Chem. Pharm. Bull.
28(4)1099—1106(1980)

Stability of Packaged Solid Dosage Forms. II.[1] Shelf-life Prediction for Packaged Sugar-coated Tablets Liable to Moisture and Heat Damage[2]

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(Received September 10, 1979)

Shelf-life prediction for solid dosage forms that are affected by the moisture content and ambient temperature was investigated in moisture-semipermeable packages. In this study, the color change of a sugar-coated tablet containing ascorbic acid in the core was examined. The kinetics of the color change was studied on the basis of the empirical formulae described by Carstensen *et al.* A mathematical model, based on the kinetics of the color change and the moisture permeabilities of the packages, was derived in order to predict the shelf life of the tablets in strip pack or press-through pack under various atmospheric conditions. The mathematical model was used with an iterative calculation procedure with a time interval of several days, taking into account the fluctuations of temperature and relative humidity during storage. Reasonable agreement was found between the actual data and the predicted values. The iteration procedure using the mathematical model derived here was found to be useful for predicting the shelf life of solid dosage forms in moisture-semipermeable packages under various conditions of humidity and temperature.

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

In a previous paper,[1] it was reported that the change of hardness of tablets composed of lactose and cornstarch was due to the variation of the moisture content, and that the hardness of the tablets in moisture-semipermeable packages, including overwrapped packaging systems, could be predicted by an iterative calculation procedure through a mathematical model based on the physico-chemical properties of the tablets and the moisture permeabilities of the packaging materials. Moreover, it was demonstrated that the change of tablet hardness was governed solely by the moisture content. However, solid dosage forms such as tablets and capsules more often deteriorate as a result of two factors, the moisture content and the ambient temperature, rather than the moisture content alone. Several workers[4] have presented methods of shelf-life prediction for solid dosage forms in moisture-semipermeable packages. They, however, paid little attention to the fluctuations of ambient temperature and relative humidity during storage, and the predictions were consequently unreliable in cases where the temperature and relative humidity varied over a wide range.

The purpose of this paper is to predict the shelf life of a packaged solid dosage form liable to damage by both the moisture content and ambient temperature by means of the iteration procedure described in the previous paper.[1] This procedure takes into account

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1) Part I: K. Nakabayashi, T. Shimamoto, and H. Mima, *Chem. Pharm. Bull.*, **28**, 1090 (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) *a*) N. Okusa, M. Fukui, and T. Nose, *Kosei Kagaku Kenkyu Hokoku of 1972*, "Studies on Stabilities of Pharmaceuticals," p. 19; *b*) T. Muraoka and A. Kanayama, *Yakuzaigaku*, **29**, 189 (1969); *c*) S. Mizrahi, T.P. Labuza, and M. Karel, *J. Food Sci.*, **35**, 797 (1970).

the fluctuations of temperature and relative humidity during prolonged storage. In this study, a sugar-coated tablet with a core containing ascorbic acid, the color of which is affected by both the moisture content and ambient temperature, was investigated in moisture-semipermeable packages. The kinetics of the color change was studied on the basis of the empirical formulae describrd by Carstensen *et al.*[5] It was found that the deterioration of the tablets could be predicted by means of the authors' iteration procedure through a mathematical model based on the kinetics of the color change and the moisture permeabilites of the packaging materials.

Theoretical

Kinetics of Deterioration

When an active ingredient in a solid dosage form is degraded by its moisture content and ambient temperature, the rate of the reaction is proportional to the n-th power of the drug concenration ,C, and to the α-th power of the moisture content, m:[5]

$$-dC/dt = k\cdot C^n\cdot m^\alpha = k'\cdot C^n \qquad (1)$$

$$k' = k\cdot m^\alpha \text{ or } \log k' = \log k + \alpha\cdot\log m \qquad (2)$$

where t denotes time, k the rate constant, k' the apparent rate constant, n the apparent reaction order, and α the interaction order between the moisture content and the drug. The value of k can be expressed in terms of the Arrhenius law:[5]

$$k = A\cdot\exp(-B/T) \qquad (3)$$

where T denotes the absolute temperature, while A and B are constants.

