 90 % of labelled claim;(- - - - -) the overage curve; (↑) time at vitamin C remaining 90 % labelled claim.