

Estimation of the Shelf Life of a Drug in Its Solid State. II.¹⁾
A Proposition for a New Kinetical Equation of Gas-Solid
Reactions for Pharmaceutical Solids

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A new kinetical equation for a gas-solid reaction which is convenient for use in predicting the degradation of a pharmaceutical solid is derived, and a procedure of analyzing accelerated storage data is proposed. The procedure is applied to the air oxidation degradation of ascorbic acid in a mannitol conglomerate. The result of the analysis was consistent with that obtained by Lacey's procedure. With the proposed procedure, operational difficulties met in Lacey's procedure were overcome. The temperature dependence of diffusivity is found to be 56 kcal/mole, with an activation energy for the chemical reaction of 26 kcal/mole. The rate constant for the chemical reaction at 25° is estimated to be $3.3 \times 10^{-6} \text{ hr}^{-1}$, a value which is consistent with the results of Tardif, which were obtained from a different point of view.

Introduction

In the previous paper, Lacey's theory³⁾ was applied to a stability study of ascorbic acid in the solid state. It was noted that theoretical requirement for obtaining decomposition rates at an early stage in the reaction was not always easy to fulfill because of experimental restrictions. If there were a rate equation for the relation between the residual solid and time, the estimation of the kinetic and diffusion parameters at room temperature would be much easier. However, the rate equation has not been given in the above theory,³⁾ as the basic differential equations have not been solved analytically except for the asymptotic values. Only numerical solutions are given for all ranges of time.

The present investigation is undertaken in an attempt to obtain a practical rate equation which relates an experimental plot of the degradation of a drug *versus* time to diffusion and reaction parameters, and to propose a simple procedure for the prediction of the shelf life of solid pharmaceuticals.

Theoretical

The model taken in this study is essentially the same as Lacey's. An equation which gives the amount of reaction as a function of time with two parameters, the diffusion constant, and the chemical rate constant, is difficult to obtain merely from Lacey's postulation. It becomes possible, however, by adding the following two assumption to those of Lacey's.

Assumption 1. The gas concentration in the diffusion layer in the solid decreases linearly with depth, and is zero beyond the diffusion front.

$$C_y = C_0(1 - (y/y_i)) \quad (y \leq y_i)$$

$$C_y = 0 \quad (y \geq y_i)$$

1) Part I of this report: S. Hirota, S. Osugi, T. Hayashi, S. Kaga, and Y. Takeya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1972 (1968).

2) Location: *Narihira, Sumidaku, Tokyo.*

3) D.T. Lacey, J.H. Bowen, and K.S. Basden, *Ind. Eng. Chem., Fundamentals*, **4**, 275 (1965).

where C_y is the gaseous reactant molarity in the solid at depth y from the solid surface, C_o that at the surface, and y_i the depth of the diffusion front, *i.e.*, the thickness of the diffusion layer.

Assumption 2. The rate of advance of the diffusion front is reciprocally proportional to its depth.

$$dy_i/dt = D'(C_o/y_i)$$

where D' is a proportionality constant.

From assumption 2,

$$y_i^2 = DC_o t \tag{11}$$

From assumption 1 and (11),

$$C_y = C_o(1 - (y/\sqrt{DC_o t})) \tag{12}$$

For the simple physical diffusion of a gas through a solid, Fick's 2nd law holds.

$$\partial C_y / \partial t = D \partial^2 C_y / \partial y^2 \tag{13}$$

The solution of this equation is⁴⁾

$$C_y = C_o(1 - \text{erf } y/2\sqrt{Dt}) \tag{14}$$

If y is small compared to \sqrt{Dt}

$$\text{erf } y/2\sqrt{Dt} = y/\sqrt{D\pi t} \tag{15}$$

(14) becomes,

$$C_y = C_o(1 - y/\sqrt{D\pi t}) \tag{16}$$

Comparing (12) with (16), it is seen that they are of the same nature. Since at an early stage of gas absorption chemical reaction has little influence on it, the following relation is anticipated.

$$DC_o \propto D \tag{17}$$

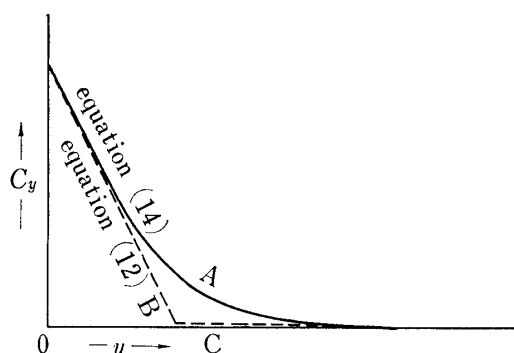


Fig. 1. Distribution of Gas Molecules in a Solid: Comparison of the Present Assumption (12), BC with Crank's Solution (14), A