The parameters, k, n, and α, can be estimated by experiments similar to a two-way layout: the solid dosage form with several levels of moisture content is kept at various temperatures, and the values of C and m are determined periodically. These values are analyzed with Eq. 1 through 3 to estimate the parameters.

Increase in Amount of Moisture of a Solid Dosage Form in a Moisture-semipermeable Package

As described in detail previously,[1] if the storage period is divided into many intervals, each of which is Δt, the moisture increase in packaged solid dosage forms, *e. g.*, a tablet, due to moisture permeation through the moisture-semipermeable package during a time, Δt, can be estimated by the following equations:

$$\Delta m_j = \Delta q_j/W \qquad (4)$$

$$\Delta q_j/\Delta t = P_j\cdot(S/N)\cdot(\Delta p_j)/L \qquad (5)$$

$$P_j = P_0\cdot\exp(-E/(R\cdot T_j)) \qquad (6)$$

$$\Delta p_j = V_j\cdot(RH_{i\cdot j} - RH_{2\cdot j-1})/100 \qquad (7)$$

$$V_j = V_0\cdot\exp(-\Delta H/(R\cdot T_j)) \qquad (8)$$

$$RH_{2\cdot j-1} = \alpha_0 + \beta_0\cdot m_{j-1} + \gamma_0\cdot m^2{}_{j-1} + \cdots\cdots \qquad (9)$$

where the subscript j denotes one of the time intervals, and Δm_j is the moisture increase in the tablet of weight W on a dry basis (N tablets per package), in the j-th interval; Δm_j is caused by the amount of moisture permeation in the j-th interval, Δq_j, through the package of area, S, thickness, L, permeability constant, P, and activation energy of moisture permeation, E, under the condition of Δp_j vapor pressure difference across the package at an absolute temperature, T_j, for the j-th interval. R is the gas constant, V_j the saturated vapor pressure for the j-th interval, and ΔH the heat of vaporization of water, while $RH_{1\cdot j}$ is the ambient relative humidity for the j-th interval, and $RH_{2\cdot j-1}$ the relative humidity in equilibrium

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5) J.T. Carstensen, E.S. Aron, D.C. Spera, and J.T. Vance, *J. Pharm. Sci.*, 55, 561 (1966).

with the moisture content of the tablet, m_{j-1}, for the $(j-1)$-th interval. P_0, V_0, α_0, β_0, γ_0, and the like are constants.

Prediction of Deterioration

As shown in Chart 1, the deterioration can be predicted by an iterative calculation procedure using a time interval of several days for Δt by means of Eq. 1 through 9. The

