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Stability of Packaged Solid Dosage Forms. I. Shelf-life Prediction for Packaged Tablets Liable to Moisture Damage

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Deterioration of solid dosage forms due to the change of moisture content was investigated in moisture-semipermeable packages, including overwrapped packaging systems. For the purpose of predicting the shelf life in a drug-package combination, a mathematical model based on the physico-chemical properties of the drug and the moisture permeabilities of the packaging materials was derived. The mathematical model was incorporated with an iteration procedure over a time interval of several days, taking into account the fluctuations of temperature and relative humidity during prolonged storage.

In this study, changes in the hardness of lactose-cornstarch tablets were investigated in strip packs and press-through packs with or without an overwrap film. The values of the hardness and the moisture content for the tablets in these moisture-semipermeable packages were studied under various atmospheric conditions, and were also predicted by means of the iteration procedure. There was reasonable agreement between the actual data and the predicted values, indicating that the iteration procedure through the mathematical model derived here is useful for the shelf-life prediction.

Keywords——shelf-life prediction; iterative calculation; tablet; hardness; moisture content; packaging material; overwrapped packaging system; moisture permeability; temperature; relative humidity

Solid dosage forms such as tablets and capsules are usually susceptible to deterioration, caused, for example, by moisture, heat, and light. Thus, drugs in moisture-semipermeable packages, such as strip packs (SP) and press-through packs (PTP), may deteriorate during prolonged storage, and it is therefore important to predict the shelf life of a drug-package combination. Some workers[2] have presented methods of shelf-life prediction for drugs and foods in such packages. However, they did not take into account the fluctuations in ambient temperature and relative humidity during storage. Furthermore, SP and PTP are usually overwrapped with another plastic film, but little work has been done on predicting the shelf life of products in such overwrapped packaging systems.

The present paper is devoted to the derivation of a mathematical model for the quantification of physico-chemical changes of tablets due to moisture absorption through multi-layer overwrapped types of packages, taking into consideration the construction of actual packages and the variations of ambient temperature and relative humidity during prolonged storage. An iterative calculation procedure is incorporated into a simulation technique for shelf-life prediction using a digital computer. In this study, we tested tablets composed of lactose and cornstarch in order to determine the dependence of the tablet hardness on the moisture content. It was demonstrated that an iteration procedure using the mathematical model derived here was useful for predicting the shelf of the tablets.

1) Location: *2-17-85, Jusohonmachi, Yodogawaku, Osaka, 532, Japan.*
2) *a*) T. Muraoka and A. Kanayama, *Yakuzaigaku*, **29**, 189 (1969); *b*) S. Mizrahi, T.P. Labuza, and M. Karel, *J. Food Sci.*, **35**, 797 (1970).

Theoretical

Increase in the Amount of Moisture of a Solid Dosage Form in a Multi-layer Overwrapped Packaging System

In the case of plastic films such as polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), *etc.*, used for SP or PTP, the rate of moisture permeation through them can be expressed for a stationary state in the form:[3)]

$$dQ/dt = P \cdot S \cdot (\Delta p)/L \qquad (1)$$

where Q is the amount of moisture diffusing through a film of area, S, with thickness, L, during a time, t, under a vapor pressure difference of Δp across the film, while P is a proportionality factor called the permeability constant. Generally, it is likely that the diffusion rate of moisture is very much larger in the air and in solid dosage forms than in plastic films. Hence, all of the water molecules permeating through a film are absorbed immediately by a solid dosage form, *e.g.*, the tablet. If the number of tablets packaged in a pocket of SP or PTP is N, the increase in the amount of moisture of each tablet, q, over a period of time, t, can be experessed as:

$$dq/dt = P \cdot (S/N) \cdot \Delta p/L \qquad (2)$$

Products of SP or PTP are often overwrapped with PE, PP, or a laminated film in order to enhance their resistance to deterioration under conditions of high humidity from a practical point of view. In a case such as this, let P_1, S_1, and L_1 represent the moisture permeability constant, the surface area, and the thickness of overwrap film, respectively, while the total number of tablets in the overwrapped packaging system is designated by N_1. Similarly, the moisture permeability constant, the surface area, and the thickness of the film for SP or PTP are written as P_2, S_2, and L_2, respectively, while the number of tablets in a pocket of SP or PTP is N_2. In the stationary state, the overwrap system may be regarded as a single package system with a laminated film which consists of an inner layer, *i.e.*, the film of SP or PTP with a thickness of L_2, and an outer layer, *i.e.*, an overwrap film with a certain thickness. Water molecules then diffuse through the presumed laminated film due to the pressure difference, Δp. On the basis of this assumption, the thickness of the inner film is effectively increased by a certain thickness, ΔL_2, by virtue of the outer film. Thus, the overall thickness of the presumed laminated film, L_2', is obtained in the form:

