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# Prediction of Stability of Drugs. III.[1] Application of Weibull Probability Paper to Prediction of Stability[2]

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The degradation rate of active ingredient of drugs in homogeneous or heterogeneous system was found to conform to a rate equation within a range of degradation ratio. The equation was obtained by using a Weibull probability paper

$$\ln\ln\left(\frac{1}{1-\alpha}\right)=\ln k+m\ln t$$

where $\alpha$ is degradation ratio, $t$ is time, and $m$ and $k$ are parameters. The rate equation was corresponded to usual reaction rate equations. As a result, it exhibits good approximation within the range of degradation ratio of 1—30%, and the Arrhenius equation can be applied to these parameters.

In the present investigation, acetylsalicylic acid solution, ascorbic acid solution, ascorbic acid–mannitol powder, and pyridoxal phosphate solution were used to exemplify those points. As a result, the degradation ratio predicted was in good agreement with those observed.

It may be concluded that a method by the Weibull probability paper suggested in the present paper is useful on account of its convenience and accuracy of the prediction compared with usual ones by reaction kinetics.

Many investigators[4] described the possibility of predicting the stability of drugs at storage temperature by using the results of short-term degradation studies at elevated temperatures. Degradation rate at a lower temperature was predicted by applying the kinetic rate equation of stoichiometric reaction and the Arrhenius equation. Such a method is very useful for active ingredients which show a simple reaction but, in the case of the active ingredient in a heterogeneous system of solid formulation, colloidal suspension, and emulsion, usual simple rate equations are not always applicable. Most of the rate equation and the order of the equation for prediction of stability of the active ingredient in practical system have been determined by trial and error.[5] In addition, Arrhenius relationship has been assumed to any formulation. Consequently, some of the drugs stored on the shelf for a long period reveals large differences in potency from the predicted values. Inaccuracy of the predicted values of stability is due to an incorrect assumption of the order of reaction and to vagueness of the temperature dependence of rate constants.

The present investigation was undertaken to propose a kinetic treatment which is applicable to any type of degradation of the active ingredient of pharmaceutical formulation in both homogeneous and heterogeneous state. An attempt was made to use the Weibull probability paper for the kinetic treatment and relationship between kinetic treatment by

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[1] Part II: N. Okusa and K. Kinuno, *Yakuzaigaku*, **28**, 23 (1968).

[2] A part of this paper was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, 1968.

[3] Location: *N.* 6-9, *Narihira* 5 *chome*, *Sumida-ku*, *Tokyo.*

[4] E.R. Garrett, *J. Pharm. Sci.*, **51**, 811 (1962); A.R. Rogers, *J. Pharm. Pharmacol.*, **15**, 101 (1963); R. Tardif, *J. Pharm. Sci.*, **54**, 281 (1965).

[5] *a*) N.G. Lordi and M.W. Scott, *J. Pharm. Sci.*, **54**, 531 (1965); *b*) B.R. Cole and L. Leadbeater, *J. Pharm. Pharmacol.*, **18**, 101 (1966); *c*) C. Resta, M. Zema and L. Braidotti, *Il. Farmaco.*, Ed. Pr., 23, 34 (1967).

this paper and chemical kinetics was theoretically and experimentally clarified. It was thereby found that selection of rate equations becomes unnecessary, and that stability at a low temperature estimated from data at elevated temperature can accurately be predicted by grasping changes of a parameter that depends on temperature. This kinetic treatment was found experimentally to be applicable to several kinds of drugs.

## Theoretical

### i) Correlation with Chemical Kinetics

If the degradation ratio, $\alpha$, is graduated against time on the Weibull probability paper,[6] there was found to be a linear line within a difinite range of degradation ratio. This relationship can be expressed by equation (1).

$$\ln\ln\left(\frac{1}{1-\alpha}\right) = \ln k + m \ln t \tag{1}$$

where ln stands for log with base $e$, and $k$ and $m$ are parameters.

