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ERRORS IN THE ESTIMATION OF THE ACTIVATION ENERGY AND THE PROJECTED SHELF LIFE IN EMPLOYING AN INCORRECT KINETIC ORDER IN AN ACCELERATED STABILITY TEST

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ABSTRACT

The errors involved in the estimation of the activation energy of the drug degradation and the projected shelf life of a drug product when employing an incorrect kinetic order in the accelerated stability test were analyzed. The activation energy of a zero order degradation and the projected shelf life of a drug product are overestimated when the kinetic data are treated in first order fashion. The overestimation in the activation energy increases with the temperature range of the accelerated test and the instability of the drug. The overestimation in the projected shelf life increases with the activation energy and increases as the normal

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storage temperature (the projecting temperature) is lowered. Conversely, when a first order degradation is treated as zero order kinetics, both the activation energy and the projected shelf life are underestimated. The application of this theoretical analysis to the data treatment and the design of an aceelerated stability test was discussed.

INTRODUCTION

The establishment of an expiry date for a drug product is required by the Current Good Manufacturing Practice (CGMP) and supporting tests and studies are an essential part of the product development in the industry. The CGMP requires that the expiry date be established through suitably designed stability testing program under normal storage conditions. Since most drug candidates are stable, obtaining an expiry date for a drug product under such conditions is a relatively time-consuming process. This is recognized in the CGMP. A tentative expiry date of a drug projected from an accelerated stability testing program is currently accepted provided that this is supported by long term stability study under normal storage conditions. In this regard, FDA has proposed that a satisfatory three-month stability test of a drug product at 37 to 40°C and 75% or higher relative humidity can be employed to project a tentative shelf life of two years from the date of

manufacture (1). The scientific support and limitations of this proposal have been analyzed (2).

Prediction of an expiry date from accelerated stability testing is based on the Arrhenius relationship. The application of the Arrhenius relationship was introduced into the pharmaceutical field in the 1950's (3). It was stated that in most studies of the thermal degradation of complex liquid preparations zero order or first order kinetics has served satisfactorily to characterize the kinetic profile of the drug degradation (4). A pseudo first order was preferred in a method using stability chart derived from Arrhenius equation (5). Without a detailed degradation mechanism the choice of the degradation order can be difficult. Thus the kinetic data concerning the degradation of ascorbic acid in three similar commercial multivitamin liquid preparations was treated with zero order kinetics in two studies and with first order kinetics in a third study (6). In one paper the degradation of ascorbic acid, folic acid and vitamin A was concluded to initially have zero order degradation followed by first order degradation in a later phase and the data were treated as such (3). In another paper, though the kinetic behavior of ascorbic acid was stated to follow the same pattern, the data were separately treated by zero order and first order (7). The degradation of vitamin A has been treated entirely

as a zero order process (6) or entirely as a first order process (8).

The standard procedure in determining the kinetic order is to fit the data with the appropriate integrated rate equation employing the least square regression method For most potential drug substances which are normally relatively stable it may be difficult to establish the true kinetic order when the degradation is not followed far enough toward its completion. In such cases, equally satisfactory coefficients of determination (r^2) can be obtained[1]. The judgement of choosing one from the other to be used for the data treatment may be difficult.

A question which naturally arises concerns the consequences of choosing a wrong kinetic order. This paper analyzes the errors involved in the data treatment process when an incorrect kinetic order is chosen in terms of the following two important parameters: 1) the activation energy of the dagradation and 2) the projected shelf life of the drug product.

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1. A good example is given in Problem 1 in Chapter 14 in "Physical Pharmacy" by Martin, Swarbrick, and Cammarata. The kinetic order of the degradation of of glucose is to be determined. Fitting the data using the integrated zero, first, and second order rate equations with the least square regression method gives three equally satisfactory straight lines with r^2 values of 0.986, 0.988, and 0.988 respectively. The reaction was followed to only 27% completion.

THEORETICAL

When the degradation kinetics of a drug is zero order and the Arrhenius relationship is applicable to describe the effect of the temperature on the rate constant of the degradation:

$$\ln \frac{k_{20}}{k_{10}} = \frac{E_0}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad \text{Eq.1}$$

where k_{20} is the zero order rate constant of the degradation at temperature T_2, k_{10} is the zero order rate constant of the degradation at temperature T_1, E_0 is the activation energy of the zero order degradation, and R is the gas constant. For the discussion in this paper, $T_2 > T_1 >$ normal storage temperature.

