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Stability of Packaged Solid Dosage Forms. VI.[1] Shelf-life Prediction of Packaged Prednisolone Tablets in Relation to Dissolution Properties

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The shelf lives of prednisolone tablets in a moisture-semipermeable package and a glass bottle were examined in relation to the *in vitro* dissolution rate. The effects of moisture and heat on the tablet dissolution rates, which were obtained by use of the Kitazawa equation, were investigated under various temperature–humidity conditions. Retardation of the dissolution rate was found to be caused by increasing moisture content at ambient temperature. The dependence of the reduction in the dissolution rate on moisture and heat was analyzed by a multiple regression technique on the basis of the Carstensen equation. Predictions of the reduction in the dissolution rates for packaged tablets kept under various conditions were performed by an iterative calculation over a time interval through a mathematical model which combined the multiple regression function with the moisture permeabilities of the packages. There were good agreements between the predicted values and the observed data. The prediction procedure utilizing the rate constants together with their confidence limits gave reliable estimates of the shelf lives of the packaged tablets.

Keywords——shelf-life prediction; prednisolone tablet; dissolution rate; temperature; moisture content; relative humidity; package; moisture permeability; iterative calculation; multiple regression analysis

It has been reported that *in vivo* availabilities of several drugs in solid dosage forms are closely related to their *in vitro* dissolution rates.[2] Thus, the *in vitro* dissolution test is considered to be important. Retardation of dissolution rates was reported to be caused by moisture and heat for some drugs in tablets, depending on the tablet formulations.[3] However, little work has been done on predicting changes in the dissolution rate in tablets in moisture-semipermeable packages under ordinary conditions.

This study was undertaken to investigate the effects of moisture and heat on the dissolution rates of prednisolone tablets on the basis of the Carstensen equations,[4] and to predict changes in the dissolution rates of the packaged tablets kept under various temperature-humidity conditions by the use of an iterative calculation described before.[5] The confidence intervals of the predicted values were estimated by a multiple regression analysis on the kinetics of the dissolution, and the confidence limits of the shelf-life estimates for the packaged tablets were determined.

Experimental

Materials——Tablets (200 mg per tablet) were prepared according to J.P. IX. Each tablet had the following ingredients: prednisolone, 5 mg; lactose, 130 mg; cornstarch, 49 mg; talc, 15 mg; and gelatin, 1 mg. It was oblong in shape (5.2 mm × 12.5 mm) with a thickness of 2.7 mm. The tablet hardness was 10.1 kg (average of ten tablets) as determined by a Toyama TH-204K hardness tester. A polyethylene-laminated cellophane strip pack (SP) containing a tablet in each pocket was prepared using a packaging machine, and each of the 100 tablets was overwrapped with a high density polyethylene (HDPE) film. The average areas of the SP pockets and the HDPE pouches were 6.0 cm^2 and 400.0 cm^2, respectively, and the mean values of the thickness of the pockets and the pouches were 0.06 mm and 0.07 mm, respectively. The moisture permeabilities of these materials were reported previously.[5] A glass bottle with a gum-lined metal screw cap was used as a reference package.

Moisture Content——The tablets were crushed into powder in a Spex mixer mill, and the powder was

dried at 100°C for 3 h to determine the moisture content. The initial value was 2.85%.

Moisture Sorption Isotherm——Usual humidity chambers filled with saturated salt solutions[5] were used to measure the isotherm for the tablets at 25°C.

Assay of Prednisolone——The J.P. IX method was used, and the initial content was found to be 100.6%.

Dissolution Test——The rotating basket method and the determination method were those of U.S.P. XIX. The determinations were performed in triplicate at certain time intervals.

Disintegration Time——The disintegration time was determined in distilled water at 37°C using the J.P. IX apparatus with disks, and the initial value was 2 min (average of six tablets).

Effects of Moisture and Temperature on the Dissolution Rate——The tablets were kept under various temperature-humidity conditions (50% relative humidity (RH) at 50°C, 50% RH to 90% RH at 40°C, or 80% RH and 90% RH at 25°C),[5] and their dissolution rates and moisture contents were determined at suitable time intervals depending on the storage conditions.

Storage Tests on Packaged Tablets——The tablets packaged in the SP overwrapped with the HDPE pouch were kept under 90% RH at 40°C[5] for four months and in a storehouse for two years. The glass bottles were kept under the same conditions. The dissolution rates, moisture contents, and so on were determined periodically. The storage period was almost the same as that reported before.[5c]

Prediction Calculation——These calculations were carried out on a Nihon Denshi JEC-5 computer using a FORTRAN program based on a flow chart similar to that described before.[5c]