The equation expressing $\alpha$ in chemical kinetics varies according to the degradation mechanism but, within a narrow range, it is represented by the following differential equation

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = Kg(a, \alpha, Pi) \tag{2}$$

where $K$ is the chemical rate constant, $a$ is the initial concentration of a drug, $\alpha$ is the degradation ratio, and $Pi$ is the parameter independent of time ($t$). Integrated form of eq. (2) is expressed as eq. (3)

$$f(a, \alpha, Pi) = Kt \tag{3}$$

Eqs. (1) and (3) can be correlated by assuming that logarithms of eq. (3) is expressed approximately as a linear function of eq. (1).

$$\ln f(a, \alpha, Pi) = \ln K + \ln t \fallingdotseq A_0 + A_1 \ln\ln\left(\frac{1}{1-\alpha}\right) \tag{4}$$

$$\ln\ln\left(\frac{1}{1-\alpha}\right) \fallingdotseq \frac{1}{A_1}(\ln K - A_0) + \frac{1}{A_1}\ln t \tag{5}$$

From eqs. (1) and (5), the relationship between constants determined by the Weibull probability paper and the one determined by chemical kinetics is shown as eq. (6).

$$\left.\begin{aligned} \ln k &= \frac{1}{A_1}(\ln K - A_0) \\ m &= \frac{1}{A_1} \end{aligned}\right\} \tag{6}$$

From eq. (6), $m$ is proved to be the parameter corresponding to the form of $f(a, \alpha, Pi)$, *i.e.*, the reaction mechanism and $k^{1/m}$ is the parameter proportional to the reaction rate constant. Therefore, even if the reaction rate constant is unknown, activation energy ($E$) can be obtained from $k^{1/m}$ *vs.* $1/T$ in eq. (7)

$$k^{1/m} \fallingdotseq \left(\frac{Z}{d}\right)\exp\left(\frac{-E}{\boldsymbol{R}T}\right) \tag{7}$$

where $d$ is exp $A_0$, $Z$ is the frequency constant, $\boldsymbol{R}$ is the gas constant, and $T$ is absolute temperature.

### ii) Consideration by Numerical Experiment

Good approximations of both eq. (4) and (7) are able to prove by following numerical experiments. As the reaction types which are able to take $a$ and $Pi$ from $f(a, \alpha, Pi)$, various

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[6] W. Weibull, *J. Appl. Mech.*, **18**, 293 (1951).

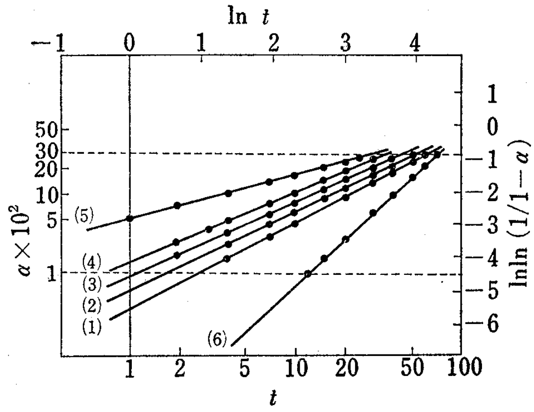

Fig. 1. Regression Lines of Degradation Ratio *vs*. Time on a Weibull Probability Paper for Typical Reaction

type: $f(\alpha)/a^{n-1}=Kt$ $a=1$, halftime=100, $0.01 \leq \alpha \leq 0.30$
(1) zero order, (2) first order, (3) second order, (4) third order, (5) Jander eq., (6) Kawakita eq. ($n=3/2$)

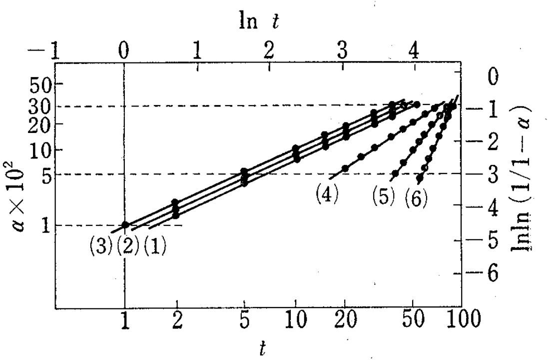

Fig. 2. Regression Lines of Degradation Ratio *vs*. Time on a Weibull Probability Paper for Typical Reaction

type: $f(a, \alpha, Pi)=Kt$ halftime=100
(1) bimolecular reaction ($a/b=0.1$)
(2) bimolecular reaction ($a/b=0.5$) } $0.01 \leq \alpha \leq 0.30$
(3) bimolecular reaction ($a/b=0.9$)
(4) autocatalyzed reaction ($a/b^*=10$)
(5) autocatalyzed reaction ($a/b^*=100$) } $0.05 \leq \alpha \leq 0.30$
(6) autocatalyzed reaction ($a/b^*=1000$)