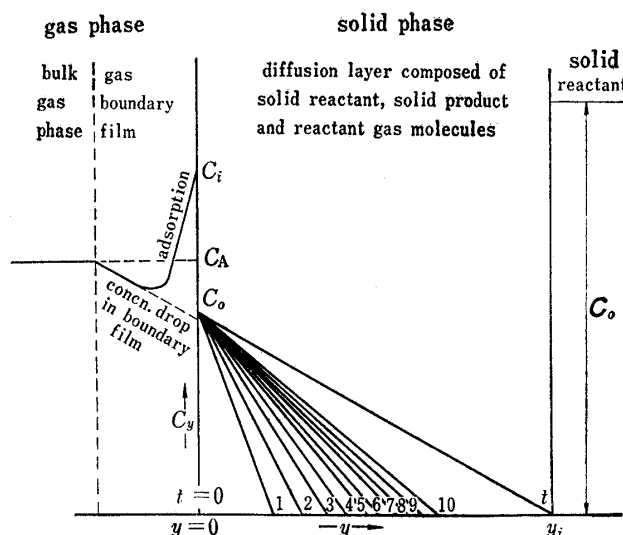


Fig. 2. Change of Concentration Profile during Absorption of a Gas into a Solid Accompanied by a Solid-Gas Reaction Governed both by Diffusion and Chemical Reaction at the Same Time

- C_A : molarity of gas reactant in bulk gas phase
- C_i : that in gas at the interface
- C_o : that in solid at the interface
- C_o : molarity of solid reactant at the beginning

4) J. Crank, "The mathematics of Diffusion," Clarendon Press, Oxford, 1956, p. 117.

Fig. 1 illustrates the comparison, and Fig. 2 shows the gas concentration profile and its change during the progress of the absorption according to the above model.

The thickness of the diffusion layer, y_i , increases proportionally to the square root of the time t , as in Fig. 2. The molarity of the reactant gas in the solid phase, which is C_o at the surface, becomes zero at depth y_i ; C_o will no doubt be related to the reactant gas molarity in the bulk gas phase outside the solid, but will not necessarily equal this value. From the above model, the rate of solid product formation for an equimolecular reaction is expressed by the following equation:

$$dx_y/dt = kC_yC_y \quad (18)$$

(k : reaction rate constant. C_y molarity of the reactant solid, at depth y)

$$C_y = C_o - x_y \quad (19)$$

(C_o initial molarity of solid)

Substituting (12) and (19) into (18)

$$dx_y/dt = k(C_o - x_y)C_o(1 - (y/\sqrt{DC_o t})) \quad (20)$$

From assumption 1 and (11)

$$C_y = 0 \quad \text{in the time range } t \leq y^2/DC_o$$

Hence,

$$x_y = 0 \quad \text{until } t = y^2/DC_o \quad (21)$$

with (21) as the initial condition, (20) is solved as,

$$x_y = C_o(1 - \exp(-kC_o z^2)) \quad (22)$$

where

$$z = \sqrt{t} - (y/\sqrt{DC_o})$$

If the solid is a plane disk with the flat surface area A large compared to its thickness Y , gas, diffusing into the solid from its periphery, can be neglected. The total amount of the reaction product X , is obtained by integrating (22) over the whole diffusion layer. As the diffusion proceeds from both sides of the disk,

$$\begin{aligned} X &= 2 \int_0^{\sqrt{DC_o t}} x_y A dy = 2AC_o \sqrt{DC_o} \int_0^{\sqrt{t}} (1 - \exp(-kC_o Z^2)) dZ \\ &= 2AC_o \sqrt{DC_o t} \left(\frac{kC_o t}{3} - \frac{(kC_o t)^2}{2! \times 5} + \frac{(kC_o t)^3}{3! \times 7} - \frac{(kC_o t)^4}{4! \times 9} + \dots \right) \end{aligned} \quad (23)$$

The average molarity of the reaction product is then,

$$x = \frac{X}{AY} = \frac{2C_o \sqrt{DC_o t}}{Y} \cdot \left(\frac{kC_o t}{3} - \frac{(kC_o t)^2}{2! \times 5} + \frac{(kC_o t)^3}{3! \times 7} - \frac{(kC_o t)^4}{4! \times 9} + \frac{(kC_o t)^5}{5! \times 11} - \dots \right) \quad (24)$$

