

[Chem. Pharm. Bull.]
28(4)1107-1111(1980)

**Stability of Packaged Solid Dosage Forms. III.¹⁾ Kinetic Studies by
Differential Analysis on the Deterioration of Sugar-coated
Tablets under the Influence of Moisture and Heat²⁾**

KIYOSHI NAKABAYASHI, TSUGIO SHIMAMOTO, and HIROYUKI MIMA

*Pharmaceutical Research Laboratories, Central Research Division,
Takeda Chemical Industries, Ltd.³⁾*

(Received September 10, 1979)

The kinetics of the color change (ΔE) of sugar-coated tablets containing ascorbic acid in the core was studied by means of a differentiation procedure. The time course of ΔE for the cores under accelerated deterioration conditions was fitted to a curve, and the curve was differentiated with respect to time. The apparent rate constant for the color change was estimated from the differential coefficient on the assumption of an appropriate reaction order. The other kinetic parameters were obtained on the basis of the formulae described by Carstensen *et al.* The values of ΔE and moisture content for the tablets were examined in moisture-semipermeable packages kept in a storehouse for two years, and compared with the values predicted by an iterative calculation procedure using a mathematical model based on the moisture permeabilities and the kinetic parameters obtained here. The predicted values of ΔE in this study coincided well with the observed data, and it was found that there was a reasonable agreement between the shelf lives predicted in this study and those predicted in the previous paper. Thus, it might be concluded that the differential analysis procedure was useful for kinetic studies of the deterioration of solid dosage forms under the influence of the moisture content and ambient temperature.

Keywords—shelf-life prediction; iterative calculation; kinetic study; differential analysis; sugar-coated tablet; color change; packaging material; moisture permeability; temperature; relative humidity

In a previous paper,¹⁾ it was reported that the color change of the ascorbic-acid core in a sugar-coated tablet was dependent on its moisture content and the ambient temperature, and that the color change of the tablet in moisture-semipermeable packages could be predicted by an iterative calculation procedure using a mathematical model based on the kinetics of the color change and the moisture permeabilities of the packaging materials. The experimental method employed in the previous paper¹⁾ was similar to a two-way layout, in which tablets with several levels of moisture content were kept under various temperature conditions, and the kinetics was analyzed on the basis of the empirical formulae described by Carstensen *et al.*⁴⁾

However, in such experiments, it is often difficult to prehumidify solid dosage forms to desired levels of moisture content, to prevent the dosage form from deteriorating during humidification, and to keep the moisture level of the dosage forms constant during the period of kinetic studies.

In the present paper, the kinetics was studied by differentiation of the data obtained from the dosage forms in moisture-semipermeable packages under various conditions of accelerated deterioration. This technique made prehumidifying of the solid dosage forms unnecessary. The color change of the cores of the sugar-coated tablets was examined as

- 1) Part II: K. Nakabayashi, T. Shimamoto, and H. Mima, *Chem. Pharm. Bull.*, **28**, 1099 (1980).
- 2) Presented in part at a Symposium on the Stabilization and Evaluation Methodology of Pharmaceutical Preparations, held by the Pharmaceutical Society of Japan, Tokyo, October, 1975.
- 3) Location: 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan.
- 4) J.T. Carstensen, E.S. Aron, D.C. Spera, and J.T. Vance, *J. Pharm. Sci.*, **55**, 561 (1966).

described in the previous paper.¹⁾ The values of the color change predicted from the kinetic parameters estimated by means of differential analysis in this paper were compared with the values predicted from the experiments reported previously.¹⁾

Theoretical

Kinetic Studies by Differentiation

When a solid dosage form which is susceptible to deterioration under the influence of its moisture content and the ambient temperature is kept at high temperature under very humid conditions, a characteristic of the dosage form, C , changes with time. In this case, the moisture content, m , and the value of C can be adequately approximated by a polynomial of time, t :

$$m = a_0 + b_0 \cdot t + c_0 \cdot t^2 + d_0 \cdot t^3 + \dots \quad (1)$$

$$C = a_1 + b_1 \cdot t + c_1 \cdot t^2 + d_1 \cdot t^3 + \dots \quad (2)$$

where a_0 , a_1 , b_0 , b_1 , and the like are constants. These relations are shown schematically in Fig. 1.

When the change in the value of C follows an n -th order process, the apparent rate constant, k' , can be estimated by differentiating the value of C with time:

$$\begin{aligned} k' &= (dC/dt) \cdot (1/C^n) \\ &= b_1 + 2c_1 \cdot t + 3d_1 \cdot t^2 + \dots \end{aligned} \quad (3)$$

According to Carstensen *et al.*⁴⁾, the apparent rate constant at the time t_j , k'_j , is

determined by the moisture content at t_j , m_j , and the ambient absolute temperature, T , as follows:

$$k'_j = k \cdot m_j^\alpha \text{ or } \log k'_j = \log k + \alpha \cdot \log m_j \quad (4)$$

$$k = A \cdot \exp(-B/T) \quad (5)$$

where the subscript j denotes a point on the time course, α the order of the interaction between C and m , and k the rate constant at T , while A and B are constants.