TABLE I. Parameter *m* and Maximum Deviation of Degradation Ratio from Regression for Typical Reaction Type:
$f(\alpha)/a^{n-1}=Kt$
$a=1$, halftime=100, $0.01 \leq \alpha \leq 0.30$

| No. | Reaction rate equations $f(\alpha)/a^{n-1}=Kt$ | | | $\ln\ln(1/1\text{-}\alpha) = \ln k + m \ln t$ | |
|---|---|---|---|---|---|
| | Types | $n$ | $f(\alpha)$ | $m$ | Max. deviation from regression (%) |
| (1) | zero order | 0 | $\alpha$ | 1.06 | 0.8 |
| (2) | 1st order | 1 | $\ln(1/1-\alpha)$ | 1.00 | 0.0 |
| (3) | 2nd order | 2 | $\alpha/(1-\alpha)$ | 0.95 | 0.6 |
| (4) | 3rd order | 3 | $(2\alpha-\alpha^2)/2(1-\alpha)^2$ | 0.89 | 1.8 |
| (5) | Jander eq. | 1 | $[1-(1-\alpha)^{1/3}]^2$ | 0.51 | 0.3 |
| (6) | Kawakita eq. | 3/2 | $\ln[(1+\alpha^{1/2})/(1-\alpha^{1/2})]$ | 1.97 | 0.4 |

TABLE II. Parameter *m* and Maximum Deviation of Degradation Ratio from Regression for Typical Reaction
Type: $f(a, \alpha, Pi)=Kt$
halftime=100, [I]: $0.01 \leq \alpha \leq 0.30$
[II]: $0.05 \leq \alpha \leq 0.30$

| $f(a, \alpha, Pi)=Kt$ | | | $\ln\ln(1/1-\alpha) = \ln k + m\ln t$ | |
|---|---|---|---|---|
| Types | No. | $a/b$ or $a/b^*$ | $m$ | max. deviation from regression (%) |
| [I] Bimolecular reaction | (1) | 0.1 | 1.00 | 0.06 |
| $\ln\left[\frac{(1-\alpha)}{1-(a/b)\alpha}\right]/(a-b)=Kt$ | (2) | 0.5 | 0.98 | 0.42 |
| | (3) | 0.9 | 0.95 | 0.60 |
| [II] Autocatalyzed reaction | (4) | 10 | 1.45 | 1.55 |
| $\ln\left[\frac{1+(a/b^*)\alpha}{(1-\alpha)}\right]/(a+b^*)=Kt$ | (5) | 100 | 2.66 | 2.00 |
| | (6) | 1000 | 4.65 | 0.80 |

$a$: initial concentration of major component
$b$: initial concentration of other component
$b^*$: initial concentration of catalyzer

Table III. Maximum Deviation of Degradation Ratio between the True and Treated Rate Equation

$a=1$, halftime$=100$, $0.01\leq\alpha\leq0.30$

| React. types | Treated eq. | | | | | |
|---|---|---|---|---|---|---|
| | Zero order | 1st order | 2nd order | Jander eq. | Kawakita eq. | Proposed rate eq.[a] |
| Zero order | 0.0 | 0.7 | 1.7 | 3.5 | 1.6 | 0.8 |
| 1st order | 0.8 | 0.0 | 0.7 | 3.3 | 2.8 | 0.0 |
| 2nd order | 1.7 | 0.7 | 0.0 | 2.3 | 3.6 | 0.6 |
| Jander eq. | 5.0 | 4.7 | 4.5 | 0.0 | 6.6 | 0.3 |
| Kawakita eq. | 1.9 | 2.5 | 3.5 | 6.2 | 0.0 | 0.4 |

a) $\ln(1/1-\alpha)=k\,t^m$

reactions such as the zero-, first-, second-, and third-order reaction rate equations, Jander equation,[7] and Kawakita equation[8] were selected for the numerical experiment. As reaction types which cannot take $a$ and $Pi$ from $f\,(a,\,\alpha,\,Pi)$, reactions such as bimolecular reaction and autocatalyzed reaction rate equation were selected. Degradation ratio *vs.* time was plotted on the Weibull probability paper with regard to selected reaction types as shown in Figs. 1 and 2. In any reaction types, the degradation ratio within the range of 1—30% indicated good straight regressions. Parameter $m$ was determined from the gradient of the straight line on the Weibull probability paper. The maximum deviation from the straight regression of degradation ratio *vs.* time in respective reaction types computed by the least squares method is shown in Tables I and II.

As a result of avobe numerical experiments, parameter $m$ was found to be an indication corresponding to the form of $f\,(a,\,\alpha,\,Pi)$ or the magnitude of initial concentration $a$. It was proved that the maximum deviation due to eq. (1) is smaller than that due to unsuitable reaction rate equation as shown in Table III.