The average residual ratio R , is

$$R = \frac{C_o - x}{C_o} = 1 - \frac{2\sqrt{DC_o t}}{Y} \left(\frac{kC_o t}{3} - \frac{(kC_o t)^2}{2! \times 5} + \frac{(kC_o t)^3}{3! \times 7} - \frac{(kC_o t)^4}{4! \times 9} + \frac{(kC_o t)^5}{5! \times 11} - \dots \right) \quad (25)$$

The n th term, in the series on the right hand side of (25), J_n , is

$$J_n = \frac{(-1)^{n+1} (kC_o t)^n}{n! (1+2n)} \quad (26)$$

for large n , using Stirling's approximation

$$n! = n^n e^{-n} \sqrt{2\pi n} \quad (27)$$

Then,

$$J_n = \frac{(-1)^{n+1}}{\sqrt{2n(1+2n)}} \left(\frac{ekC_0t}{n} \right)^n \tag{28}$$

$$J_n = \left(\frac{kC_0t}{3} - \frac{(kC_0t)^2}{10} + \frac{(kC_0t)^3}{42} - \frac{(kC_0t)^4}{216} + \frac{(kC_0t)^5}{1320} - \frac{(kC_0t)^6}{9350} + \frac{(kC_0t)^7}{75700} - \frac{(kC_0t)^8}{685000} + \frac{(kC_0t)^9}{6890000} - \frac{(kC_0t)^{10}}{76200000} + \dots \right) \tag{29}$$

For $kC_0t \geq 5$, a tiring calculation, taking more than ten terms of the series, is required. But, it can be avoided as follows: (25) is written as,

$$R = \frac{C_0 - x}{C_0} = 1 - \frac{2\sqrt{DC_0}}{Y} \int_0^{\sqrt{t}} (1 - \exp(-kC_0Z^2)) dz \tag{30}$$

$$\int_0^{\sqrt{t}} (1 - \exp(-kC_0z^2)) dz = \sqrt{t} \sum J_n \tag{30.0}$$

In Fig. 3.

$$A = \int_0^{\sqrt{t}} (1 - \exp(-kC_0z^2)) dz \tag{30.1}$$

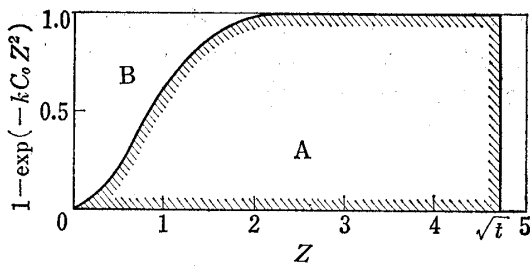


Fig. 3. $A = \int_0^{\sqrt{t}} 1 - \exp(-kC_0Z^2) dZ$

$$B = \int_0^{\sqrt{t}} \exp(-kC_0Z^2) dZ$$

$$B = \int_0^{\sqrt{t}} \exp(-kC_0z^2) dz = \frac{1}{\sqrt{kC_0}} \int_0^{\sqrt{kC_0t}} \exp(-x^2) dx \tag{30.2}$$

And

$$\int_0^{\sqrt{kC_0t}} \exp(-x^2) dx = \int_0^{\infty} \exp(-x^2) dx = \frac{\sqrt{\pi}}{2} \tag{30.3}$$

for a large value of kC_0t .

An approximation,

$$B = \frac{1}{\sqrt{kC_0}} \int_0^{\infty} \exp(-x^2) dx = \frac{\sqrt{\pi}}{2\sqrt{kC_0}} \tag{30.4}$$

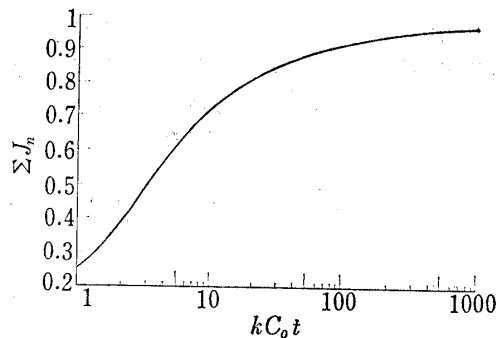
holds with an error of less than 0.1% for $kC_0t \geq 5$.

$$A + B = \sqrt{t} \tag{30.5}$$

$$A = \sqrt{t} - \frac{\sqrt{\pi}}{2\sqrt{kC_0}} \tag{30.6}$$

$$J_n = \frac{A}{\sqrt{t}} = 1 - \frac{\sqrt{\pi}}{2\sqrt{kC_0t}} \tag{30.7}$$

$\sum J_n$ is calculated by (29) for $kC_0t > 5$, and by (30.7) for $kC_0t < 5$, and Fig. 4 is obtained.