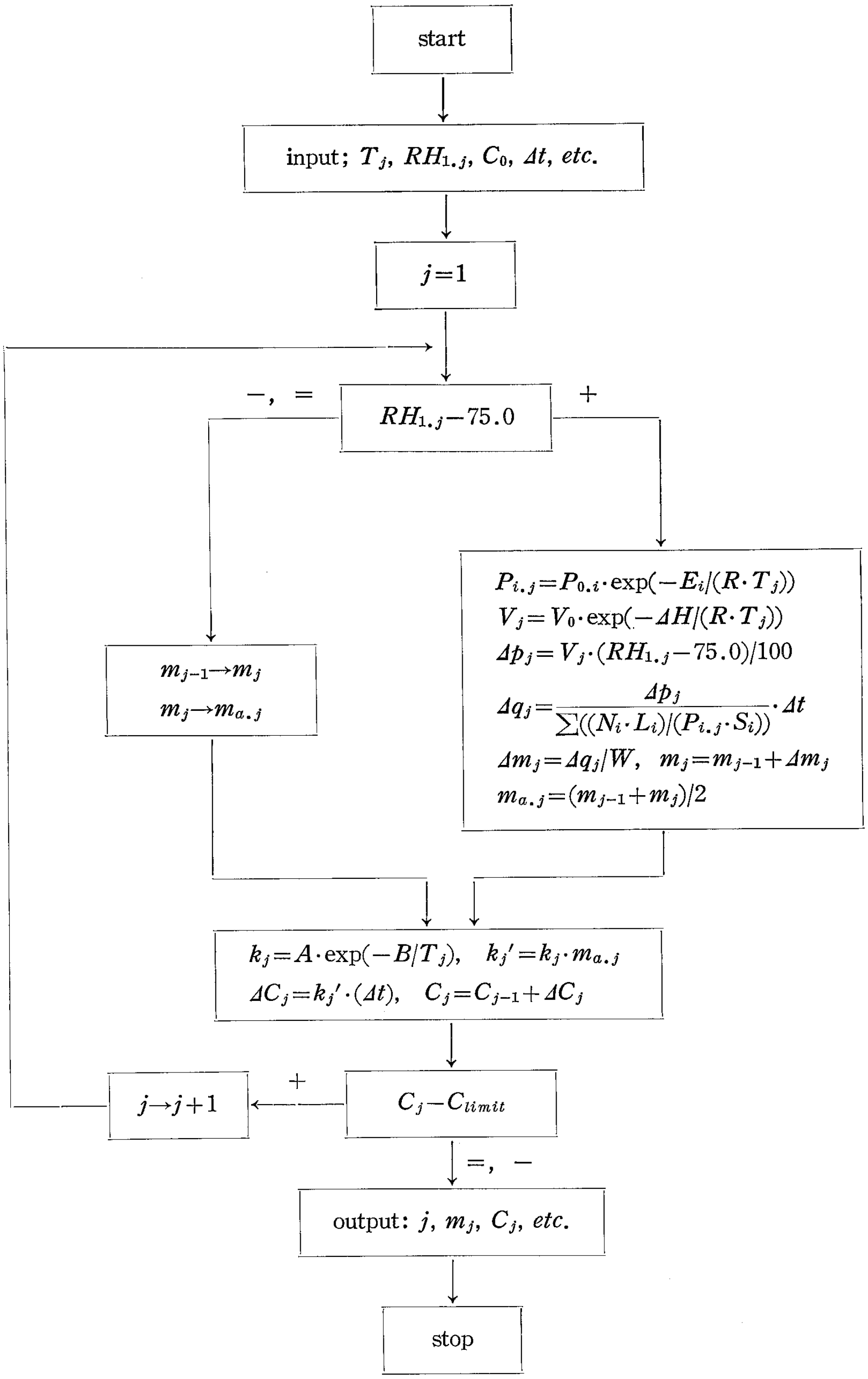

Chart 1. Flow Sheet for Prediction of the Deterioration of a Sugar-coated Tablet Caused by Moisture Content and Temperature

C_0, C_j, and C_{limit} are the initial value of C, the value at the j-th interval, and the allowable limit, respectively. Other symboles are given in the text.

iteration procedure was described in detail previously.[1] Chart 1 shows that n is zero, and that the moisture content of the tablet for the j-th interval, $m_{a\cdot j}$, is an average value (*i. e.*, $m_{a\cdot j}=(m_{j-1}+m_j)/2$); morever, the flow sheet shows that the tablet has a critical relative humidity, 75% RH, and that moisture decrease dose not occur, as will be described later.

Experimental

Materials——Sugar-coated tablets (560 mg per tablet) with the core composition described below were prepared by the usual method. The core had the following active ingredient composition per tablet (360 mg): ascorbic acid, 75 mg; calcium pantothenate, 10 mg; and thiamine hydrochloride, 5 mg. The excipient used in the core was lactose–starch (7: 3), with small amounts of dextrin, gelatin, and magnesium stearate. All of these were JP IX-grade chemicals. One type of strip pack (SP) and two kinds of press-through packs (PTP), described in Table I, were prepared using packaging machines.