Therefore, the kinetics can be studied by differentiation in the following manner:

- 1) store a solid dosage form with or without packaging at several temperatures under very humid conditions, and determine the values of C and m periodically,
- 2) fit the curve of Eq. 2 to C by the least-squares method at each temperature-humidity combination, and fit the curve of Eq. 1 to the increase in the value of m in the same manner,
- 3) differentiate the curve for C at the time t_j to estimate the value of $(dC/dt)_{t=t_j}$, and calculate the value of m at the time t_j , m_j , under each temperature-humidity combination,
- 4) calculate the value of k'_j from the value of $(dC/dt)_{t=t_j}$ at each temperature, assuming several kinds of reaction order,
- 5) choose the most suitable reaction order to obtain a linear relationship between $\log k$ and $\log m$ at each temperature, substituting k'_j and m_j into Eq. 4, and
- 6) estimate $\log k$ and α at each temperature by the method of least square from Eq. 4.

The differential analysis described above makes it unnecessary to prehumidify the solid dosage form for kinetic studies.

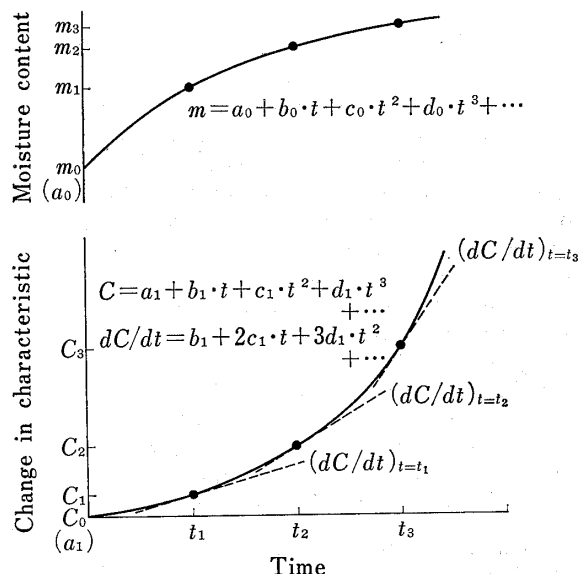


Fig. 1. Schematic Diagram of Curve Fitting and Differentiation on a Characteristic of a Solid Dosage Form Liable to Moisture Damage

Prediction of Deterioration

Deterioration of packaged solid dosage forms can be predicted by an iterative calculation procedure using mathematical model based on the moisture permeabilities of the packaging materials and the kinetic parameters, as described in detail previously.¹⁾

Experimental

Materials and Methods—The materials and methods used in this study were described in full in the previous paper.¹⁾ Characteristics of the three kinds of packages studied are summarized in Table I.

TABLE I. Characteristics of the Packages

No.	Package	Packaging materials	$S^a)$ (cm^2)	$L^a)$ (mm)	$N^b)$
1	Strip pack (SP)	LDPE ^{c)} -laminated cellophane	42.0	0.060	3
2	Press-through pack 1 (PTP-1)	Rigid PVC ^{d)} /aluminium foil ^{e)}	2.0	0.060	1
3	Press-through pack 2 (PTP-2)	PVDC ^{f)} -coated and LDPE ^{c)} -laminated rigid PVC ^{d)} /aluminium foil ^{e)}	2.0	0.085	1

a) Average area (S) and thickness (L) of packs.

b) Number of tablets in a pack.

c) Low density polyethylene.

d) Polyvinyl chloride.

e) Hard type, thickness 0.02 mm.

f) Polyvinylidene chloride.

Determination of the Apparent Rate Constant of Color Change—The sugar-coated tablets were packed in the three kinds of packages listed in Table I, and the samples were kept under 83% relative humidity (RH) at 25°, 90% RH at 40°, and 80% RH at 50° using the humidity cabinets described previously.¹⁾ The values of moisture content, m , and the color change, ΔE , for the cores of the tablets were determined periodically. The values of apparent rate constant, k' , were estimated in the manner described under "Theoretical" in this paper, by substituting the value of ΔE for C in Eq. 2 and Eq. 3.

