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Stability of Packaged Solid Dosage Forms. V.[1] Prediction of the Effect of Aging on the Disintegration of Packaged Tablets influenced by Moisture and Heat

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The effects of moisture and temperature on tablet disintegration time were investigated on a tablet containing gelatin as a binder under accelerated conditions. The higher the ambient temperature was and the more moisture the tablet contained during storage, the longer the disintegration time became. Among several kinetic models investigated, a half-order reaction model was found to be most suitable, when the ratio of the disintegration time of the aged samples to that of the initial ones was taken as a variable to be predicted. The effects of moisture and heat on the disintegration time ratio were analyzed by a multiple regression technique on the basis of the Carstensen equation. In order to estimate the effect of aging on the disintegration time ratio, tablets in several kinds of moisture-semipermeable packages, including an overwrapped package, were examined in artificial climate laboratories. The effect of aging could be predicted by an iterative calculation through a mathematical model in which the kinetics of the increase in the disintegration time ratio was combined with the moisture permeabilities of the packages. It was found that the simulated values could represent the observed data fairly well, though the confidence intervals of the predicted values were rather wide owing to the variances of the experimental data obtained.

Keywords——tablet; disintegration time; moisture content; temperature; relative humidity; package; moisture permeability; multiple regression analysis; iterative calculation; aging effect

The importance of tablet disintegration has already been recognized as a first step to achieving rapid bioavailability of the active ingredients.[2] It has been reported that storage time and temperature have some influence on tablet disintegration time.[3] Those results are closely related to the tablet formulations; in particular, tablets containing gelatin as a binder show a marked increase in the disintegration time during storage.[3a,b] However, so far few studies have been presented on means to predict the change in the disintegration time of packaged tablets stored under ordinary conditions.

The purposes of this paper were to examine the effects of moisture and heat on the disintegration time of an analgesic tablet containing gelatin as a binder, and to predict the effect of aging on the disintegration time of the tablets in several packages kept in the artificial climate laboratories reported previously.[4] The retardation of the disintegration time of the tablets was investigated by a multiple regression analysis based on the Carstensen equations.[5] The predictions were performed by an iterative calculation already described in detail,[1,6] with an explanation of the confidence limits of the disintegration time for the aged samples on the basis of the multiple regression model.

Experimental

Materials——Plain tablets (250 mg per tablet) having the following ingedients were prepared by a usual method: difenamizole (a pyrazole derivative),[7] 75 mg; lactose, 100 mg; cornstarch, 71.5 mg; gelatin, 3 mg;

and magnesium stearate, 0.5 mg. These excipients were of J.P. IX grade. The tablet was 8.6 mm in diameter and 3.6 mm in thickness. The tablet hardness was 9.5 kg (average of ten tablets), as determined with a Toyama TH-204K hardness tester. The three packages, including an overwrapped package, were prepared by using packaging machines, and the characteristics of these packages are summarized in Table I. The permeability parameters of these packaging materials were reported previously.[6]

Table I. Characteristics of Packages

No.	Package	Packaging material	$S^{a)}$ (cm^2)	$L^{a)}$ (mm)	$N^{b)}$
1	Strip pack (SP)	LDPE[c)]-laminated cellophane	9.0	0.060	1
2	Press-through pack (PTP)	Rigid PVC[d)]/aluminum foil[e)]	2.0	0.085	1
3	PTP overwrapped with HDPE[f)] pouch	Rigid PVC[d)]/aluminum foil[e)] and HDPE[f)]	2.0[d)] 240.0[f)]	0.085[d)] 0.070[f)]	1[d)] 100[f)]

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) Polyvinyl chloride.
e) Hard type with thickness of 0.02 mm.
f) High density polyethylene.

Measurements of Moisture Content and Moisture Absorption of the Tablets——These experiments were carried out in the manner described previously.[6] The initial moisture content was 4.25%.

Determination of the Tablet Disintegration Time——The disintegration time was determined in distilled water at 37°C using the apparatus of J.P. IX without disks. The initial value was 6.3 min (average of six tablets).

Effects of Moisture and Heat on the Tablet Disintegration Time——The tablets were adjusted to four levels of moisture content (5.02%, 5.70%, 6.01%, and 6.48%) by humidification over different saturated salt solutions.[6] These humidified tablets were packaged in glass bottles (completely full) with gum-lined metal screw caps, and placed in constant temperature ovens[6] at 50°C, 40°C, or 30°C for several months. The disintegration time and the moisture content of the tablets were determined at suitable time intervals depending on the storage temperature.