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)	PVC[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 Moisture Content——After removal of the sugar layer from the sugar-coated tablet in a manner similar to that described by Maekawa *et al.*,[6] the moisture content of the remaining core was measured by the method reported previously.[1] The initial moisture content of the core was found to be 3.90%.

Measurement of Moisture Sorption——The experiments on the sugar-coated tablets were carried out in the manner reported previously.[1] The moisture contents of the sugar layer and the core were determined separately two months later, by subtracting the moisture content of the core from the sugar-coated tablet.

Determination of Color Change (ΔE)——The color of the cores was determined with a Suga AU-SCH integrating sphere-type color difference meter, in order to obtain lightness and chromaticity coordinates in the *L-a-b* system. From these values, Hunter's color difference, ΔE, was calculated as:[7]

$$\Delta E = (\Delta L^2+\Delta a^2+\Delta b^2)^{1/2} \tag{10}$$

where ΔL, Δa, and Δb indicate the deviation of L, a, and b values of the aged samples from those of the initial samples. The measurements were performed on five cores in all instances, and the average values were taken.

Determination of the Apparent Rate Constant of Color Change——In addition to the initial moisture content of the core, 3.90%, two levels of moisture content (4.42% and 5.81%) were obtained by humidification under conditions of 83% and 93% relative humidity (RH) at 25° for several days. Each of the tablets was sealed in an aluminium-foil-laminated film so as to prevent moisture loss, and was kept for one to sixteen weeks at 30°, 40°, 50°, or 60° in ovens as described previously.[1] The values of moisture content and ΔE of the core were determined periodically, and the apparent rate constant for the color change, k', was estimated by substituting ΔE for C in Eq. 1:

$$d(\Delta E)/dt = k'\cdot(\Delta E)^n \tag{11}$$

Determination of Moisture Permeability of Packaging Materials——Moisture permeabilities of packaging materials used in the packages in Table I were determined as reported previously.[1]

Storage Experiments with Packaged Tablets——The sugar-coated tablets in the packages listed in Table I were kept for 16 to 24 weeks under 83% RH at 25°, using a humidity cabinet as described previously.[1] They

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[6] H. Maekawa, K. Yamano, and H. Saeki, *Yakuzaigaku*, **21**, 270 (1961).
[7] R.S. Hunter, *J. Opt. Soc. Am.*, **38**, 601 (1948).

were also kept in a storehouse without air conditioning for two years. The values of moisture content and ΔE of the cores were determined periodically. The temperature and the relative humidity in the storehouse were recorded in the manner reported previously.[1]

Prediction Calculation——The prediction calculations were performed on a Nihon Denshi JEC-5 computer using a FORTRAN program.

Results and Discussion

Dependence of Color Change on Temperature and Moisture Content

The time courses of the color change in the cores of the tablets at various temperatures are shown in Fig. 1. The values of ΔE increased linearly with time in all instances. The coefficient of variation for the actual data on ΔE was about 10%. Since the moisture content of the cores remained unchanged during the experiments, it was evident that the color change of the ascorbic-acid cores followed apparent zero-order kinetics, as Muraoka *et al.*[4b] reported for the color change of a powder composed of ascorbic acid and cornstarch. The apparent rate constant for the color change, k', was estimated by the least-squares method from the plots in Fig. 1, and the relation between log k' and log m was obtained at each temperature in the manner described by Carstensen *et al.*[5] Figure 2 shows the resulting linear relationship. The value of the rate constant, k, was determined from the intercept of each line in Fig. 2 by the least-squares method, and the values of the interaction order, α, was similarly estimated from the slope of each line. The values of k and α obtained at various temperature are summarized in Table II. In this study, it was osberved that α was dependent on the temperature. The value of α at normal temperature was estimated by extrapolation to be about 4. Such a high value of α might reflect the complexity of the reaction in this dosage form due to the change in the moisture content. The plots of log k against the reciprocal of the absolute