The deviation from eq. (1) attributable to errors of degradation ratio was computed by a numerical experiment. When absolute error $\delta\alpha$ of degradation ratio is given, deviation $\varepsilon$ of lnln $(1/(1-\alpha))$ on the Weibull probability paper was computed as shown in Fig. 3. It is evident from Fig. 3 that value of lnln $(1/(1-\alpha))$ is far more deviation $\varepsilon$ at a low than a high value. It was evident from computation of $d$ values of eq. (7) for typical reaction types as shown in Table IV, that deviations appear two digits below the decimal point for those within the range of $0.01\leq\alpha\leq0.30$. Therefore, $d$ values can be regarded as approximately constant.

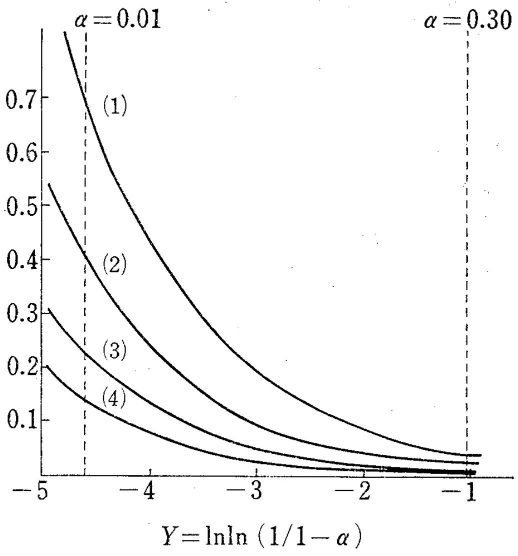

Fig. 3. Deviation $\varepsilon$ of lnln $(1/1-\alpha)$ on Weibull Probability Paper against Absolute Error $\delta\alpha$ of Degradation Ratio

$Y=\ln\ln(1/1-\alpha)$, $Y+\varepsilon=\ln\ln(1/1-\alpha')$, $\delta\alpha=\alpha-\alpha'$
Levels of $\delta\alpha$ are (1) $1\times10^{-2}$, (2) $0.5\times10^{-2}$, (3) $0.25\times10^{-2}$ and (4) $0.15\times10^{-2}$

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[7] W. Jander, *Z. Anorg. Chem.*, **163**, 1 (1927).

[8] K. Kawakita, *Rev. Phys. Chem. Japan*, **14**, 79 (1940).

TABLE IV. Calculated Values of $d$ for Respective Reaction Types

$a=1,\ 0.01 \leq \alpha \leq 0.30$

Calculation Equation of $d$:

$$d=\exp A_0=f(\alpha)/\left[\frac{1}{m}\,a^{n-1}\cdot\ln\left(\frac{1}{1-\alpha}\right)\right]$$

| $\alpha$ | Zero order ($n=0$) $m=1.06$ | 1st order ($n=1$) $m=1.00$ | 2nd order ($n=2$) $m=0.95$ | 3rd order ($n=3$) $m=0.89$ | Jander eq. ($n=1$) $m=0.51$ | Kawakita eq. ($n=3/2$) $m=1.97$ |
|---|---|---|---|---|---|---|
| 0.05 | 0.84 | 1.00 | 0.82 | 1.51 | 0.10 | 2.05 |
| 0.10 | 0.85 | 1.00 | 0.83 | 1.47 | 0.10 | 2.05 |
| 0.15 | 0.85 | 1.00 | 0.83 | 1.48 | 0.10 | 2.05 |
| 0.20 | 0.83 | 1.00 | 0.82 | 1.51 | 0.10 | 2.06 |
| 0.25 | 0.82 | 1.00 | 0.81 | 1.58 | 0.10 | 2.07 |
| 0.30 | 0.80 | 1.00 | 0.78 | 1.66 | 0.10 | 2.08 |

## Experimental

Accelerated storage tests were carried out on several drugs presented below.

(1) **Acetylsalicylic Acid Solution**——In a 100 ml volumetric flask, 200 mg of acetylsalicylic acid (J.P. VII) was accurately weighed, dissolved in 100 ml of Sörensen's buffer solution (glycocol, NaCl, and HCl). The pH value of this solution was 2.6. The solution was filled in a 2 ml glass ampule and sealed. Salicylic acid was determined by the following colorimetric method. The amount of decomposed acetylsalicylic acid was calculated from that of salicylic acid.

**Determination of Degradation Product (Salicylic Acid)9)**——One ml of the sample was pipetted into 20 ml of Sörensen's buffer solution and 1 ml of 1% $Fe(NO_3)_3$ (in 0.075N $HNO_3$) solution was added. The color that appeared was measured spectrophotometrically at 530 nm.