Storage Tests on the Packaged Tablets——As shown in Table I, the tablets in the three types of packages, including an overwrapped package, were kept in two artificial climate laboratories: one was a summer in Japan (Osaka, June 10 to September 10, 1969) and the other a tropical climate (Bangkok, Thailand, March 1 to May 31, 1969).[4] The moisture content and the disintegration time of the tablets were measured periodically.

Prediction Calculation——This was performed on a Nihon Denshi JEC-5 computer using a FORTRAN program on the basis of a flow chart similar to that given in a previous paper.[1]

Results and Discussion

Effects of Moisture and Heat on Tablet Disintegration

It was found that moisture and heat markedly influenced the disintegration time of the tablets studied here. The more moisture the tablets contained and the higher the ambient temperature was during storage, the longer the disintegration time became. Various kinetic models were investigated, and when the ratio of the disintegration time of the aged samples to that of the initial ones, D, was taken as an variable to be predicted, a half-order kinetic model gave the best fit to the time-course data of the D-value:

$$D^{1/2} = 1.00 + k' \cdot t \quad \text{or} \quad dD/dt = 2 \cdot k' \cdot D^{1/2} \qquad (1)$$

where t denotes time, and k' the apparent increasing rate constant of the disintegration time ratio. Typical plots of the samples placed at 40 °C are shown in Fig. 1.

Table II shows the k'-values estimated by the method of least squares[8] under various experimental conditions. These apparent rate constants were analyzed on the basis of the

Table II. The Apparent Increasing Rate Constants[a] of the Disintegration Time of Tablets with Several Moisture Contents under Various Conditions

Temperature (°C)	Moisture content (%)			
	5.02	5.70	6.01	6.48
30	—[b]	8.13×10^{-4}	1.74×10^{-3}	7.29×10^{-3}
40	2.35×10^{-3}	2.21×10^{-2}	2.65×10^{-2}	5.40×10^{-2}
50	2.13×10^{-2}	9.05×10^{-2}	1.30×10^{-1}	—[b]

a) The apparent rate constants, k', are expressed as the square root of the ratio of the disintegration time of the aged samples to that of the initial ones, $D^{1/2}$, in the form: $D^{1/2}=1.00+k't$. The dimension is day^{-1}.
b) These experimental conditions failed to give statistically significant rate constants.

empirical formulae of Carstensen *et al.*[5] through a multiple regression technique.[1,8] As a final result of the analysis, a multiple regression model was obtained in the form:

$$\ln k' = 43.2204 + 12.3352\cdot \ln m - 21645.2407/T \qquad (2)$$

where m indicates the moisture content of the tablets, and T the absolute ambient temperature. Each term of Eq. 2 was statistically significant. The multiple correlation coefficient obtained was as high as 0.983, so that Eq. 2 is appropriate for describing the dependence of the retardation of the tablet disinteration on mositure and heat. Equation 2 also shows that the coefficients of the terms related to the moisture content and temperature were very large; hence, moisture and heat had greater influences on the retardation of the tablet disintegration than on both color change of a sugar-coated tablet[6b] and the degradation of aspirin aluminum in a tablet.[1] Thus, the tablet disintegration studied here was found to be very susceptible to moisture and heat.

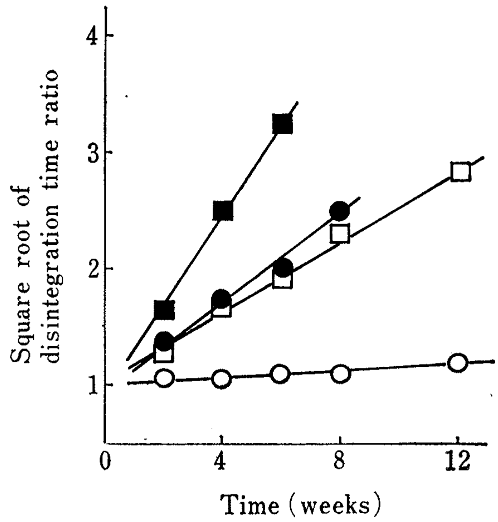

Fig. 1. Increase in Disintegration Time Ratio[a] of Tablets with Several Moisture Contents at 40 °C

○, 5.02%; □, 5.70%; ●, 6.01%; ■, 6.48%.
a) This is the ratio of disintegration time of the aged samples to that of the initial ones.