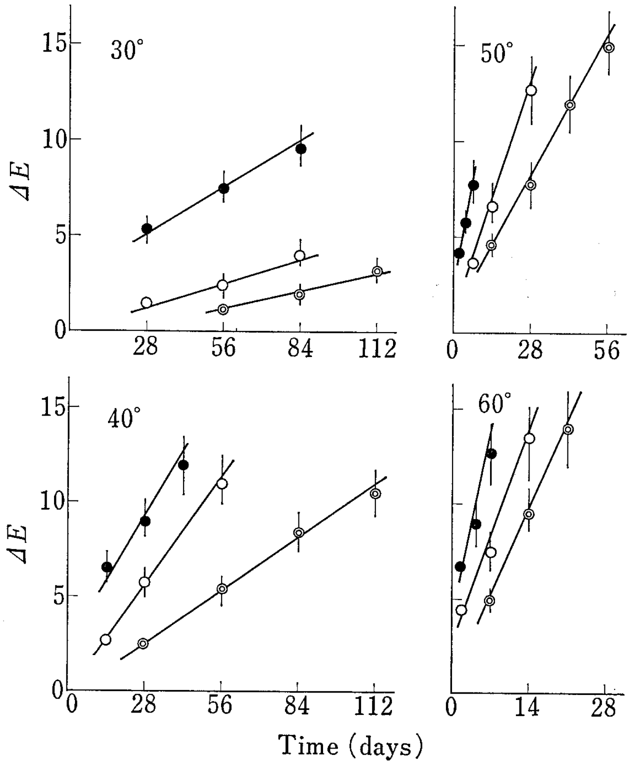

Fig. 1. Effect of Temperature and Moisture Content on the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets

Moisture content: ●, 5.81%; ○, 4.42%; ◎, 3.90%.

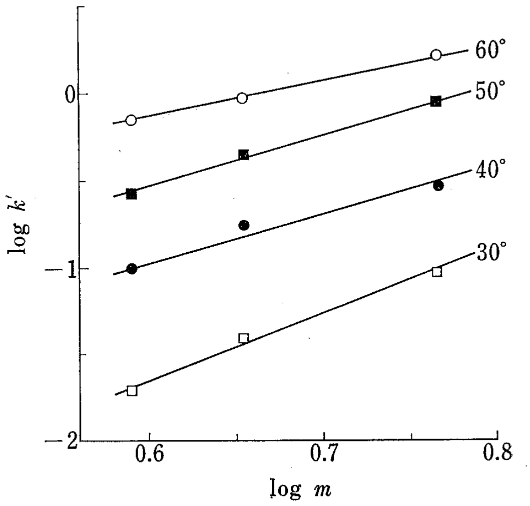

Fig. 2. Plot of the Apparent Rate Constant of the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets as a Function of Moisture Content at Various Temperatures

Table II. Rate Constants of Color Change and α-Values of the Ascorbic-acid Core in Sugar-coated Tablets at Various Temperatures

Temp.	$k^{a)}$	α
30°	1.83×10^{-4}	3.78
40°	1.03×10^{-3}	3.17
50°	5.13×10^{-3}	3.39
60°	2.37×10^{-2}	2.36

a) Day^{-1}.

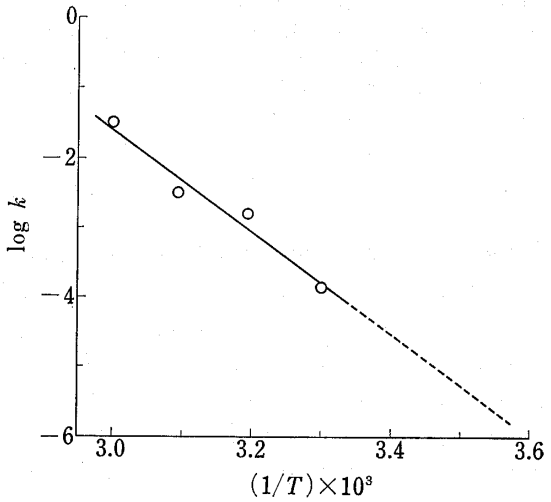

Fig. 3. Plot of the Rate Constant of the Color Change of the Ascorbic-acid Core in Sugar-coated Tablets *vs.* the Reciprocal of Absolute Temperature

temperature, $(1/T)$, give a straight line as shown in Fig. 3. Thus the values of A and B were estimated by the method of least squares, and these kinetic parameters were used to predict the color change of the cores.