$$L_2' = L_2 + \Delta L_2 \qquad (3)$$

The presumed increase in the thickness of the inner layer, ΔL_2, is expressible in terms of the parameters of the inner and outer layers; the moisture-permeation rate of the outer layer is assumed to be equal to that of the inner layer with thickness, ΔL_2, at any pressure difference in the stationary state. Therefore, the value of ΔL_2 can be derived from Eq. 2:

$$\Delta L_2 = ((P_2 \cdot S_2/N_2)/(P_1 \cdot S_1/N_1)) \cdot L_1 \qquad (4)$$

Substituting the value of L_2' for L in Eq. 2 gives an equation for the rate of increase in the amount of moisture for each tablet in SP or PTP overwrapped with monolayer film:

$$\frac{dq}{dt} = \frac{\Delta p}{((L_1 \cdot N_1)/(P_1 \cdot S_1)) + ((L_2 \cdot N_2)/(P_2 \cdot S_2))} \qquad (5)$$

Equation 5 may be extended to multi-layer overwrapped packaging systems, *i.e.*,:

$$\frac{dq}{dt} = \frac{\Delta p}{\sum((L_i \cdot N_i)/(P_i \cdot S_i))} \qquad (6)$$

3) P. Doty, W.H. Aiken, and H. Mark, *Ind. Eng. Chem. Anal. Ed.*, **16**, 686 (1944); *idem*, *Ind. Eng. Chem.*, **38**, 788 (1946); I. Matsuura and M. Kawamata, *Yakugaku Zasshi*, **98**, 986 (1978).

where the subscript i denotes one of the multi-layers. If N_i is equal to one, Eq. 6 expresses the permeability rate of a multi-laminated film instead of a multi-layer overwrapped packaging system, and it coincides with Rogers' equation.[4)]

Prediction of Deterioration

In order to predict the deterioration of packaged solid dosage forms caused by moisture absorption, it is necessary to estimate the increase in the moisture content of the dosage forms due to moisture permeation through the packaging materials, which can be done using Eq. 6. Generally, the ambient temperature and relative humidity vary during prolonged storge. The value of Δp depends on both the amibent temperature, which is expressed in terms of the absolute temperature, T, and the amibent relative humidity, RH_1, while the value of P_i of hydrophobic films such as PE, PP, and PVC depends solely on the temperature. In order to obtain the dependences of the value of Δp on the temperature and the relative humidity and the dependence of P_i on the tempetraure, the storage period is divided into many intervals, each of which is equal to Δt; the mean values of the absolute temperature and the relative humidity for the individual intervals are given by T_j and $RH_{1\cdot j}$, respectively, where the subscript j denotes one of the intervals. Thus, the value of P_i at the j-th interval, $P_{i\cdot j}$, is given by Eq. 7,[3)] and that of Δp_j can be obtained from Eq. 8 by means of the Clausius-Clapeyron equation, Eq. 9:

$$P_{i\cdot j} = P_{0\cdot i}\cdot \exp(-E_i/(R\cdot T_j)) \quad (7)$$

$$\Delta p_j = V_j\cdot(RH_{1\cdot j} - RH_{2\cdot j-1})/100 \quad (8)$$

$$V_j = V_0\cdot \exp(-\Delta H/(R\cdot T_j)) \quad (9)$$

where E_i is the activation energy of moisture permeation for the i-th layer film, ΔH is the heat of vaporization of water, R is the gas constant, and $RH_{2\cdot j-1}$ is the relative humidity in equilibrium with the moisture content of a solid dosage form, *e.g.*, the tablet, at the (j-1)-th interval; $P_{0\cdot i}$ and V_0 are constants. Therefore, substituting Eq. 7 and Eq. 8 into Eq. 6 yields an equation for the increase in the amount of moisture for each tablet for given Δt, Δq_j. If the weight of each tablet is W on a dry basis, the increase in the moisture content of the tablet for the j-th interval, Δm_j, can be obtained in the form:

$$\Delta m_j = \Delta q_j/W \quad (10)$$

The value of $RH_{2\cdot j}$ can be estimated as a polynomial of total moisture content from the initial stage to the j-th interval, m_j, at the maen value of ambient temperature during storage:

$$RH_{2\cdot j} = \alpha_0 + \beta_0\cdot m_j + \gamma_0\cdot m_j^2 + \cdots\cdots \quad (11)$$

where α_0, β_0, γ_0, and the like are constants.