The rate constants k_{20} and k_{10} can be expressed by the following equations:

$$k_{10} = (A_0 - A_1)/t \qquad \text{Eq.2}$$

$$k_{20} = (A_0 - A_2)/t \qquad \text{Eq.3}$$

where A_1 is the drug level at time t at the temperature T_1, A_2 is the drug level at time t at the temperature T_2.

Let's further assume that this zero order degradation can also be perfectly described by a first order process and the Arrhenius relationship is also applicable in assessing the effect of the temperature on the first order rate constants of the degradation:

$$\ln \frac{k_{21}}{k_{11}} = \frac{E_1}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad \text{Eq.4}$$

where k_{21} is the first order rate constant of the degradation at temperature T_2, k_{11} is the first order rate constant of the degradation at temperature T_1 and E_1 is the activation energy of the first order degradation.

The rate constants k_{21} and k_{11} can be expressed by the following equations:

$$k_{11} = \ln(A_0/A_1)/t \qquad \text{Eq.5}$$

$$k_{21} = \ln(A_0/A_2)/t \qquad \text{Eq.6}$$

The ratio of the first order activation energy to the zero order activation energy can be obtained by dividing Eq.4 by Eq.1:

$$\frac{E_1}{E_0} = \frac{\ln(k_{21}/k_{11})}{\ln(k_{20}/k_{10})} \qquad \text{Eq.7}$$

Dividing Eq.5 by Eq.2 and rearranging:

$$k_{11} = ak_{10} \qquad \text{Eq.8}$$

where:

$$a = \ln(A_0/A_1)/(A_0-A_1) \qquad \text{Eq.9}$$

Likewise:

$$k_{21} = bk_{20} \qquad \text{Eq.10}$$

where:

$$b = \ln(A_0/A_2)/(A_0-A_2) \qquad \text{Eq.11}$$

Substituting Eq.8 and Eq.10 into Eq.7 and rearranging:

$$\frac{E_1-E_0}{E_0} = \frac{\ln(b/a)}{\ln(k_{20}/k_{10})} \qquad \text{Eq.12}$$

In an accelerated stability test the effect of treating zero order degradation with first order kinetics on the projected shelf life at the normal storage temperature is treated as following. The projected shelf life is calculated from the extrapolated rate constant at that temperature. When the shelf life is defined as the time period needed for the drug concentration to reach 90% of the initial level the shelf life for the zero order process is:

$$t_{90}^{0} = \frac{10 \exp\left(\frac{E_0}{R}\left(\frac{1}{T_0} - \frac{1}{T_1}\right)\right)}{k_{10}} \qquad \text{Eq.13}$$

where t_{90}^{0} is the projected shelf life for the zero order degradation at temperature T_0.

Similarly for the first order kinetics:

$$t_{90}^{1} = \frac{0.105 \exp\left(\frac{E_1}{R}\left(\frac{1}{T_0} - \frac{1}{T_1}\right)\right)}{k_{11}} \qquad \text{Eq.14}$$

where t_{90}^{1} is the projected shelf life for the first order degradation at temperature T_0.

Dividing Eq.14 by Eq. 13 and rearranging:

$$\frac{t_{90}^{1}}{t_{90}^{0}} = \frac{0.0105 \exp\left(\frac{(E_1-E_0)}{R}\left(\frac{1}{T_0} - \frac{1}{T_1}\right)\right)}{a} \qquad \text{Eq.15}$$

This ratio can be expressed in terms of T_2:

$$\frac{t_{90}^{1}}{t_{90}^{0}} = \frac{0.0105 \exp\left(\frac{(E_1-E_0)}{R}\left(\frac{1}{T_0} - \frac{1}{T_2}\right)\right)}{b} \qquad \text{Eq.16}$$

RESULTS AND DISCUSSION

The error in the estimation of the activation energy for zero order degradation when it is treated as first order kinetics is expressed by the ratio $(E_1-E_0)/E_0$ in Eq.12. Since $b>a$ and $k_{20}>k_{10}$, the term on the right hand side of Eq.12 is positive. Therefore choosing an incorrect kinetic order in this situation results in overestimation for the activation energy of the degradation.