It was observed in all instances that the color change of the cores became visible through the sugar layer when the values of ΔE for the cores rose above about 10. Therefore, the limit of the shelf life of this tablet is reached when the value of ΔE for the core is about 10.

Moisture Sorption

The results obtained over two months showed that the sugar-coated tablets neither absorbed nor desorbed moisture under conditions of less than 75% RH, but did absorb moisture at 75% RH or above; *i. e.*, the tablets had a critical relative humidity of 75% RH. Thus, α_0 was 75.0, and β_0, γ_0, and the like were zero. This seemed to be due to the dense crystallization of sugar in the sugar layer of the tablets.

After two months, the distribution of moisture was investigated in both the sugar layer and the core, and it was observed that below 80% RH the moisture content in the sugar layer was between 1.0% and 1.5%. Therefore, the change in the amount of moisture in the sugar layer was small compared with that in the core. On the basis of this finding, it was assumed that the moisture content of the sugar layer was essentially constant during the storage experiments, and that the whole of the moisture increase in the tablets was accounted for by the core. Thus, W denotes the weight of the core. This assumption was added to the flow sheet in Chart 1 in order to predict the shelf life.

Moisture Permeability of Packaging Materials

Table III shows the permeability parameters, obtained in the manner reported previously;[1] these parameters were employed in prediction calculations.

Comparison between Predicted Values and Actual Data from Storage Experiments

In the iterative calculation procedure, it is important to employ suitable time intervals, as described in the previous paper.[1] Time intervals from one to fourteen days were investigated in the case of samples kept under 83% RH at 25°. These calculations yielded the following results: there was essentially no difference among the predicted values of moisture content and color change using these time intervals, though the predicted values with a time interval of one days were a little larger than those with an interval of fourteen days, probably

Table III. Moisture Permeability of Packaging Materials

Packaging material	P[a]	P_0	E[b]
LDPE[c]-laminated cellophane	0.577	1.47×10^6	8.73×10^3
Rigid PVC[d]	1.415	2.56×10^2	3.07×10^3
PVDC[e]-coated and LDPE[c]-laminated rigid PVC[d]	0.530	7.06	1.51×10^3

[a] g·0.1 mm/(m^2·cm Hg·day) at 25°.
[b] cal/mol.
[c] Low density polyethylene.
[d] Polyvinyl chloride.
[e] Polyvinylidene chloride.

because of the accumulation of errors during calculation. Figure 4 shows the actual data and the predicted values with $\Delta t=7$ days when the samples were kept under 83% RH at 25°. It can be seen from Fig. 4 that there was a good agreement between the actual data and the predicted values of the samples in Package No. 2 and No. 3, but not in Package No. 1. A possible explanation for this discrepancy in the case of Package No. 1 is that the strip pack of this sample was flat, and thus tended to lie upon another pack during storage in the humidity cabinet, reducing the effective moisture-permeable area of the pack. Furthermore, Fig. 4 shows that the actual moisture content of each sample increased linearly with time. These results support the view that RH_2 of the sugar-coated tablets used in this study was not depend on the moisture content, but was virtually constant at 75% RH.