When the value of a certain characteristic of a solid dosage form, C, does not change with temperature, but changes quickly with the moisture content of the dosage form, m, or with the moisture uptake, Δm, the rate of the deterioration can be exressed as:

$$dC/dm = k\cdot C^n \text{ or } dC/d(\Delta m) = k'C^{n'} \quad (12)$$

where k, k', n, and n' are constants independendent of temperature.

Therefore, as shown in Chart 1, the moisture uptake can be predicted by an iterative calculation using a time interval of several days if the initial moisture content, m_0, the initial value of RH_2, $RH_{2\cdot 0}$, and other constants are known. In addition, the deterioration can be estimated from the moisture uptake. Chart 1 shows the case of $n=1$, and also includes procedures for predicting an increase and a decrease in the moisture content and for excluding an improbable increase or decrease in the moisture content by the use of the equation which expresses the dependence of the moisture content on $RH_{1\cdot j}$:

$$m_j = \alpha_1 + \beta_1\cdot RH_{1\cdot j} + \gamma_1\cdot RH_1{}^2{}_{\cdot j} + \cdots\cdots \quad (13)$$

where α_1, β_1, γ_1, and the like are constants.

4) C.E. Rogers, V. Stannett, and M. Szwarc, *Ind. Eng. Chem.*, **49**, 1933 (1957).