It is desirable to obtain numerical values of the error term $(E_1-E_0)/E_0$ in order to assess the extent of the overestimation. This can be computed using the following sequences. 1) Assuming a value for A_1 at time t, the value of k_{10} is calculated using Eq.2. 2) Assuming a value (greater than 1) for the ratio k_{20}/k_{10}, the value of k_{20} is computed. 3) Using Eq.3 the value of A_2 at time t is calculated. 4) Calculate a and b using Eq. 9 and Eq.11. 5) Compute the value of the error term $(E_1-E_0)/E_0$. To simplify the calculation the amount or concentration of the drug is expressed as the percentage of the initial level which is also the label claim.

Figure 1 shows the relationship of the error term $(E_1-E_0)/E_0$ and the ratio k_{20}/k_{10} at different k_{10} values. Note that no time unit is specified for k_{10}. This allows the flexibility to choose any time unit for the situation under study. For example a k_{10} value

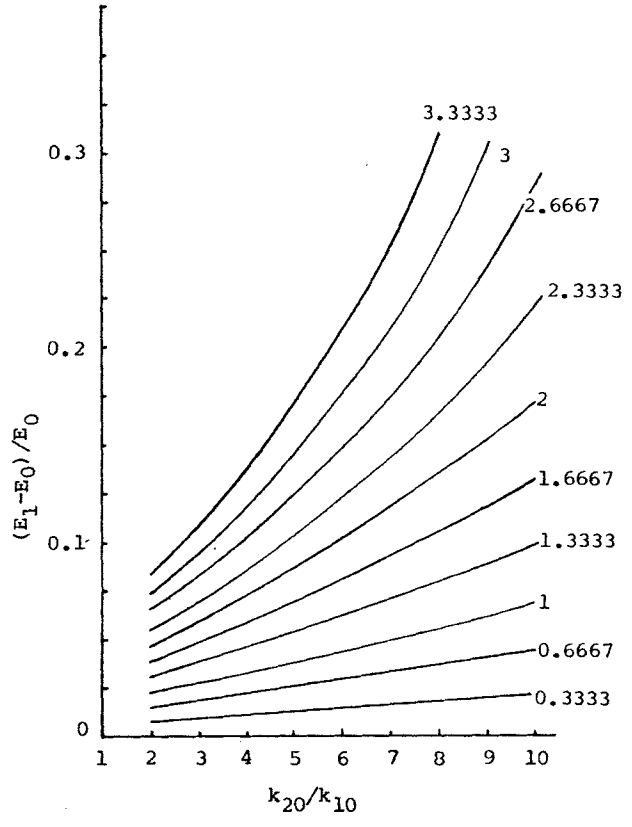

FIGURE 1

The relationship between $(E_1-E_0)/E_0$ and k_{20}/k_{10} at different k_{10} values. The numbers beside the curves represent the values of k_{10}'s. The unit of k_{10} is %/time.

of 0.3333%/month means that 99% (A_1) of the drug remains intact after three months at a given temperature (T_1).

For a given k_{10}, as the ratio k_{20}/k_{10} increases the value of the error term $(E_1-E_0)/E_0$ is increased.

The ratio k_{20}/k_{10} is dependent upon the temperature range of the accelerated stability test. Taking the rule of thumb of doubling the reaction rate for a ten-degree rise in temperature, a k_{20}/k_{10} value of 8 is equivalent to a range of approximate 30°C. Therefore as the temperature range of the accelerated stability test is increased, so is the extent of the overestimation when an incorrect kinetic order is chosen.

For a given E_0 and k_{20}/k_{10}, the error $(E_1-E_0)/E_0$ is increased as k_{10} increases. Thus for a given temperature range of the accelerated stability test the degree of the overestimation in the activation energy is increased when the drug is increasingly unstable.

The effect of choosing an incorrect kinetic order on the projected shelf life of the drug product is expressed by Eq.15. Figure 2 shows a situation where the zero order activation energy is 20 kcal/mole and T_1=35°C. As can be seen in Figure 2, the projected shelf life is overestimated. For a given k_{10}, as the ratio k_{20}/k_{10} is increased so is the ratio t^1_{90}/t^0_{90}. Thus when the temperature range of the accelerated stability test is increased, the extent of the overestimation in the projected shelf life is also increased.