In order to predict the aging effect reliably, the confidence limits of the individual k'-values were estimated at the 95% confidence level.[1,8] For example, the individual k'-value, under the condition of $T=298$ °C and $m=6.50\%$, was estimated to lie between 6.36×10^{-4} day^{-1} and 5.03×10^{-3} day^{-1}, while the most probable value was 1.79×10^{-3} day^{-1}: the upper limit was about 2.8 times the most probable value, while the lower limit was about 0.4 times the most probable value. These predicted values showed rather wide confidence intervals owing to the large variance arising from the variation of the experimental data.

A simulation was carried out on the retardation of disintegration time for tablets with several moisture contents placed at 30°C through an iterative calculation[1,6] over a time interval of seven days by means of Eq. 2 as follows; the increase in the D-value for a j-th interval, ΔD_j, could be estimated by using the D-value at the (j-1)-th interval, D_{j-1}, in the form:

$$\Delta D_j = 14\cdot k'\cdot(D_{j-1})^{1/2} \qquad (3)$$

and summing the values of ΔD_j gives the total amount of estimated increase in the disintegration time ratio up to the j-th interval, D_j, while the upper and the lower limits of the k'-value were used to obtain the confidence intervals of the D-values.[1] The simulated values could

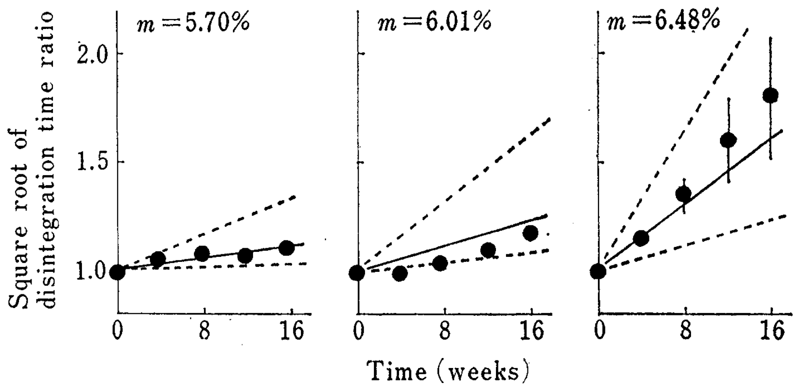

Fig. 2. Comparison of Predicted Disintegration Time Ratio[a] with Observed Data for Tablets with Several Moisture Contents Kept at 30°C

●, the observed data;[b] ——, the most probable value predicted; ----, the upper and lower limits predicted at the 95% confidence level.
a) This is the ratio of disintegration time of the aged samples to that of the initial ones.
b) Each point represents the mean value of the six tablets and vertical lines show the ranges.

represent the increasing tendency of the observed data reasonably well, as shown in Fig. 2, though the former had rather a wide confidence interval because of the larger variance.

Moisture Sorption

Under ordinary conditions, the relative humidity in equilibrium with the moisture content of the tablets, RH_2, was obtained as a polynomial from the moisture sorption experiments:

$$RH_2 = -60.385 + 22.069 \cdot m + 1.365 \cdot m^2 - 0.221 \cdot m^3 \quad (4.20\% \leqq m \leqq 8.50\%) \tag{4}$$

The average moisture content of the tablets for a j-th interval, $m_{a \cdot j}$, was adopted in the prediction calculations, and a correction procedure for the moisture content was also involved in the mathematical model for the predictions in order to prevent excessive increase or decrease in the moisture content of the tablets, as described previously.[1,6]

Moisture Permeabilities of Packaging Materials

The moisture permeability constants, P, of three kinds of packaging materials for strip pack (SP), press-through pack (PTP), and the overwrapping film were expressed in the following forms, respectively:[6]

$$P = 1.47 \times 10^6 \cdot \exp(-4.39 \times 10^3/T) \tag{5}$$

$$P = 2.56 \times 10^2 \cdot \exp(-1.54 \times 10^3/T) \tag{6}$$

$$P = 6.70 \times 10 \cdot \exp(-1.66 \times 10^3/T) \tag{7}$$

where the dimensions of the P-value are g·0.1 mm/(m²·cmHg·day).