Results and Discussion

Kinetic Studies on Color Change by Means of Differential Analysis

The time courses of values of ΔE and m for the ascorbic-acid cores of the tablets under various temperature and humidity conditions are shown in Fig. 2. From these observational data, the values of m under each storage condition could be estimated as a linear equation with respect to time by the least-squares method, while the values of ΔE were obtained as a quadratic function of time in the same manner. These estimated values are shown as solid lines in Fig. 2. However, the ΔE data for the cores in package No. 1 under 90% RH at 40°, and 80% RH at 50° had to be omitted from the curve fitting, because these data increased rapidly than could be accounted for.

On the assumption that the color change followed zero-order kinetics, the value of k' was estimated at each time when the value of ΔE and m were actually determined. Figure 3 shows the relationship obtained between $\log k'$ and $\log m$; good straight lines were obtained at various temperatures. Thus, it was found that the color change followed zero-order kinetics as described previously.¹⁾ From the plots in Fig. 3, the values of k and α were estimated at each temperature by the method of least squares, and these values are summarized in Table II. The values of α was considered to be about three at all the temperatures studied, being slightly different from that in the previous paper ($\alpha=4$).¹⁾

Figure 4 illustrates the relationship between $\log k$ and $(1/T)$ obtained from the data in Table II. The plots in Fig. 4 show good linearity, as indicated by a solid line, which was estimated by the least-squares method. The relation estimated in the previous paper¹⁾

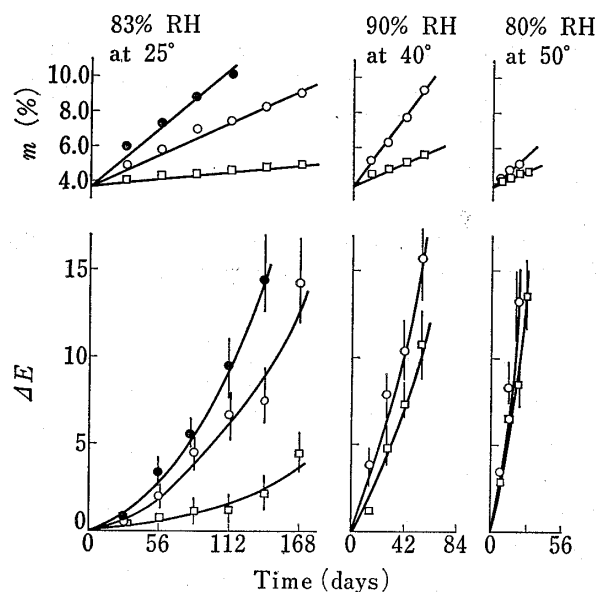


Fig. 2. Increase in Moisture Content and Color Change of the Ascorbic-acid Core in Sugar-coated Tablets in 3 Types of Packages under Accelerated Deterioration Conditions

Actual data: ○, press-through pack 1; □, press-through pack 2; ●, strip pack.
Estimated values by the least-squares method: —.

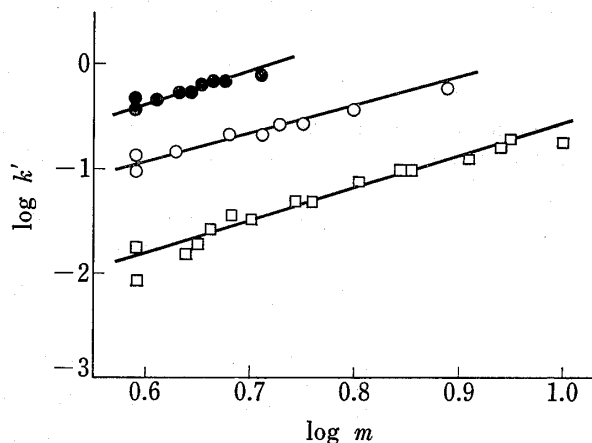


Fig. 3. Plot of the Zero-order Apparent Rate Constant of the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets vs. the Moisture Content of the Core at Various Temperatures

□, 25°; ○, 40°; ●, 50°.

TABLE II. Rate Constant and α -Value for the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets at Various Temperatures

Temperature (°C)	k^a	α
25	2.91×10^{-4}	3.02
40	1.72×10^{-3}	2.83
50	5.10×10^{-3}	3.17

^a) Day⁻¹.

is shown as a dashed line in Fig. 4. Figure 4 shows that there is a little difference between the two lines. The slight discrepancy of α and $\log k$ between the present experiments and the previous ones may be due to the difference in the experimental method, and also due to the fact that Eq. 4 and Eq. 5 are not theoretical, but empirical formulae. Although certain differences were observed in the values of k and α between the two experiments, they proved to result in only a slight difference in the predicted value of k' in the ranges of moisture content and temperature during the storage in the storehouse. Table III shows the ratio of k' predicted in the present paper to k' in the previous paper.¹⁾