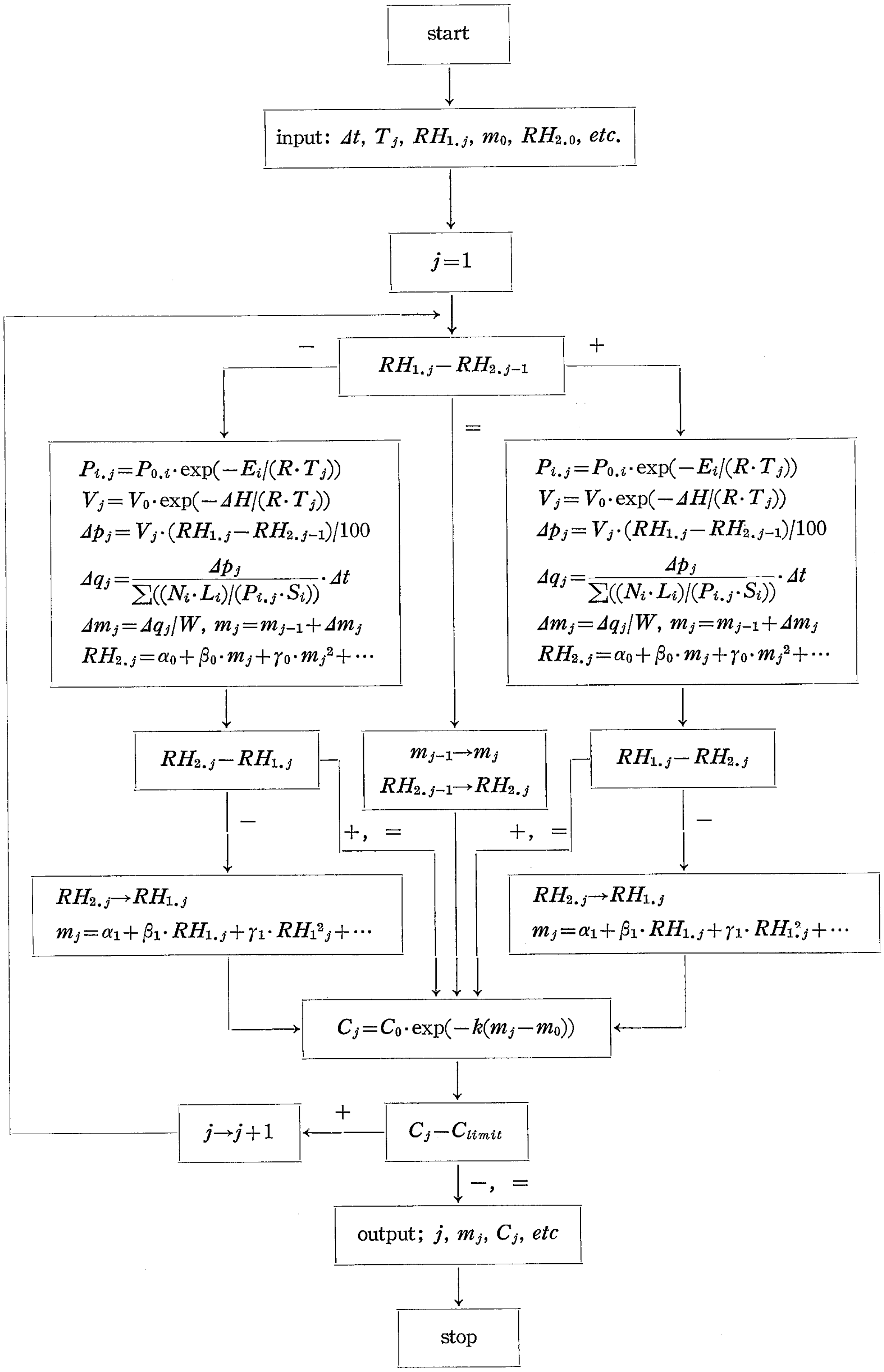

Chart 1. Flow Sheet for Prediction of the Physico-chemical Stability of Solid Dosage Forms in Relation to Moisture Content

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 notations are given in the text.

Experimental

Materials——A mixture of lactose (JP IX) and cornstarch (JP IX) in a ratio of 7: 3 was wet-granulated, and after drying and mixing with a small amount of a lubricant, the granules were compressed into two types of plain tablets in a Stokes model B-2 tabletting machine. After keeping these samples in a tight container for a month for strain relaxation, they were used for various experiments, as described later. Table I shows the characteristics of the tablets. Two kinds of SP and two kinds of PTP, including one overwrapped with a high density polyethylene film, were prepared using packaging machines. Table II shows the characteristics of these packages.

Table I. Characteristics of Lactose-Cornstarch Tablets

Sample	Diameter (mm)	Thickness (mm)	Weight (mg)	Apparent density	Moisture content (%)	Hardness (kg)
A	9.10	3.10	278.0	1.42	4.57	6.47
B	7.10	2.35	119.5	1.28	4.76	4.75

Table II. Charateristics of Packages

No.	Package	Packaging materials	$S^{a)}$ (cm^2)	$L^{a)}$ (mm)	$N^{b)}$
1	Strip pack-1 (SP-1)	LDPE[c]-laminated cellophane	6.0	0.06	1
2	Strip pack-2 (SP-2)	LDPE[c]-laminated and PVDC[d]-coated cellophane	6.0	0.07	1
3	Press-through pack (PTP)	Rigid PVC[e]/aluminium foil[f]	1.2	0.08	1
4	PTP overwrapped with HDPE[g] pouch	Rigid PVC[e]/aluminium foil[f] and HDPE[g]	1.2[e] 216.0[g]	0.08[e] 0.07[g]	1[e] 100[g]

a) Average area(S) and thickness(L) of packs or pouches.
b) Number of tablets in a pack or a pouch.
c) Low density polyethylene.
d) Polyvinylidene chloride.
e) Polyvinyl chloride.
f) Hard type, thickness 0.02 mm.
g) High density polyethylene.

Determination of Moisture Content in Tablets——Ten tablets were crushed into powder in a Spex mixer mill, model 8000, and one gram of the powder was dried with an Abderhalden apparatus for 5 hr at 60° at a pressure of 5 mmHg in order to determine the moisture content. The measurements were performed in duplicate in all instances.

Determination of Tablet Hardness——Diametrical compression was carried out on a Toyama TH-204K hardness tester. The measurements were performed on ten tablets in all instances.

Measurement of Moisture Sorption Isotherm——Usual humidity chambers[5] (10 to 90% relative humidity (RH)) filled with saturated solutions of appropriate salts[6] were used in order to measure isotherms of the tablets. These chambers were kept at $20\pm0.5°$ and $40\pm0.5°$ using Satake model 176-7 ovens with Chino Mini-7 thermocontrollers.