Storage Tests on Packaged Tablets

The effects of aging on the disintegration time of the tablets in the three packages were predicted by means of an iterative calculation using a mathematical model (mainly consisting of Eq. 1 to Eq. 7) over an interval of seven days.[1,6] Figure 3 shows the results obtained for the tablets in the two packages kept in the artificial climate laboratories corresponding to a summer in Japan for two cycles (six months). Since the estimated moisture contents of the tablets under the conditions were less than 6.0% and the temperature was in the range of 25 °C to 30 °C, the D-value was predicted not to increase very much. The observed data supported this prediction, as shown in Fig. 3. Figure 4 illustrates the time courses of the D-value

of the tablets in the three packages, including an overwrapped package, placed in the artificial climate laboratory (Bangkok) for two cycles (six months). Since the average temperature was about 30 °C and the average relative humidity was about 80% RH, the *D*-value of the tablets in poorly moisture-proof packages was expected to increase considerably. The predicted *D*-values could represent the increasing tendency of the observed data reasonably well, though the confidence intervals were rather wide because of the large variance of the experimental data. The overwrapped package was found to be the most suitable one under such severe climate conditions.

Though the retardation ratio of the tablet disintegration time (*D*-value) studied in this paper was assumed to follow apparent half-order kinetics, the *D*-value could be simulated by the iterative calculation procedure described in detail previously.[1,6] Thus, it was demonstrated that the iterative calculation procedure was useful for predicting the effects of aging when an appropriate kinetic model could be determined. Furthermore, it was concluded that the mathematical model described in this paper made it possible to select the most suitable package for a solid dosage form which is very susceptible to moisture and heat.

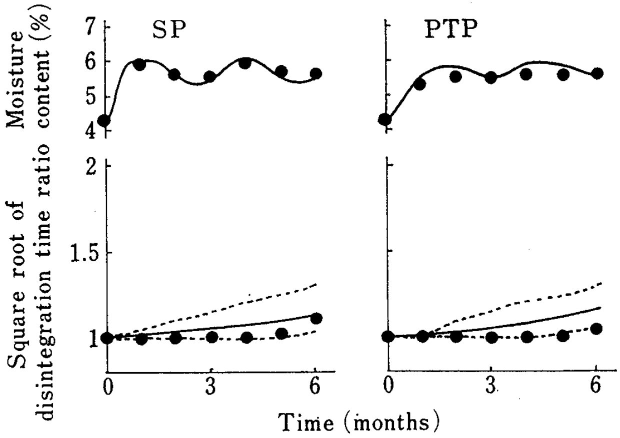

Fig. 3. Comparison of Predicted Values with Observed Data for the Disintegration Time Ratio[a] and the Moisture Content of Tablets in Two Packages Kept in an Artificial Climate Laboratory (Summer in Japan)

●, the observed data; ——, the most probable value predicted; ----, the upper and lower limits predicted at the 95% confidence level.

a) This is the ratio of disintegration time of the aged samples to that of the initial ones.

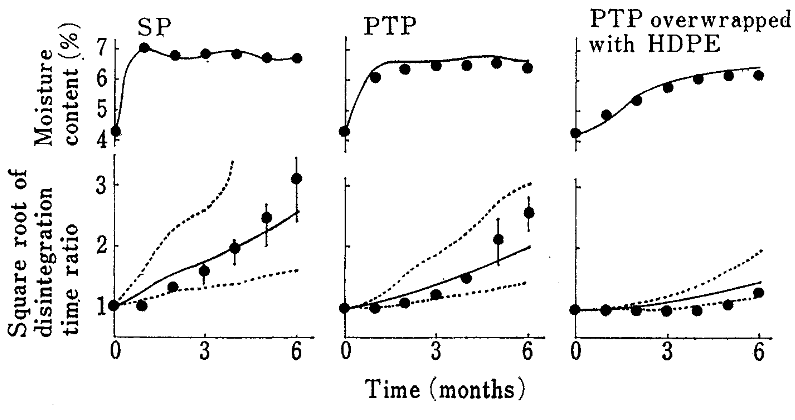

Fig. 4. Comparison of Predicted Values with Observed Data for the Disintegration Time Ratio[a] and the Moisture Content of Tablets in Three Packages Kept in an Artificial Climate Laboratory (Bangkok)

●, the observed data;[b] ——, the most probable value predicted; ---, the upper and lower limits predicted at the 95% confidence level.

a) This is the ratio of disintegration time of the aged samples to that of the initial ones.

b) Each point represents the mean value of the six tablets and vertical lines show the ranges.

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