$\sum J_n$ versus kC_0t plot
Fig. 4.

When $\sqrt{DC_0 t}$ reaches $Y/2$, the diffusion layers of both sides of the disk meet. The postulated condition ceases to hold thereafter. The validity of (25) is confined to the time range

$$t \leq Y^2/4DC_0 \quad (31)$$

At $t_A = Y^2/4DC_0$, (25) becomes,

$$R = 1 - \sum J_n \quad (32)$$

In the time range $t > Y^2/4DC_0$, no further enlargement of the reaction zone takes place, and diffusion has a minor influence on the total reaction rate. The major rate controlling factor in this ranges is the chemical reaction. There will be little error if we consider that (32), with no diffusional factor, remains valid for this time range.

For very rapid reaction, kC_0 is large and $\sum J_n$ soon approaches unity, as is seen in Fig. 4., or (30.7). Equation (25) now becomes

$$R \doteq 1 - \frac{2\sqrt{DC_0 t}}{Y} \quad (33)$$

Equation (32) formally represents the chemical reaction controlled process, while (33) refers to the diffusion controlled process.

In the derivation of (25), there has been a tacit understanding that consumption of the reaction gas is always sufficiently supplied by diffusion that is, C_y does not become zero because of the reaction in the diffusion layer. The largest gas consumption takes place at the gas-solid interface. The gas consumption at the interface r (mole), per unit volume, is given by putting $y=0$ in (22), and differentiating with respect to t ,

$$r = \frac{1}{1000} \times \frac{dx_0}{dt} = \frac{kC_0 C_0}{1000} \exp(-kC_0 t) \quad (33.1)$$

The gas absorption at the interface q (mole), per unit area per unit time is

$$q = \frac{dm}{dt} = D \frac{C_0}{y_i} = \frac{DC_0}{\sqrt{DC_0 t}} \quad (33.2)$$

Anticipating (44.1), under the conditions of the present investigation,

$$q = \frac{\sqrt{DC_0} \times 10^2 \times C_0}{\sqrt{t}} \quad (33.3)$$

Comparing r and q ,

$$P = \frac{r}{q} = \frac{kC_0 \exp(-kC_0 t) \sqrt{t}}{\sqrt{DC_0} \times 10^5} < 1 \quad (33.4)$$

must be satisfied. The time limit t_B , for this requirement is

$$t_B = \frac{54DC_0 \times 10^{10}}{k^2 C_0^2} \quad (33.5)$$

The smaller of the two, t_A and t_B , indicates the validity limit of (25).

The diffusional and chemical parameters, DC_0 and kC_0 , for a gas-solid reaction, are given by solving the simultaneous equations,

$$R_1 = 1 - \frac{2\sqrt{DC_0 t_1}}{Y} \left(\frac{kC_0 t_1}{3} - \frac{(kC_0 t_1)^2}{2! \times 5} + \frac{(kC_0 t_1)^3}{3! \times 7} - \dots \right)$$

$$R_2 = 1 - \frac{2\sqrt{DC_0 t_2}}{Y} \left(\frac{kC_0 t_2}{3} - \frac{(kC_0 t_2)^2}{2! \times 5} + \frac{(kC_0 t_2)^3}{3! \times 7} - \dots \right)$$

where R_1 and R_2 are the experimental residual ratios of ascorbic acid at time t_1 and t_2 . With more than four terms of the series in parentheses in each simultaneous equation, strenuous calculations are required. However, (25) can be approximated by (35), with an error of less than 15% when it is shorter than t_c , which is defined by

$$t_c = 2/kC_o \quad (34)$$

t_c indicates the applicability limit of (35)

$$R = 1 - \frac{2\sqrt{DC_o t}}{Y} \left(\frac{kC_o t}{3} - \frac{(kC_o t)^2}{10} + \frac{(kC_o t)^3}{42} \right) \quad (35)$$

kC_o and DC_o are obtained at several elevated temperatures, from which those at room temperature are estimated using an Arrhenius equation for kC_o , and the Nernst-Einstein equation for DC_o . Introducing the estimated kC_o and DC_o values into (25), or (35), again, the rate equation (R as a function of t) at room temperature is obtained.

Analysis of Experimental Data

As an example of an application of (25), or (35), for the prediction of the shelf life of a pharmaceutical solid, heat acceleration data for an air oxidation of ascorbic acid in a mannitol conglomerate containing 10% ascorbic acid in a solid state is analysed by the proposed theory.