For a given E_0 and k_{20}/k_{10}, the ratio t^1_{90}/t^0_{90} is increased as k_{10} increases. Therefore for a given tem-

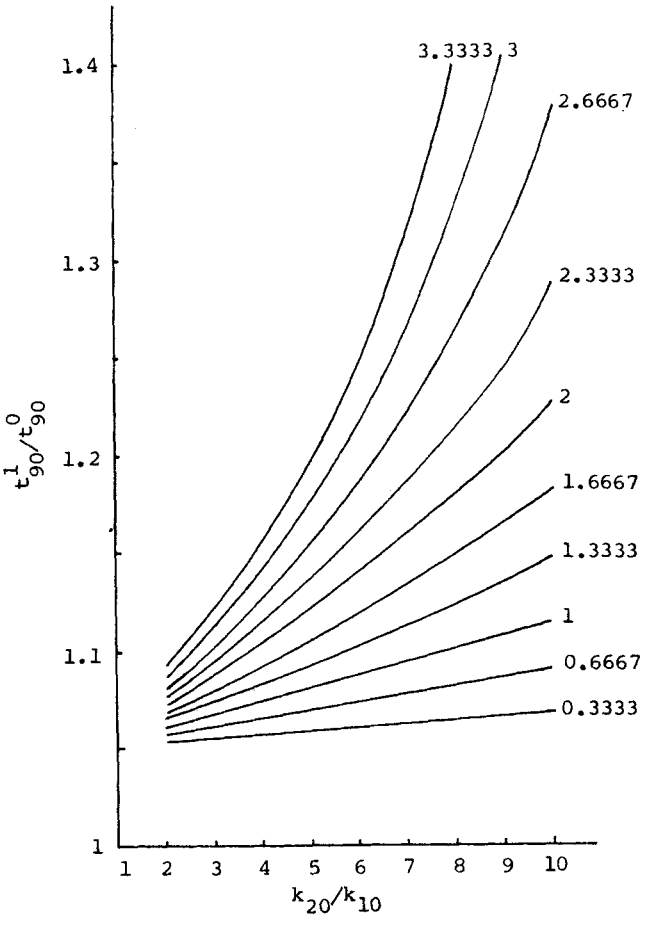

FIGURE 2

The relationship between t^1_{90}/t^0_{90} and k_{20}/k_{10} at different k_{10} values when E_0=20 kcal/mole and T_1=35°C. The numbers beside the curves represent the values of k_{10}'s. The unit of k_{10} is %/time.

perature range of the accelerated stablity test, the extent of the overestimation in the projected shelf life is increased when the drug is increasingly unstable.

Table I presents the projected shelf life at 25°C when different kinetic orders are employed as well as the t^1_{90}/t^0_{90} ratio for the situation where $k_{20}/k_{10}=8$, $E_0=20$ kcal/mole, and $T_1=35°C$. The table is useful to appreciate the actual time period overestimated for different k_{10} values.

It is noted that the ratio t^1_{90}/t^0_{90} in Eq.15 depends on the zero order activation energy E_0 (and thus also on E_1-E_0) and the temperature at which the projection of the shelf life will be made (T_0) for a given T_1.

Figure 3 shows the relationship among t^1_{90}/t^0_{90}, k_{10}, and E_0 when $T_0=25°C$, $T_1=35°C$, and $k_{20}/k_{10}=8$. It can be concluded from Figure 3 that for a given k_{10}, the extent of the overestimation in the projected shelf life increases with the zero order activation energy. This is consistent with the conclusion arrived previously because the combination of a constant k_{20}/k_{10} ratio and an increasing E_0 has the same effect as a combination of a constant E_0 and an increasing k_{20}/k_{10} ratio. Both combinations lead to a greater temperature range for the accelerated stability test. It is also noted that in Figure 3 the degree of the overestimation in the