Storage in Storehouse

As the sugar-coated tablets in the packages shown in Table I had already been examined, the actual data for ΔE and m given in the previous paper¹⁾ were employed. The prediction of these values was carried out in the manner described previously¹⁾ using the kinetic parameters obtained in this study. The actual data and the predicted values are shown as symbols

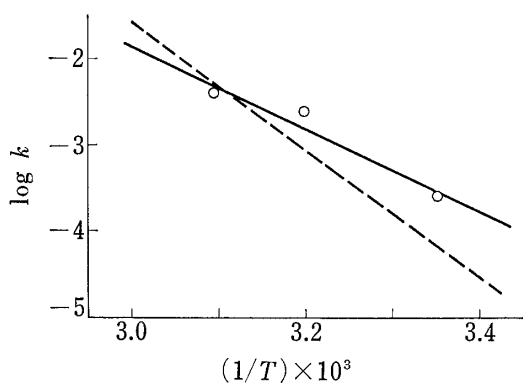


Fig. 4. Plot of the Logarithm of the Rate Constant of the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets vs. the Reciprocal of Absolute Temperature

—○—: differentiation;
 - - - - : two-way layout (K. Nakabayashi, T. Shimamoto, and H. Mima, *Chem. Pharm. Bull.*, **28**, 1099 (1980)).

TABLE III. Ratio of the Apparent Rate Constant of the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets Obtained by Differentiation Procedure to That Obtained by the Two-way Layout^{a)}

Temperature (°C)	Moisture content ⁺ (%)				
	4.0	4.5	5.0	5.5	6.0
5	3.5	3.1	2.8	2.6	2.4
10	2.5	2.2	2.0	1.8	1.7
15	1.8	1.6	1.5	1.3	1.2
20	1.3	1.2	1.1	1.0	0.9
25	1.0	0.9	0.8	0.7	0.7
30	0.7	0.6	0.6	0.5	0.5

a) K. Nakabayashi, T. Shimamoto, and H. Mima, *Chem. Pharm. Bull.*, **28**, 1099 (1980).

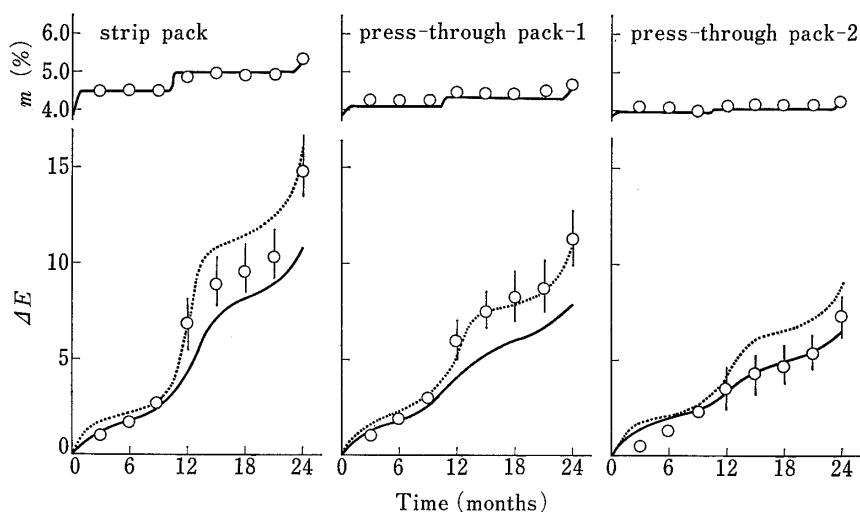


Fig. 5. Comparison of Actual Data with Predicted Values of Moisture Increase and Color Change of the Ascorbic-acid Core in Sugar-coated Tablets in 3 Types of Packages Kept in a Storehouse

○, actual data; —, values predicted by differentiation ($\Delta t=30$ days); ·····, values predicted by two-way layout (K. Nakabayashi, T. Shimamoto, and H. Mima, *Chem. Pharm. Bull.*, **28**, 1099 (1980)).

and solid lines, respectively, in Fig. 5, in which the values predicted by use of kinetic parameters in the previous paper¹⁾ are also shown as dotted lines. It was found that there was a reasonable agreement between the actual data and the predicted values of ΔE in this study, taking into account that the actual ΔE data had a coefficient of about 10%, and that the predicted values of ΔE were affected by errors in the estimated parameters, as described previously.¹⁾ The predicted shelf lives in this paper were essentially consistent with those in the previous paper.¹⁾ Therefore, it can be concluded that the kinetic studies by means of differential analysis, as described here, were as useful for the prediction of shelf life as kinetic studies by means of experiments such as the two-way layout in the previous paper.¹⁾

Acknowledgement The authors thank Mr. Takuo Tsuchida and Miss Masae Inai for their assistance in the experimental work.