In order to simplify the situation, highly compressed, non-porous compacts with well defined surfaces are used. A clear fused mixture of 10% ascorbic acid and 90% mannitol is cooled to congealing, and then finely pulverized. 0.3–0.4 g of the material powder is compressed into a compact disk 20 mm in diameter, and 0.64–0.78 mm thick, by a 7 ton oil press, as described in a previous report¹⁾ (part I of this series).

Two experimental values (R_1, t_1) and (R_2, t_2) are picked arbitrarily from the R versus t curve at some elevated temperature, and are introduced into (35) to obtain a set of simultaneous equations.

On solving them to find kC_o and DC_o , the following trial and error steps are taken:

1. Three sets of kC_o 's and DC_o 's are calculated from any three simultaneous equation, and their averages taken.
2. The averages are introduced into the test equations (31), (33.5) and (34), to examine whether (35) is applicable or not.

The results of the examinations are listed in Table I. It is seen that all data at 135°, and the datum for 10 hr at 128° do not satisfy the requirement $t \leq t_A$, while all data at 120° and below are valid.

TABLE I. Examination of Validity of the Temporary Value of kC_o and DC_o

Temperature T (°C)	Temporary value of DC_o	$t_A = \frac{Y^2}{4DC_o}$	Temporary value of kC_o	t_B	$t_C = \frac{2}{kC_o}$
135	8.2×10^{-3}	0.15 hr	4.72×10^{-1}	4×10^6 hr	4.2 hr
128	2.1×10^{-4}	5.8 hr	1.8×10^{-1}	7×10^5 hr	11 hr
120	0.47×10^{-4}	26 hr	1.4×10^{-1}	2.6×10^5 hr	14 hr

3. Averages are taken again without the false data that do not satisfy the test equations.

The kC_o and DC_o , determined according to the above steps, are listed in Table II.

TABLE II. Confirmed values of kC_o and DC_o

Temperature T ($^{\circ}\text{C}$)	DC_o ($\text{cm}^2 \text{hr}^{-1}$)	kC_o (hr^{-1})
128	1.9×10^{-4}	1.8×10^{-1}
120	4.7×10^{-5}	1.4×10^{-1}
95	1.7×10^{-6}	1.9×10^{-2}
80	2.3×10^{-8}	2.3×10^{-3}

The log of DC_o plotted against $1/T$, T being the absolute temperature, gives a straight line.

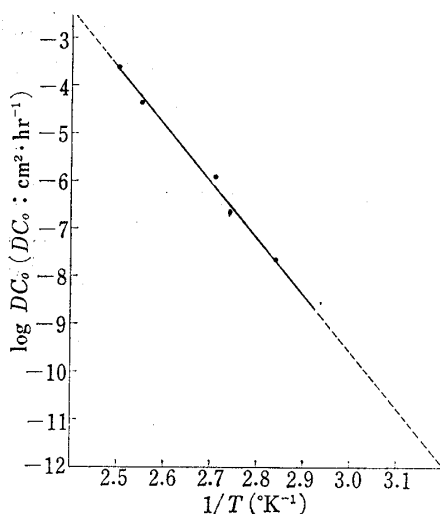


Fig. 5. Temperature Dependence of Diffusivity of Oxygen through Ascorbic Acid-Mannitol Conglomerate

$$\log DC_o = 25.51 - 11670/T$$

$$\Delta E = 54 \text{ kcal/mole}$$

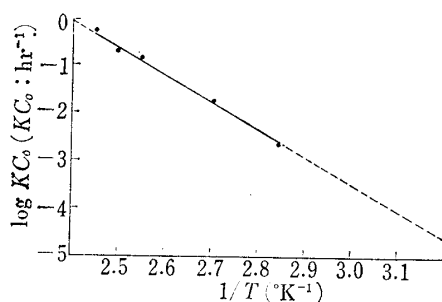


Fig. 6. Temperature Dependence of Rate Constant of Gas-Solid Oxidation of Ascorbic Acid

$$\log kC_o = 13.34 - 5600/T$$

$$\Delta E = 26 \text{ kcal/mole}$$

The Nernst-Einstein equation is applied as,

$$\log DC_o = 25.51 - 11670/T \quad (38)$$

$$DC_o: \text{cm}^2/\text{g} \quad T: ^{\circ}\text{K}$$

The temperature dependence of the diffusivity expressed as an activation energy is 54 kcal/mole.