TABLE I

The Extent of the Overestimation of the Projected Shelf Life at 25°C When $k_{20}/k_{10}=8$, $E_0=20$ kcal/mole and $T_1=35$°C

k_{10}(%/Month)	$(E_1-E_0)/E_0$	E_1(kcal/mole)	t^0_{90}(Month)	t^1_{90}(Month)	t^1_{90}/t^0_{90}
0.3333	0.0175	20.35	89.85	95.66	1.065
0.6667	0.0365	20.73	44.90	48.59	1.082
1	0.0572	21.14	29.94	32.98	1.102
1.3333	0.0800	21.60	22.46	25.22	1.123
1.6667	0.1053	21.11	19.96	20.65	1.149
2	0.1339	22.68	14.97	17.65	1.179
2.3333	0.1666	23.33	12.83	15.60	1.216
2.6667	0.2050	24.10	11.23	14.16	1.261
3	0.2516	25.03	9.98	13.18	1.321
3.3333	0.3110	26.22	8.89	12.59	1.402
3.6667	0.3952	27.90	8.17	12.48	1.528

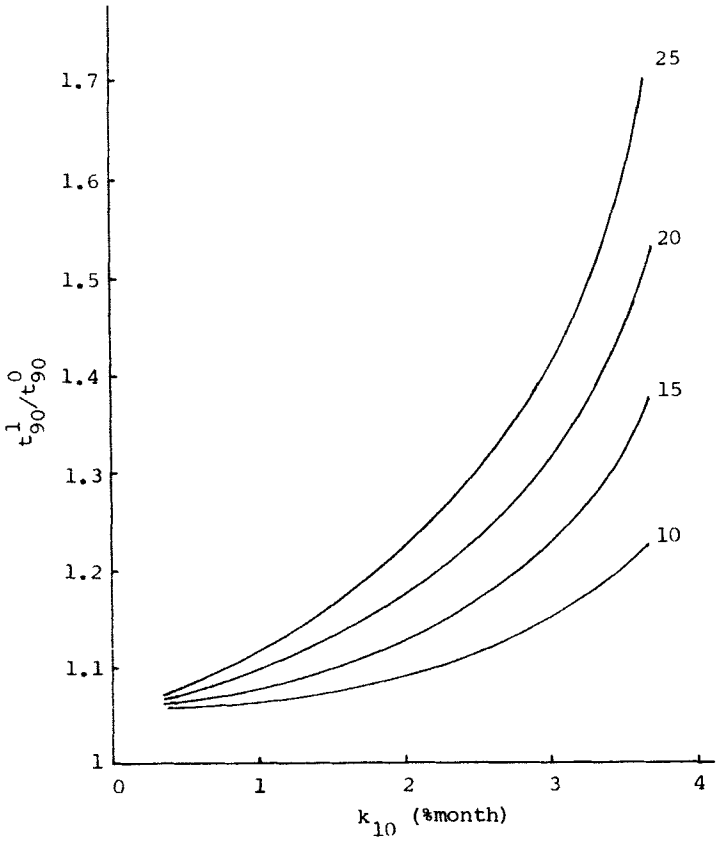

FIGURE 3

The relationship between t^1_{90}/t^0_{90} and k_{10} at different zero order activation energy (E_0) values when T_0=25°C, T_1=35°C and k_{20}/k_{10}=8. The numbers beside the curves represent the values of the zero order activation energy. The unit of E_0 is kcal/mole.