(2) **Ascorbic Acid Solution and Ascorbic Acid-Mannitol Powder**

**Ascorbic Acid Solution**——Five grams of ascorbic acid (J.P. VII) was accurately weighed and dissolved in 100 ml of deionized water. The solution was filled in a 5 ml glass ampule and sealed.

**Ascorbic Acid-Mannitol Powder**——Ascorbic acid (J.P. VII) and mannitol (N.F. XII) were mixed in a ratio of 1:9 by a V-type mixer. The mixed powder was screened through a 100 mesh sieve. One gram of the powder was placed in a 2 ml glass ampule, 20 μl of purified water was added, and the ampule was sealed. The sealed ampules were shaken to blend the powder with water and then preserved in a refrigerator (5°) for 2 days. The powder contained 2% moisture. The intact ascorbic acid was determined by the iodometry (J.P. VII).

(3) **Pyridoxal Phosphate Solution**——One gram of pyridoxal phosphate,10) accurately weighed, was dissolved in 100 ml of 0.1N NaOH solution. The pH value of this solution was 9.5. The solution was filled in a 1 ml glass ampule and sealed. The intact pyridoxal phosphate was determined by paper chromatography as described below.

**Determination of Intact Pyridoxal Phosphate**——The paper chromatography11) was used, in which degradation products-pyridoxal, pyridoxic acid phosphate, pyridoxic acid and unknown substances can be separated from pyridoxal phosphate. The sample (0.02 ml) was spotted on the origin, 7 cm from one end of a strip of filter paper (2×40 cm). The spotted strips were developed for 7 hr in a developing solvent of AcOEt: $C_3H_7OH$: $(C_2H_5O)_2NH$: $H_2O$=40: 30: 5: 25 (by volume). After the development, part of the strip corresponding to the $Rf$ value of 0.1 was eluted from the paper with 0.1N NaOH solution. The absorbance of the eluate was measured at 388 nm by spectrophotometry. As a control, part of the same filter paper below the original line was given the same treatment. The mean recovery ratio was 95±2%.

**Accelerated Storage Test**——Samples immersed in a constant temperature water baths (accuracy, ±0.5°).

## Results

The degradation ratio of acetylsalicylic acid in solution, ascorbic acid in solution, ascorbic acid in powder, and pyridoxal phosphate in solution after storage at elevated temperatures

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9) H. Nogami, S. Awazu and N. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **10**, 503 (1962).

10) Daiichi Seiyaku Co., Ltd.

11) K. Ohike, M. Yokoi and H. Hiruta, *Bitamin*, **19**, 466 (1960).

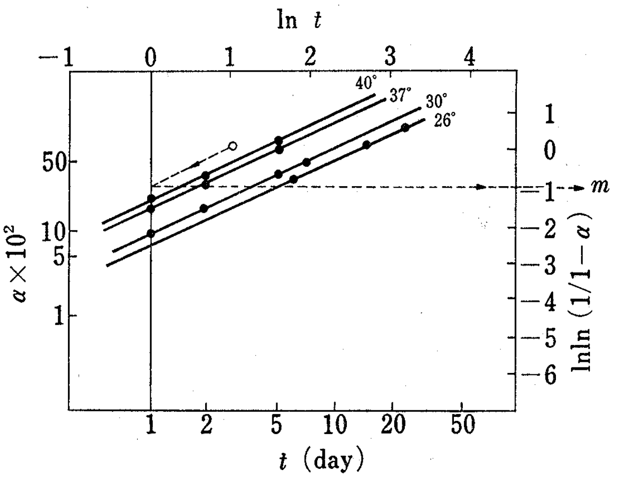

Fig. 4. Regression Lines of the Degradation Ratio of Acetylsalicylic Acid in Solution (pH 2.6) *vs*. Time at Various Elevated Temperatures

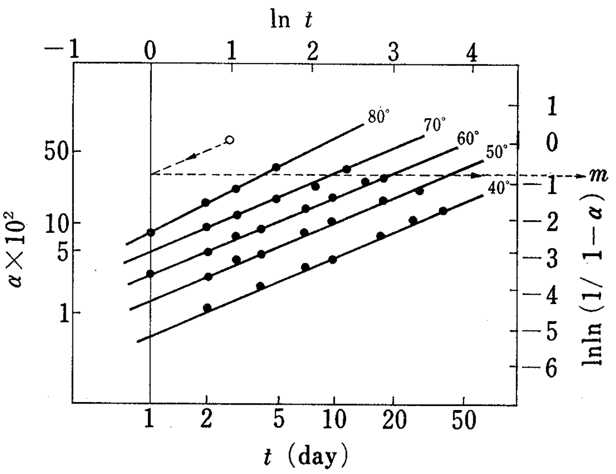

Fig. 5. Regression Lines of the Degradation Ratio of Ascorbic Acid in Solution *vs*. Time at Various Elevated Temperatures