As for the chemical reaction rate kC_o , the Arrhenius equation is applied to Fig. 6 as,

$$\log kC_o = 13.34 - 5600/T \quad (39)$$

$$kC_o: \text{hr}^{-1} \quad T: ^{\circ}\text{K}$$

The activation energy of the chemical reaction is 26 kcal/mole.

DC_o and kC_o at 25° is estimated, using (38) and (39), to be $2.6 \times 10^{-14} \text{ cm}^2/\text{hr}$ and $3.3 \times 10^{-6} \text{ hr}^{-1}$, respectively. Introducing these values into (35), a rate equation at 25° for the air oxidation of ascorbic acid in a mannitol conglomerate disk, 1 mm thick, is given as,

$$R = 1 - \frac{2\sqrt{2.9 \times 10^{-14}t}}{0.1} \left(\frac{3.3 \times 10^{-6}t}{3} - \frac{(3.3 \times 10^{-6}t)^2}{10} + \frac{(3.3 \times 10^{-6}t)^3}{42} \right)$$

$$= 1 - 3.4 \times 10^{-8} \sqrt{t} (1.1 \times 10^{-6}t - 1.1 \times 10^{-12}t^2 + 8.6 \times 10^{-19}t^3) \quad (40)$$

In this case,

$$t_A = 8.6 \times 10^{10} \text{ hr (about } 10^7 \text{ years)}$$

$$t_B = 2.8 \times 10^5 \text{ hr (about 30 years)}$$

$$t_C = 6 \times 10^5 \text{ hr (about 70 years)}$$

The time limit of the validity of (40) is determined by the shortest time t_B , about 30 years. The decomposition ratio after 10 years is estimated to be 0.00875%.

Discussion

1. Chemical Kinetics

The same data are analysed by a modification of Lacey's procedure,³⁾ and by the present proposed procedure. By comparing (39) with (12) from part I of this report¹⁾ it is understood that both results for kC_o are in good agreement, and kC_o at 25° is estimated to be $3.3 \times 10^{-6} \text{ hr}^{-1}$.

The thermodegradation rate of ascorbic acid in the solid state was determined by Tardif.⁵⁾ He used a coated tablet with a 400 mg core whose composition is,

Sucrose or mannitol	200 mg
Ascorbic acid	100 mg
Vitamin A	7500 I.U.
Vitamin D	1500 I.U.
Thiamine	1.5 mg
Coatings	250 mg

The change in the residual amount of each ingredient during 30–400 days at 50, 60 and 70° was measured. Arrhenius plots of the above determined k (pseudo-first order reaction rate constant) were extrapolated to 21°. His estimation is supported by actual storage at room temperature for 400 days.

TABLE III. Tardif's Estimation of k of Ascorbic Acid Degradation at Room Temperature (21°)

Formulation	Excipient	Moisture (%)	k at 21°	
			$\times 10^{-4} \text{ 1/day}$	$\times 10^{-6} \text{ 1/hr}$
A	sucrose	3–4	1.3	5.4
B	mannitol	3–4	1.1	4.6
C	sucrose	1>	0.4	1.7

The moisture condition of formulation C is the closest to ours among the three. The influence of excipients is known to be small from a comparison of formulation A with B, so that with mannitol instead of sucrose for formulation C, k at 21° will not differ much from $1.7 \times 10^{-6} \text{ hr}^{-1}$. Tardif's k , having the dimension of a first order rate constant, corresponds to our kC_o , k being a second order rate constant. Our estimation of kC_o at 25° is $3.3 \times 10^{-6} \text{ hr}^{-1}$. Such good agreement can not naturally be expected because k includes the effect of diffusion, while k does not. The reason for the good agreement is considered to be the following: The unit solid in Tardif's sample is not the tablet mass, but the individual particles composing the tablet, because his tablet is an ordinary one with large pores through which oxygen is supplied very rapidly. The thickness of the unit solid particle is very small, say 1μ . DC_o at 70° is estimated to be $3 \times 10^{-9} \text{ cm}^2/\text{hr}$. Then,

5) R. Tardif, *J. Pharm. Sci.*, **54**, 281 (1965).

$$t_A = Y^2/4DC_0 = (10^{-4})^2/4 \times 3 \times 10^{-9} \approx 1 \text{ hr}$$

may be regarded negligible compared with his total storage period of 30—40 days. The reaction may be expressed by a rate equation without a diffusion parameter, such as equation (32).

Now, it is understood that we have been discussing the problem in a system where the diffusional effect may be neglected and k is equal to kC_0 . The agreement of our result with Tardif's indicates that there is not much difference between the effect of mannitol as a solid solvent, and as a mere excipient on the oxidation of ascorbic acid.