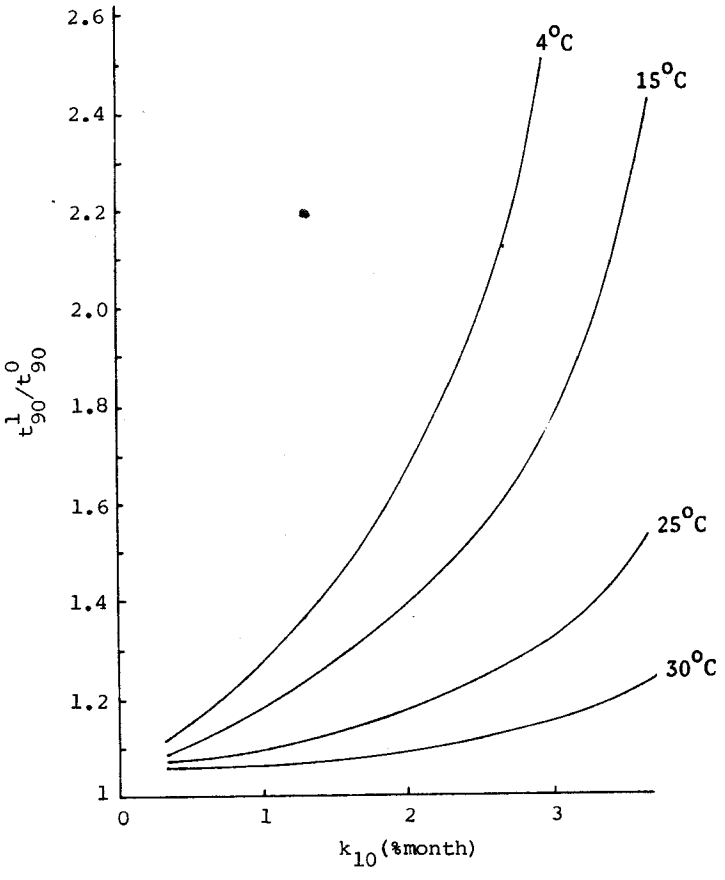

FIGURE 4

The relationship between t_{90}^1/t_{90}^0 and k_{10} at different projecting temperature (T_0) when T_1= 35°C, E_0=20 kcal/mole and k_{20}/k_{10}=8. The temperatures beside the curves represent those of the projecting temperature.