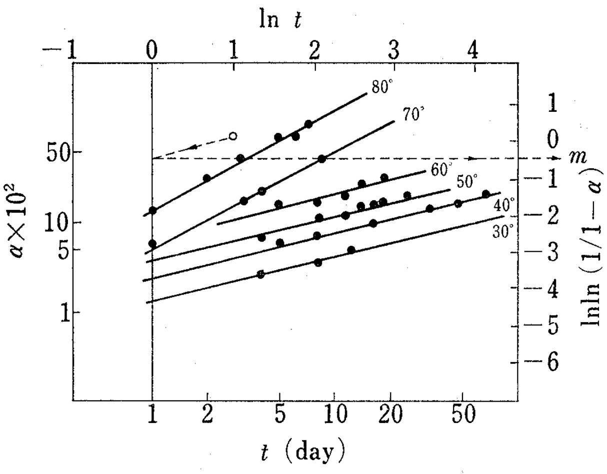

Fig. 6. Regression Lines of the Degradation Ratio of Ascorbic Acid in Ascorbic Acid–Mannitol Powder (Moisture 2%) *vs*. Time at Various Elevated Temperatures

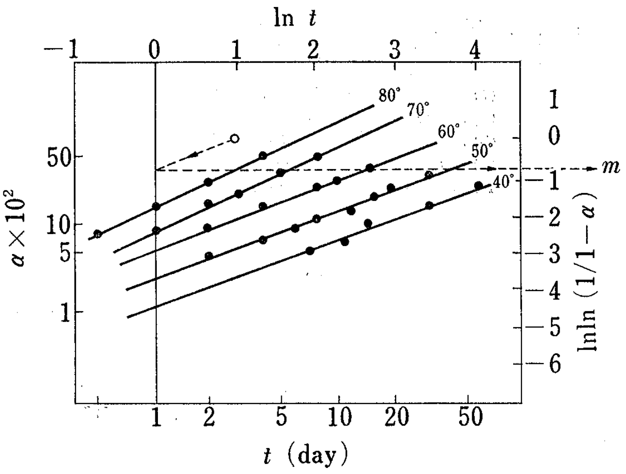

Fig. 7. Regression Lines of the Degradation Ratio of Pyridoxal Phosphate in Solution (pH 9.5) *vs*. Time at Various Elevated Temperatures

TABLE V. Parameters $k$ and $m$ Estimated by Graphic Calculation for the Degradation of Respective Drugs Preserved at Various Elevated Temperatures

| Elevated temp. (°C) | Acetylsalicylic acid sol. (pH 2.6) | | Ascorbic acid sol. | | Ascorbic acid–mannitol powder ($H_2O=2\%$) | | Pyridoxal phosphate sol. (pH 9.5) | |
|---|---|---|---|---|---|---|---|---|
| | ln $k$ | $m$ | ln $k$ | $m$ | ln $k$ | $m$ | ln $k$ | $m$ |
| 26 | −2.64 | 1.00 | | | | | | |
| 30 | −2.35 | 1.00 | | | −4.33 | 0.50 | | |
| 37 | −1.63 | 1.00 | | | | | | |
| 40 | −1.45 | 1.00 | −4.50 | 0.80 | −3.78 | 0.50 | −5.16 | 0.90 |
| 50 | | | −3.73 | 0.80 | −3.25 | 0.50 | −4.26 | 0.90 |
| 60 | | | −2.92 | 0.80 | −2.68 | 0.50 | −3.57 | 0.90 |
| 70 | | | −2.48 | 0.96 | −2.97 | 1.12 | −2.94 | 0.90 |
| 80 | | | 1.80 | 0.96 | −1.88 | 1.12 | −2.38 | 1.03 |