Effects of Temperature and Moisture Content on Tablet Hardness——Many tablets were kept in the same humidity chambers (20 to 80% RH at 20°, 30°, and 40°, separately), as in the isotherm experiments. The hardness and the moisture content of the samples were determined periodically.

Determination of Moisture Permeability of Packaging Material——Moisture permeabilities of packaging materials used in the packages shown in Table II were determined by the usual cup method.[7] The measurements were carried out in duplicate in all instances under the following conditions: $90\pm5\%$ RH at $20\pm0.5°$, $90\pm5\%$ RH at $30\pm0.5°$, and $90\pm5\%$ RH at $40\pm0.5°$, using Tabai model PL-3 humidity cabinets. The values of P, P_0, and E of each packaging material were estimated from Eq. 1 and Eq. 7.

5) W.A. Strickland, Jr., *J. Pharm. Sci.*, **51**, 310 (1962).
6) D.S. Carr and B.L. Harris, *Ind. Eng. Chem.*, **41**, 204 (1949).
7) JIS Z 0208-53; ASTM E 96-63T.

Storage Experiments on Packaged Tablets——The tablets in the packages shown in Table II were kept for a month under conditions of 83±5% RH at 25±0.5°, and 90±5% RH at 40±0.5° using separate Tabai model PL-3 humidity cabinets. The tablets were also kept in a storehouse without air conditioning for four months or a year. The hardness and the moisture content of the tablets were determined periodically. The temperature and the relative humidity in the storehouse were recorded with an Ohta bimetal thermometer and an Ohta hair hygrometer.

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

Results and Discussion

Moisture Sorption Isotherm

The sorption isotherm of Sample A was a sigmoidal curve similar to that of cornstarch reported by Strickland.[5] It was observed that the curve was virtually independent of temperature at ordinary temperatures. Since the composition of sample B was the same as that of sample A, the sorption isotherm of sample B coincided with that of sample A. Thus, the value of RH_2, which is in equilibrium with the moisture content of the samples, m, could be estimated from the third order equation derived from the sorption curve at 20°:

$$RH_2 = -342.88 + 142.00 \cdot m - 16.23 \cdot m^2 + 0.64 \cdot m^3 \quad (4.4\% \leqq m \leqq 9.0\%) \qquad (14)$$

Since the resistance of the tablets to the diffusion of water molecules is negligibly smalll compared with that of the packaging materials, RH_2 could be assumed to be equal to the relative humidity inside the pocket of SP or PTP during storage. Therefore, Eq. 14 was thought to be applicable for shelf-life prediction.

Dependence of Tablet Hardness on Moisture Content and Temperaure

Typical experimental results on the dependence of the tablet hardness, H, on the moisture content, m, are shown for Sample A at 30° in Fig. 1. In all instances, as shown in Fig. 1, the hardness decreases rapidly as the moisture content increases, whereas the hardness remains at the initial value, H_0, even if the moisture content became smaller than its initial value,

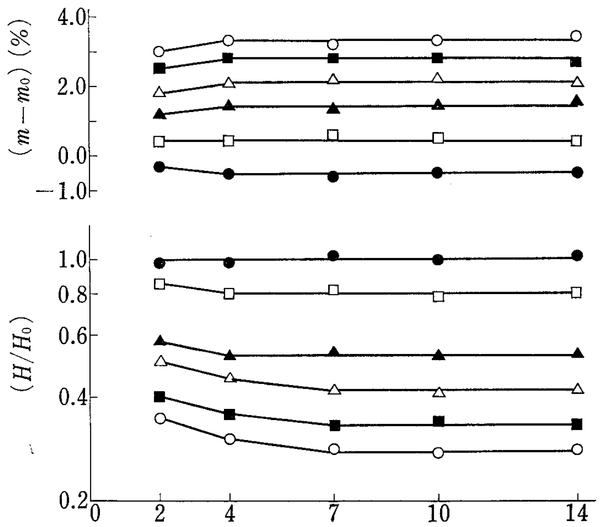

Fig. 1. Moisture Uptake and Residual Hardness of Lactose–Cornstarch Tablets (Sample A) at Various Relative Humidities at 30°

—○—, 82%; —■—, 75%; —△—, 65%; —▲—, 56%; —□—, 35%; —●—, 22%.