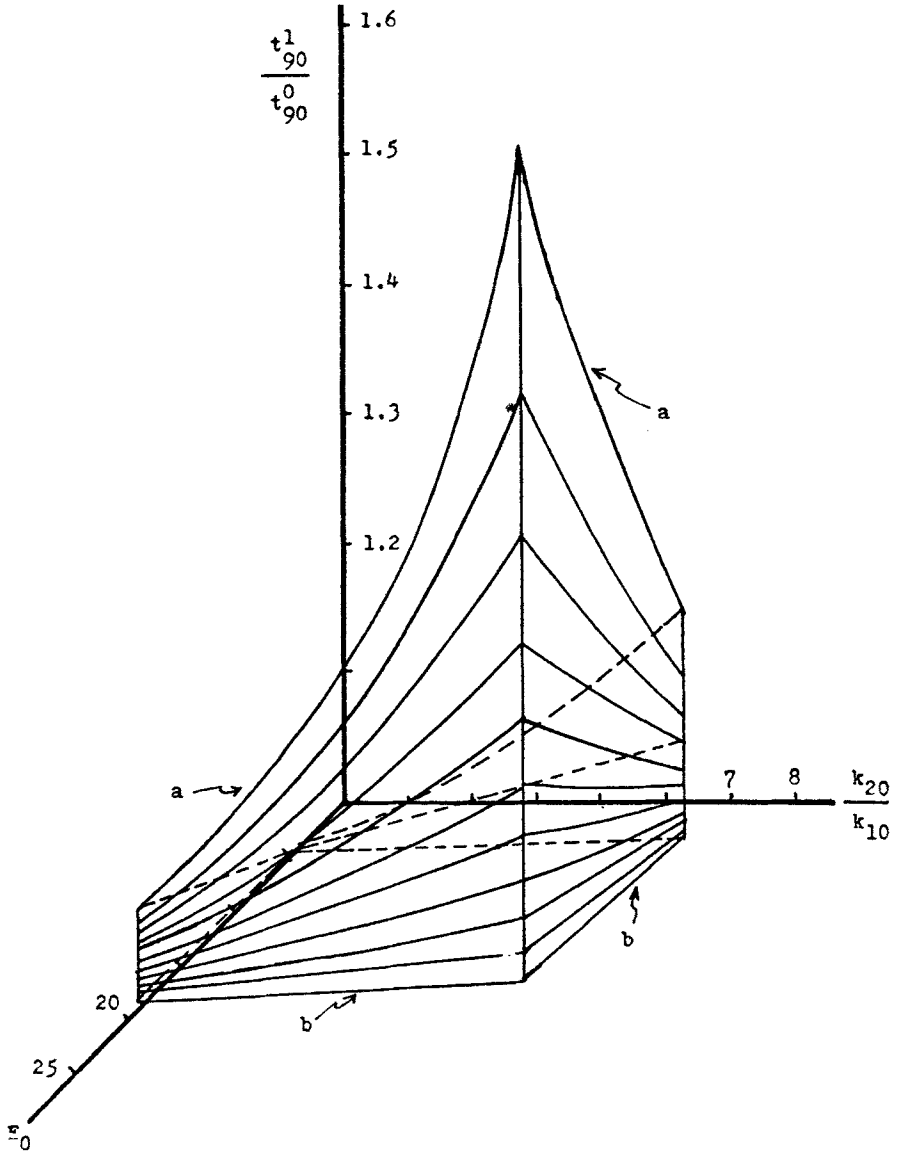

FIGURE 5

The relationship among t^1_{90}/t^0_{90}, k_{20}/k_{10}, E_0, and k_{10} when T_1=35°C and T_0=25°C. The k_{10} value for the curves marked a is 3.6667%/time and that for the curves marked b is 0.3333%/time. The corresponding k_{10} values between a and b are, from the top to bottom: 3.3333, 3, 2.6667, 2.3333, 2, 1.6667, 1.3333,1, 0.6667%/time.

projected shelf life with respect to E_0 worsens when the drug is increasingly unstable.

The relationship among t^1_{90}/t^0_{90}, k_{10}, and T_0 when T_1=35°C, E_0=20 kcal/mole, and k_{20}/k_{10}=8 is shown in Figure 4. It indicates that the degree of the overestimation in the projected shelf life is enlarged when the normal storage temperature is lowered for a given k_{10} value when an incorrect kinetic order is chosen.

The relationship among t^1_{90}/t^0_{90}, k_{20}/k_{10}, E_0, and k_{10} as discussed above can be represented in a three-dimensional graph as shown in Figure 5. This figure represents the situation in which T_1=35°C and T_0=25°C. It can be easily comprehended from this graph that the error in the estimation of the projected shelf life is greater at larger k_{20}/k_{10}, E_0, and/or k_{10} values. It should be pointed out that this three dimensional graph is only a portion of its entirety, but it should serve adequately to show the general shape of the graph.

Similarly, a three dimensional graph can also be drawn as shown in Figure 6 to exhibit the relationship among t^1_{90}/t^0_{90}, k_{20}/k_{10}, T_0, and k_{10} for the situation in which T_1=35°C and E_0=20 kcal/mole. Again it is easily seen that the degree of the overestimation in the projected shelf life increases with k_{20}/k_{10} and k_{10} values, but it decreases when T_0 increases.