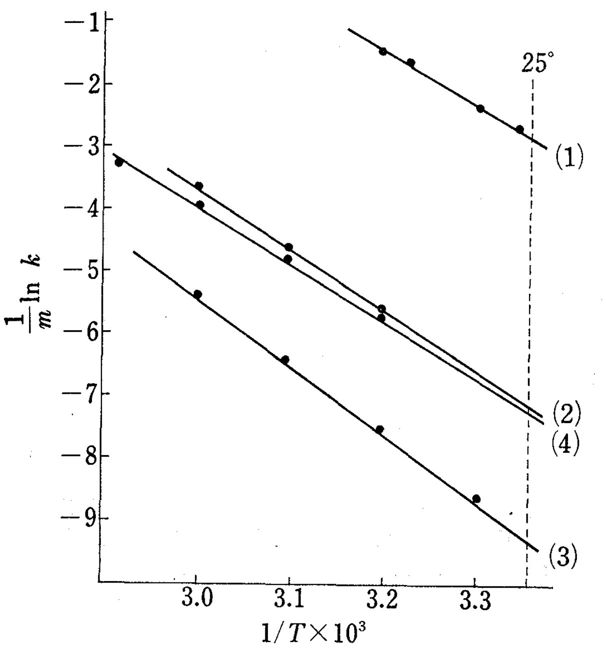

Fig. 8. Temperature Dependence for Parameters $k$ and $m$ of Respective Drugs

(1) acetylsalicylic acid solution (pH 2.6)
(2) ascorbic acid solution
(3) ascorbic acid-mannitol powder
(4) pyridoxal phosphate solution (pH 9.5)
$T$: absolute temperature (°K)

was plotted against time using the Weibull probability paper as shown in Fig. 4, 5, 6, and 7. The parameters $m$ and $k$ obtained by graphic calculation are shown in Table V. If $m$ value is independent of temperature, parallel lines are obtained for each elevated temperature but if $m$ value is dependent on temperature, their relation cannot be demonstrated in such a simple manner as pointed out by Murty.[12] The $m$ values estimated from the degradation ratio of ascorbic acid in solution, ascorbic acid in powder, and pyridoxal phosphate in solution were proved to differ for each temperature. For the prediction in the present paper, $k$ values for a temperature range having equal $m$ values will be adopted for eq. (7) and its result is shown in Fig. 8 as straight regressions of $(1/m) \ln k$ and $1/T$. By extrapolating the straight regression line, $(1/m) \ln k$ for 25° was estimated. From the slope of this line, activation energy was determined. These data are shown in Table VI. The degradation ratio of respective drugs preserved at

TABLE VI. Estimated Parameters at 25° and Activation Energies of Respective Drugs

| Preparation | Estimated parameters | | Activation energy (kcal/mole) |
|---|---|---|---|
| | $m$ | $(1/m)\ln k$ (25°) | |
| Acetylsalicylic acid solution (pH 2.6) | 1.0 | −2.83 | 16.97 |
| Ascorbic acid solution | 0.8 | −7.15 | 19.06 |
| Ascorbic acid–mannitol powder (moisture 2%) | 0.5 | −9.28 | 21.20 |
| Pyridoxial phosphate solution (pH 9.5) | 0.9 | −7.21 | 18.22 |

TABLE VII. Comparisons of Predicted and Observed Degradation Ratio of Respective Drugs Preserved at 25°

| Preparation | Period | Predicted degradation ratio (25°) % | Observed degradation ratio (25°) % |
|---|---|---|---|
| Acetylsalicylic acid solution (pH 2.6) | 30 days | 82.6 | 86.0 |
| Ascorbic acid solution | 1 year | 30.4 | 30.5 |
| Ascorbic acid-mannitol powder (moisture 2%) | 2 years | 22.9 | 21.2 |
| Pyridoxal phosphate solution (pH 9.5) | 1 year | 26.5 | 25.5 |

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[12] H.N. Murty, D.L. Biederman and E.A. Heintz, *J. Phys. Chem.*, 72, 746 (1968).

25° was calculated by using $(1/m)$ $\ln k$ estimated at 25°. On the other hand, actual values of the degradation ratio of drugs preserved at 25° were measured, and the two values were in good agreement as shown in Table VII.

## Discussion

We propose a method using the Weibull probability paper to reduce the prediction errors arising from an assumption of an inappropriate reaction rate equation, and eq. (1) was presented for this method. It can be proved by chemical kinetics derived from the theory of stochastic process that eq. (1) applied to the Weibull probability paper is a chemical reaction rate equation.