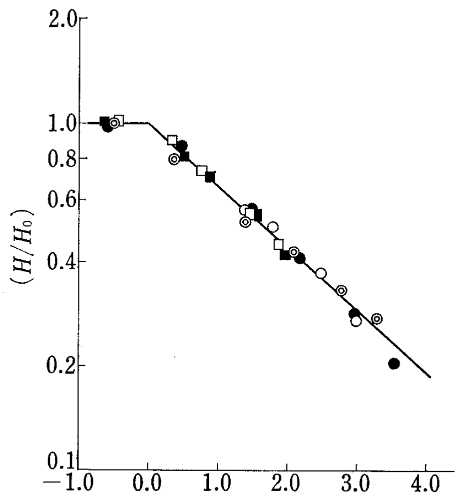

Fig. 2. Relationship between Residual Hardness and Moiture Uptake of Lactose–Cornstarch Tablets

Sample A: ○, 40°; ◎, 30°; ●, 20°. Sample B: □, 40°; ■, 20°.

m_0. It was observed that the value of H became constant when the moisture content attained equilirium under the storage conditions.

It was also found that there was a linear relation between the logarithm of residual hardness, log (H/H_0), and the moisture uptake, $(\Delta m = m - m_0)$, as illustrated in Fig. 2. Furthermore, Fig, 2 shows that log (H/H_0) was independent of the ambient temperature, and that sample A and sample B, which had the same composition and same apparent density, gave the same results for hardness change due to moisture increase or decrease. It was clear from the plots in Fig. 2 that the change in the tablet hardness could be predicted with the following two equations, which were independent of the ambient temperature and were applicable to both Sample A and Sample B. These equations were employed for shelf-life predictions for the samples.

$$dH/d(\Delta m) = -0.399 \cdot H \quad (m > m_0) \tag{15}$$

$$H/H_0 = 1.0 \quad (m \leqq m_0) \tag{16}$$

Moisture Permeability of Packaging Materials

On the basis of the data obtained from the moisture permeation through packaging materials at 20°, 30°, and 40°, the permeability constant, P, was estimated from Eq. 1 for each material. The plots of the logarithm of P *vs.* the reciprocal of the absolute temperature, $(1/T)$, were linear for each packaging material. The values of P_0, and E of each film, which were estimated from Eq. 7, are summarized in Table III. These parameters were applied to prediction calculations.

TABLE III. Moisture Permeability of Packaging Materials

Packaging material	P[a] (25°)	P_0	E[b]
LDPE[c]	0.577	1.47×10^6	8.73
LDPE[c]/PVDC[d]/cellophane	0.118	5.02×10^3	6.30
Rigid PVC[e]	1.416	2.56×10^2	3.07
HDPE[f]	0.249	6.70×10	3.30

a) g·0.1 mm/(m²·cmHg·day).
b) kcal/mol.
c) Low density polyethylene.
d) Polyvinylidene chloride.
e) Polyvinyl chloride.
f) High density polyethylene.

Comparison between Predictcd Values and Actual Data from Storage Experiments

Though Karel *et al.*[2b)] referred only to time intervals of 1/10 of a day under an accelerated deterioration condition, it is of importance to consider what time intervals are suitable for shelf-life prediction by means of an iterative calulation procedure. For example, if the time interval, Δt, is too short, errors in calculation may accumulate, while, if Δt is too long, the values of T_j and $RH_{1 \cdot j}$ may be far from the real ones, and in addition, $RH_{2 \cdot j}$ may be different from its real value if RH_2 depends on the moisture content.

On the basis of the flow sheet in Chart 1, time intervals of one through seven days were investigated for the prediction of the moisture increase in samples kept under accelerated deterioration conditions in order to seek a suitable Δt. The results indicated that there was no significant difference in the predicted values of the moisture increase for the samples among several time intervals, except in the case of the most permeable package, package No. 1, under the severest condition of 90% RH at 40°. In the case of package No. 1 under the severest condition, a longer time interval gave a larger moisture content. A possible explanation for this is that the predicted amount of water permeating through the package was so great at long time interval that the dependence of RH_2 on the moisture contrent could