According to the proposed rate equation (25)

$$\Sigma J_n \approx kC_0 t/3 \quad (54)$$

at the beginning of the reaction, the reaction ratio, $1-R$, becomes

$$1-R = 2kC_0 \sqrt{DC_0} t^{3/2}/3Y \quad (55)$$

Equation (55) indicates that the reaction rate increases with time. Let this type of reaction be called an "accelerating reaction" against a "decelerating reaction," an example of the latter being an ordinary pseudo first order reaction. The enlargement of the reaction zone (diffusional layer) is the reason for the acceleration. The t_A indicates roughly the end of the accelerating reaction period.

$$t_A = Y^2/4DC_0 \quad (57)$$

As the reaction proceeds, after t_A , the reaction ratio may be expressed by (32), which describes a decelerating reaction. An accelerating reaction followed by a decelerating reaction makes a sigmoid reaction curve, as is seen in Fig. 5 and 6 in Part I of this report.¹⁾ When t_A is short as compared with the observation time, an accelerating reaction can not be observed, and the reaction curve appears as if the reaction has been decelerating from the beginning. This may be the reason why Tardif looked upon the degradation of ascorbic acid in the tablet as a pseudofirst order reaction. That there is an accelerating reaction followed by a decelerating reaction in a gas-solid reaction where both diffusion and chemical change are controlling the reaction can also be deduced from Lacey's theory. As $M_t/t^{1/2}$ is proportional to ϕ_{av} , the $M_t/t^{1/2}$ versus $t^{1/2}$ curve becomes sigmoid (Fig. 7), just as the ϕ_{av} versus $t^{1/2}$ curve is sigmoid.⁶⁾ Fig. 7 is converted to an M_t versus t curve (Fig. 8). The concave (upward) portion means an accelerating reaction, and the convex portion a decelerating reaction.

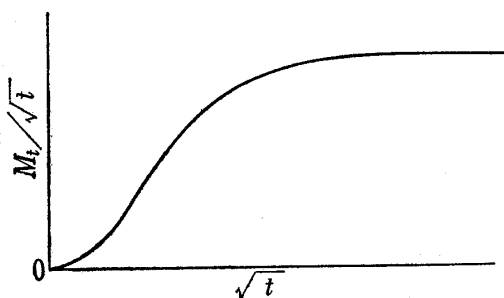


Fig. 7. M_t/\sqrt{t} versus \sqrt{t} plot

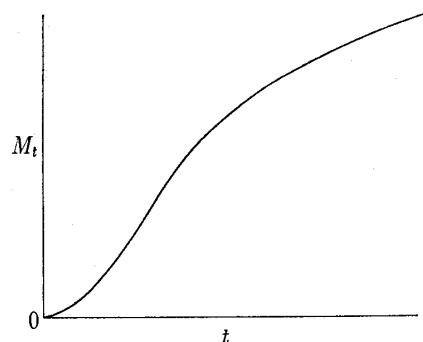


Fig. 8. M_t versus t plot

6) Fig. 3 in Lacey's paper³⁾ or Fig. 1 in Part I of this report.¹⁾

Tardif assumes that the degradation of solid ascorbic acid is a pseudo first order reaction at room temperature, basing it on his observations at high temperature. If t_A remains negligible even at room temperature, his assumption is reasonable. But this is not always the case. It is a considerable risk to anticipate a monotonous decelerating reaction at room temperature merely from elevated temperature storage data, because even when t_A is not observable at high temperature, it is very likely that D decreases rapidly as the temperature is lowered, and the shelf period ends before t_A . In that case, degradation must be regarded as an accelerating reaction, and a prediction based upon a decelerating reaction will lead to an erroneous result.

2. Diffusion

D is considered to be related to Lacey's D . The approximately parallel relationship between the plots in Fig. 5 in this report and Fig. 9 in the previous report (part I of this report) indicates the following experimental equation to hold in the temperature range of this study.

$$DC_o \doteq 10^{-2} D \quad (44.1)$$

In general,

$$D = \beta D \quad (44.2)$$

where β is a proportionality constant. β is given readily from a comparison of (12) with (16), for physical diffusion alone.