The time courses of the moisture content and the color change of samples kept in the storehouse for two years were predicted using a Δt of 30 days. The average temperature and relative humidity values for each month shown in Table IV were employed for prediction. The actual data and the predicted values are shown in Fig. 5. The predicted values of ΔE

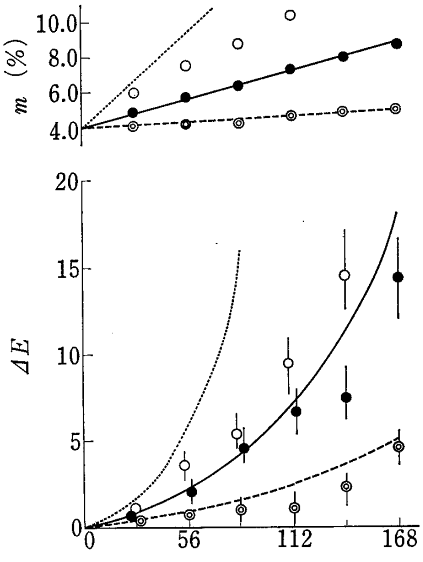

Fig. 4. Comparison of the Predicted Values with the Actual Data for Moisture Increase and Color Change of Ascorbic-acid Cores in Sugar-coated Tablets in Three Types of Packages under 83% RH at 25°

Actual data: ○, SP; ●, PTP-1; ◎, PTP-2.
Predicted values ($\Delta t=7$ days): ····, SP; ——, PTP-1; ----, PTP-2.

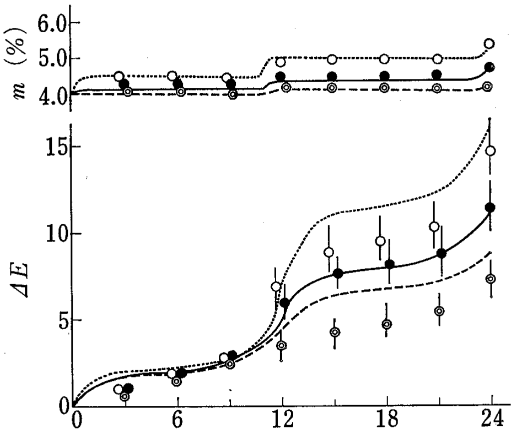

Fig. 5. Comparison of the Predicted Values with the Actual Data for Moisture Increase and Color Change of Ascorbic-acid Cores in Sugar-coated Tablets in Three Types of Packages Kept in a Storehouse

Actual data: ○, SP; ●, PTP-1; ◎, PTP-2.
Predicted values ($\Delta t=30$ days): ····, SP; ——, PTP-1; ----, PTP-2.

TABLE IV. Mean Values of Temperature and Relative Humidity in Each Month in the Storehouse (1973—1975)

Month	1 st year		2 nd year	
	Temp. (°C)	RH (%)	Temp. (°C)	RH (%)
August	30.6	69	31.0	62
September	26.5	76	26.2	65
October	20.8	64	19.1	62
November	15.3	67	15.2	58
December	9.9	63	10.2	65
January	8.6	63	7.8	65
Fabruary	8.8	64	8.0	65
March	11.5	60	10.8	58
April	17.8	65	16.0	65
May	20.0	65	22.7	65
June	24.5	76	26.2	62
July	28.2	74	27.8	76

are affected by errors in the estimated parameters and the accumulation of errors in the calculations, while the actual data on ΔE had a coefficient of variation of about 10% in this study. Therefore, it was considered that there was a reasonable agreement between the actual data and the predicted values of ΔE for all the tablets kept in the storehouse. Moreover, the data on the moisture content shown in Fig. 5 support the finding that the sugar-coated tablets in this study hardly desorbed moisture even when RH_2 was higher than RH_1.

It is interesting to note that significant color change was observed in the rainy season and summer, because this is an indication of the dependence of the deterioration on the temperature and the moisture content, and also of the dependence of the moisture permeability of the packaging film on the temperature and the relative humidity. The relation between the moisture permeabilities of the packages and the shelf lives of the sugar-coated tablets is of interest in connection with the functional design of packages; *i. e.*, though the moisture permeability of Package No. 3 is about one-tenth of that of No. 1, as can be seen in Fig. 5, the shelf life of the tablets in the former package is only twice that in the latter, since the shelf life ended when the value of ΔE for the cores reached about ten.

It was concluded that the iteration procedure using the mathematical model derived here made it possible to predict the shelf life of packaged solid dosage forms which are affected by both the ambient temperature and the moisture content.

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