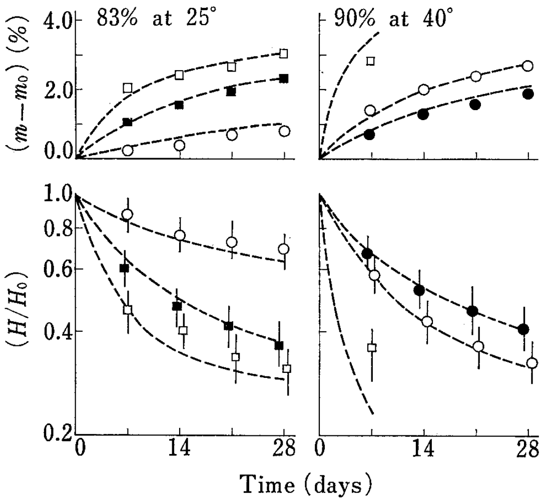

Fig. 3. Comparison of Predicted Values with Actual Data on Moisture Increase and Residual Hardness of Lactose–Cornstarch Tablets in Four Types of Packages under Accelerated Deterioration Conditions

Sample A was packaged in Packages No. 1 and No. 2, while Sample B was in No. 3 and No. 4. Symbols show the actual data, while the dashed lines show the predicted values (Δt=1 day).

□, Package No. 1; ○, Package No. 2;

■, Package No. 3; ●, Package No. 4.

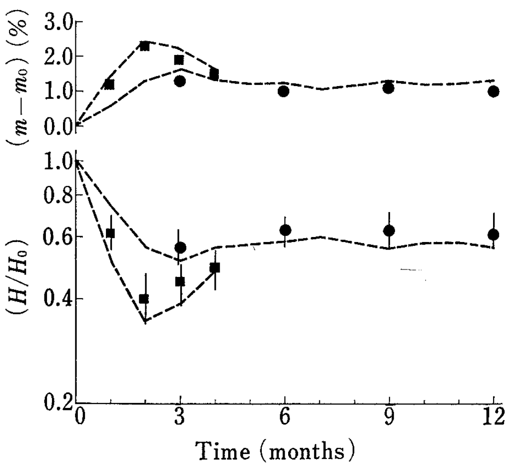

Fig. 4. Comparison of Predicted Values with Actual Data on Moisture Change and Residual Hardness of Lactose–Cornstarch Tablets (Sample B) in Two Types of Packages Kept in a Storehouse

Symbols show the actual data, while dashed lines show the predicted values (Δt=30 days). The storage period began in May.

■, Package No. 3; ●, Package No. 4.

Table IV. Mean Values of Temperature and Relative Humidity in Each Month (1974—1975) in the Storehouse

Month	Temperature (°C)	Relative humidity (%)	Month	Temperature (°C)	Relative humidity (%)
May	20.0	65	November	15.2	58
June	24.5	76	December	10.2	65
July	28.2	74	January	7.8	65
August	31.0	62	Febuary	8.0	65
September	26.3	65	March	10.8	58
October	19.1	62	April	16.0	65

not be followed. However, these data indicate that Δt of one day was usually suitable for the shelf-life prediction of samples under such accelerated conditions. The actual data and the predicted values with Δt=1 day are shown in Fig. 3. Excellent agreement between the actual data and the predicted values was obtained for both moisture increase and the residual hardness.

Time intervals of 30 days were employed for prediction of the shelf life of the samples kept in the storehouse for four months or a year. The mean values of the temperature and the relative humidity for each month shown in Table IV were adopted as T_j and $RH_{1,j}$. Figure 4 shows both the actual data and the predicted values for the samples in the storehouse; there is reasonable agreement between them.

In view of the above results, the mathematical model derived here appears to be suitable for the prediction of deterioration not only in the case of moisture increase, but also in the case of moisture decrease in solid dosage forms in moisture-semipermeable packages, including

multi-layer overwrapped packaging systems. In addition, this procedure has practical relevance, because the deterioration of packaged solid dosage forms under ordinary conditions could be predicted by using mean values of temperature and relative humidity for each month which might be available from published climatic tables.

Sample B investigated here became quite fragile below a residual hardness of 0.4; *i. e.*, it was often broken on pressing it through a pocket of PTP when its hardness fell blow about 2.0 kg. This corresponded to the limit of the shelf life of the samples, and could be predicted by the procedure reported here. Thus, the present partial iteration procedure using the mathematical model derived here made it possible to predict the shelf life of packaged solid dosage forms kept under conditions of variable temperature and relative humidity.

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