$$\beta = \pi/C_o = \pi/8 \times 10^{-3} = 400$$

By an equimolecular reaction with $k = \infty$, amount of reaction, R_n , in a thin-layer with unit area and thickness of dy at depth y (the layer being the n th from the surface), and amount of gas reactant supplied, Q_n , to this layer are

$$R_n = C_o dy$$

$$Q_n = DC_o/y$$

Time to end the reaction in this layer, $t_n (=dt)$, is

$$t_n = R_n/Q_n = (C_o y / DC_o) dy = dt$$

Then, the total reaction time, t , is

$$t = \sum t_n = \int_0^{y_i} dt = \int_0^{y_i} (C_o y / DC_o) dy = C_o y_i^2 / 2DC_o$$

and

$$y_i^2 = 2DC_o t / C_o \quad (44.3)$$

Comparing (44.3) with (11)

$$D = 2D/C_o$$

$$\beta = 2/C_o = 2/0.567 = 3.5$$

By an equimolecular reaction with a finite k ,

$$3.5 < \beta < 400$$

is expected. In this study, however, (44.1) indicates

$$\beta = 10^{-2}/C_o = 1.25$$

Although it is difficult to explain the discrepancy, the following seems to compose the cause:

1. M_t , in the previous paper, is calculated assuming surface of the disc as smooth without any pores.

2. Calculations are made basing upon a rough approximation that C_o , the reactant gas molarity just "below" the surface, is equal to that in the bulk gas phase.

It should be admitted that absolute value of D includes considerable error. But, since it is the ratio of D at high and room temperature that is required, it is expected that errors in each D would tend to cancel, and the errors have very little influence on an estimation of a shelf life.

The temperature dependence of the diffusivity, as an activation energy, is 54 kcal/mole from Fig. 5, while in the previous report,¹⁾ it is 48 kcal/mole. The difference between them is not important when the fact is considered, that both of them are very large compared with the activation energy of the oxidation reaction of ascorbic acid, 26 kcal/mole. The air oxidation of ascorbic acid is controlled by the chemical reaction at high temperature because of the large diffusivity of oxygen through the solid. But, as the temperature is lowered, the diffusivity decreases more rapidly than the chemical reaction rate, and the diffusion become the more important factor for the over all reaction rate.

Further studies, elsewhere, would be necessary on the unexpectedly large temperature dependence of diffusion.

Conclusion

The following rate equation is obtained for a gas-solid reaction where both diffusion and chemical reaction are controlling the overall reaction rate:

$$R = 1 - \frac{2\sqrt{DC_o t}}{Y} \sum_{n=1}^{\infty} \frac{(-1)^{n+1} (kC_o t)^n}{n!(1+2n)}$$

where C_o ; molarity of gas reactants in the solid at the interface (mole/liter)

D ; diffusivity (cm² liter/mole hr)

k ; rate constant of the chemical reaction (liter/mole hr)

R ; residual ratio of the solid

t ; time (hr), applicability of which is limited by t_A and t_B

$$t_A = Y^2/4DC_o$$

$$t_B = 54DC_o \times 10^{10}/k^2 C_o^2 \quad (C_o; \text{initial molarity of solid})$$

Y ; thickness of the solid disc (cm)

The following approximation to the above equation may be taken when

$$t \leq t_0 = 2/kC_o$$

$$R = 1 - \frac{2\sqrt{DC_o}}{Y} \left(\frac{kC_o t}{3} - \frac{(kC_o t)^2}{10} + \frac{(kC_o t)^3}{42} \right)$$

The data for heat acceleration storage are introduced into the equation to calculate DC_o and kC_o . The logarithms of DC_o and kC_o are plotted against $1/T$, and extrapolated toward room temperature. By introducing the estimated values of DC_o and kC_o into the above equation, the shelf life of the solid is obtained. The rate equation above is found to be consistent with Lacey's theory, and the proposed procedure for predicting the shelf life is more convenient for practical application than that of Lacey, for initial data which are not easy to obtain because of experimental restrictions, are not always necessary, while they are indispensable to Lacey's procedure.

The proposed procedure is applied to an air oxidative degradation of ascorbic acid in a mannitol conglomerate containing 10% ascorbic acid. The residual ratio at 25°, after time t , is expressed by the following equation:

$$R = 1 - 3.4 \times 10^{-6} \sqrt{t} (1.1 \times 10^{-6} - 1.1 \times 10^{-12} t^2 + 8.6 \times 10^{-16} t^3 - \dots)$$

The time limit of the applicability of the equation is about 30 years. The decomposition ratio of ascorbic acid at 25° after 10 years is estimated to be 0.00875%. The solid phase oxidation rate constant of ascorbic acid at 25° is estimated to be 3.3×10^{-6} (1/hr), which is consistent with Tardif's result, 1.7×10^{-6} (1/hr) at 21°. In this case the temperature dependence of diffusivity is larger than that of the chemical reaction rate constant, and the reaction is obviously controlled by the chemical reaction at high temperature. However, diffusion has a considerable effect on the overall reaction rate at room temperature.

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