The course of chemical reaction is essentially a stochastic process. Bartholomay[13a] and Isida[13b] presented a reaction rate theory using a stochastic model for the unimolecular gas reaction. The probability $P_j\ (t)$ when $j$ is the number of survival molecules at time $(t)$ is given by eq. (8).

$$P_j(t) = {}_{j_0}C_j\{\exp(-\lambda_1 t)\}^j\{1-\exp(-\lambda_1 t)\}^{j_0-j} \tag{8}$$

where $\lambda_1$ is the probability that one molecule will react at unit time and $j_0$ is the total number of molecules at time zero. Equation (8) is the same as the result arrived by Cohen,[14] who reasoned from the sampling process by the Monte Carlo simulation of reaction kinetics. From eq. (8), the mean value $j(t)$ for the number of survival molecules at time $(t)$ is given by eq. (9).

$$j(t) = j_0 \exp(-\lambda_1 t) \tag{9}$$

$\exp(-\lambda_1 t)$ of eq. (9) is nothing but survival ratio. From eq. (9), by rewriting $j(t)/j_0$ in the survival ratio $S$ and (1-$S$) in the degradation ratio $\alpha$, a rate equation is shown as eq. (10).

$$-\frac{dS}{dt} = \frac{d\alpha}{dt} = \lambda_1 S \tag{10}$$

From eq. (10), the degradation rate is determined by survival ratio. This applies when the stochastic model is for a unimolecular reaction where $\lambda_1$ is invariable with time. However, a more general case will be where $\lambda_1$ varies with time. In such a case, eq. (11) is given instead of eq. (8).

$$P_j(t) = {}_{j_0}C_j\left\{\exp\left(-\int_0^t \lambda(t)dt\right)\right\}^j\left\{1-\exp\left(-\int_0^t \lambda(t)dt\right)\right\}^{j_0-j} \tag{11}$$

the mean value $j(t)$ for the number of survival molecules at time $(t)$ is given by eq. (12).

$$j(t) = j_0 \exp\left(-\int_0^t \lambda(t)dt\right) \tag{12}$$

From eq. (12), the degradation rate equation is shown as eq. (13)

$$\frac{d\alpha}{dt} = \lambda(t)\exp\left(-\int_0^t \lambda(t)dt\right) \tag{13}$$

Such stochastic processes with the variable parameter $\lambda(t)$ can be applied to actual cases. The general equation for $\lambda(t)$ is expressed by eq. (14).

$$\lambda(t) = B_0 + B_1 t + B_2 t^2 + \cdots + B_r t^r \cdots \qquad t > 0 \tag{14}$$

As a function which satisfies the condition where degradation ratio $\alpha$ increases with time, and $\lambda(t)$ also increases with time, and which is convenient to handle, attention was directed to eq. (15) instead of eq. (14)

$$\lambda(t) \fallingdotseq B_r t^r \tag{15}$$

Equation (16) is obtained by substituting eq. (15) in eq. (13)

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13) *a)* A.F. Bartholomay, *Bull. Math. Biophys.*, **20**, 175 (1958); *b)* K. Ishida, *Bull. Chem. Soc. Japan*, **33**, 1030 (1960).

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$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = B_r t^r \exp\left\{-\frac{B_r}{(r+1)} t^{r+1}\right\} \qquad (16)$$

$$r > -1$$

Hence, eq. (17) is introduced by putting $(r+1)$ and $B_r/(r+1)$ as $m$ and $k$, respectively

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = mkt^{m-1} \exp(-kt^m) \qquad (17)$$

$$m > 0, \quad k > 0$$

Equation (1) is obtained by integrating eq. (17). Thus, eq. (17) is considered as a reaction rate equation introduced by indicating eq. (15) as a function of $\lambda(t)$. Moreover, eq. (17) is similar to Avrami equation[15] concerned with kinetics in the interface of a solid phase.

The rate equation, eq. (17) proposed here, is characterized by two parameters. Of the two parameters $m$ and $k$, magnitude of $m$ determines the type of many reaction rate equations. Hence, it is not necessary to select a rate equation by trial and error for prediction, and yet it could improve the accuracy of prediction by applying parameter $k$ within the temperature range where $m$ value is equal, as was the case for ascorbic acid solution, ascorbic acid–mannitol powder, and pyridoxal phosphate solution.

In general, it appears from an examination of stability studies in the literature that the selection of temperature levels for the accelerated storage test has been somewhat arbitrary. Therefore, application of temperature range where $m$ values is equal, is useful for considerations of the effect of high temperature on products which may cause changes not occurring at room temperature.

On the above basis, it can be concluded that a rate equation proposed in the present paper is useful in view of the two advantages; (1) it is applicable to a wide range of degradation types having a degradation ratio within a range of 1—30%, and (2) the accuracy of prediction can be improved by an application of parameter $k$ within the temperature range where $m$ is equal.

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