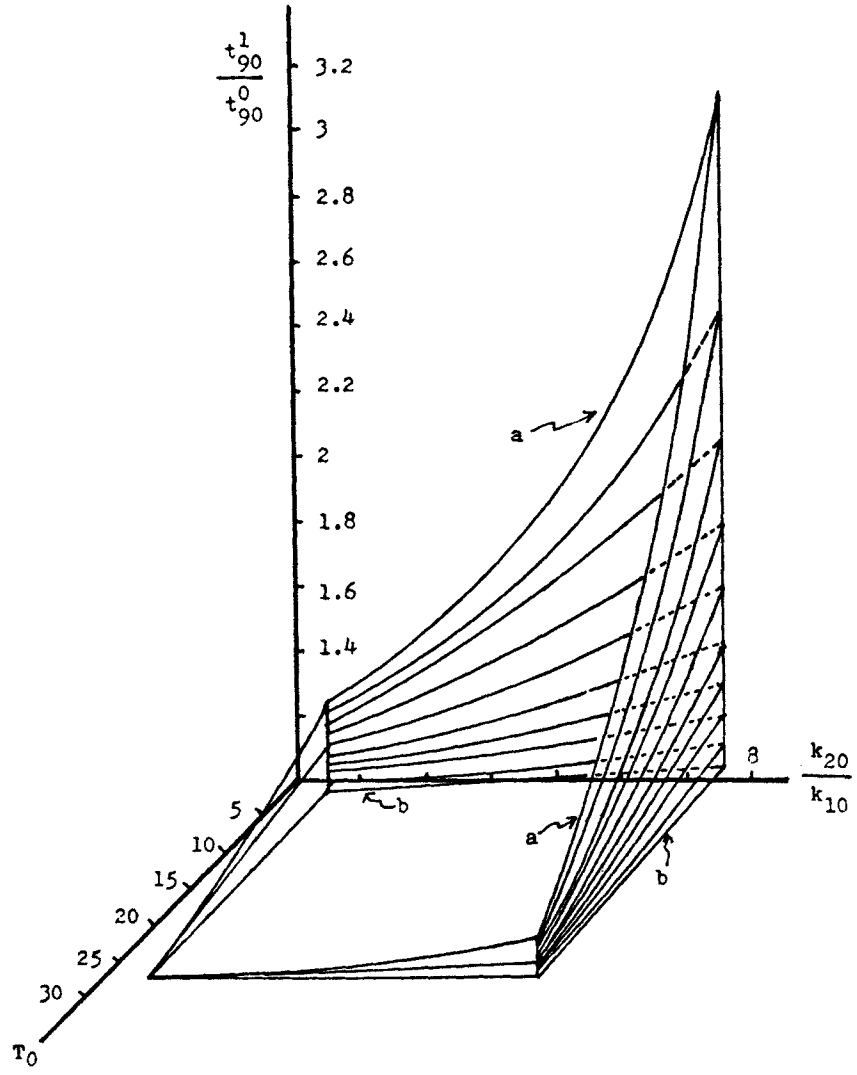

FIGURE 6

The relationship among t^1_{90}/t^0_{90}, k_{20}/k_{10}, E_0, and k_{10} when T_1=35°C and E_0=20 kcal/mole. The k_{10} value for curves marked a is 3.3333%/time and that for the curves marked b is 0.3333%/time. The corresponding k_{10} values between a and b are, from the top to the bottom: 3, 2.6667, 2.3333, 2, 1.6667, 1.3333, 1, 0.6667%/time.

The degradation of ascorbic acid in a liquid multivitamin emulsion was treated according to both zero order and first order kinetics (6). Table II presents the data reported and the theoretical values calculated using the method described in this paper by treating the real degradation kinetics as zero order. It is emphasized that the theoretical values represent an ideal situation and serve as limiting values for the comparison. The departure of the experimental values from the theoretical values reflects in part the experimental variation of the data. Nevertheless it can be seen that the error in estimating the activation energy and the projected shelf life can be quite large when an incorrect kinetic order is chosen for the data treatment.

The theoretical discussion described above is equally applicable to the situation when a first order degradation is treated as a zero order process. The following equations can be used for such treatment for easier comprehension:

$$\frac{E_0-E_1}{E_1} = \frac{\ln(a/b)}{\ln(k_{21}/k_{11})} \qquad \text{Eq.17}$$

$$\frac{t^0_{90}}{t^1_{90}} = 95.238a \exp\left(\frac{(E_0-E_1)}{R}\left(\frac{1}{T_0}-\frac{1}{T_1}\right)\right) \qquad \text{Eq.18}$$

$$\frac{t^0_{90}}{t^1_{90}} = 95.238b \exp\left(\frac{(E_0-E_1)}{R}\left(\frac{1}{T_0}-\frac{1}{T_2}\right)\right) \qquad \text{Eq.19}$$

TABLE II

Comparison between the Theoretical and Experimental Values for the Degradation of Ascorbic Acid

Preparation	$(E_1-E_0)/E_0$ (%)		t_{90}^1/t_{90}^0	
	Theoretical	Experimental	Theoretical	Experimental
I	2.1	10.4	1.251	1.552
II	1.7	8.6	1.222	1.443

As anticipated both the activation energy and the projected shelf life are underestimated in this case.

Several recommendations can be made from the above discussion about the design of an accelerated stablity testing program and the data treatment when uncertainty about the kinetic order is anticipated. 1) It is desirable to keep the temperature range of the accelerated test as narrow as possible, but at the same time as wide as possible to allow at least three different temperatures within the range to obtain significantly different rate constants. 2) It is recommended that the lowest temperature of the accelerated test be as close as possible to the desired projecting temperature (the normal storage temperature), but should be far apart to be able to take the advantage of the accelerated test. 3) When it is virtually impossible to determine the kinetic order from the data, it is recommended that zero order be adopted to allow a conservative estimation of the projected shelf life.

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