Results and Discussion

Effects of Moisture and Temperature on Dissolution

In the experiments to examine the effects of moisture and heat on the retardation of dissolution, the moisture contents of the tablets attained equilibrium in a few days under every condition. Thus, the moisture contents of the tablets were assumed to be virtually constant during the experiments. Prednisolone in the tablets was fairly stable; for example, it hardly decomposed for 56 days under 90% RH at 40 °C. The results of the dissolution tests showed that the concentration of prednisolone in the test solution converged to a constant value which was equivalent to the initial content of prednisolone in the tablet without lag time each run. Therefore, the dissolution rate, k, could be estimated by means of the Kitazawa equation:[6]

$$\ln\{C_s/(C_s-C_t)\} = k\cdot t' \quad (1)$$

where C_s denotes the whole content of prednisolone in the tablets, and C_t the whole content at time t' (min) in the test solution. In this study, the k values were determined by fitting the dissolution data over the range of 0% to 80% to Eq. 1; the k values studied here corresponded to the k_1 values of Kitazawa *et al.*[6] Typical plots are shown in Fig. 1, and a reduction in the k value, *i.e.*, retardation of dissolution, is apparent as the storage period is prolonged. On the other hand, the disintegration time decreased, for example, the disintegration time was found to be 50 sec after 56 days under 90% at 40 °C. Visual observation revealed that this apparent contradiction between dissolution and disintegration behavior was caused by the fact that the particles formed after disintegration were too large for the prednisolone to dissolve readily. The initial k value, k_0, was 0.291 min^{-1}, and when the ratio of the k value at time t, k_t, to k_0 was taken, a linear relationship was found between the natural logarithm of (k_t/k_0) and the time, t (d), in the form:

$$\ln(k_t/k_0) = -K\cdot t \text{ or } dk/dt = -K\cdot k \quad (2)$$

where K indicates the apparent constant of the reduction rate of the dissolution. A typical plot is illustrated in Fig. 2, and the slope was defined as the K value. The K values obtained under several conditions are listed in Table I, and they are dependent on moisture and heat. The K values were analyzed by a multiple regression technique[7] on the basis of the Carstensen equations,[4] and the multiple regression model was obtained in the form:

$$\ln k = 4.5241 + 3.4936\cdot\ln m - 4556.0491/T \quad (3)$$

where m denotes the moisture content, and T the absolute temperature. Each term of Eq. 3 was statistically significant, and the multiple correlation coefficient obtained was as high as

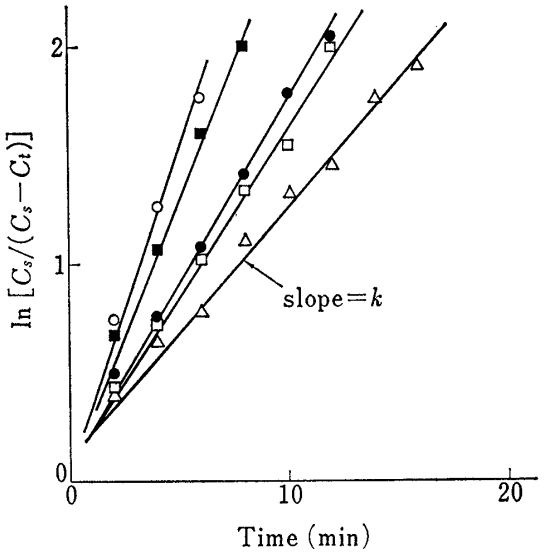

Fig. 1. Dissolution Rate Constant (k) expressed by the Kitazawa Equation[a] for Prednisolone Tablets (Moisture Content: 5.41%) kept at 40 °C

C_s denotes the whole content of prednisolone in the tablets, and C_t the whole content in the test solution at time t.

○, the initial sample; ■, after 14 d; ●, after 28 d; □, after 42 d; △, after 56 d.

a) S. Kitaza wa, I. Johno, Y. Ito, S. Teramura, and J. Okada, *J. Pharm. Pharma col.*, **27**, 765 (1975).

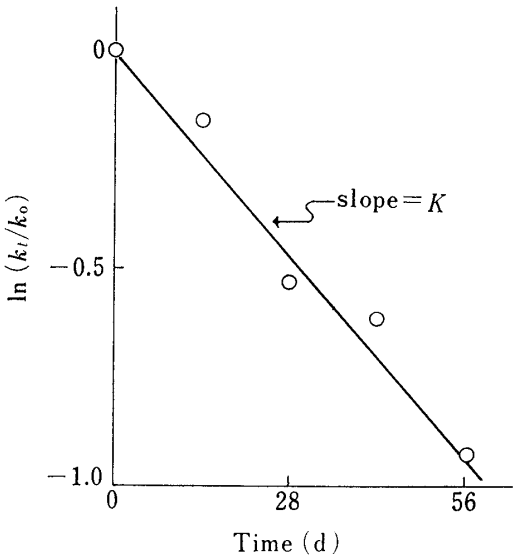

Fig. 2. A Plot to determined the Reduction Rate Constant (K) of Dissolution for Prednisolone Tablets (Moisture Content: 5.41%) kept at 40 °C

k_0 denotes the initial value of the dissolution rate constant, and k_t the rate constant at time t.

Table I. Apparent Reduction Rate Constants (K) of Dissolution of Prednisolone Tablets with Various Moisture Contents at Several Temperatures

Temperature (°C)	Moisture content (%)	K (d^{-1})
25	5.60	0.0091
25	4.77	0.0049
40	5.41	0.0165
40	4.64	0.0092
40	4.12	0.0055
40	3.54	0.0037
50	3.10	0.0038

0.994. Thus, Eq. 3 was considered to be suitable for expressing the dependence of the K value on moisture and heat. For the purpose of reliably predicting the shelflives of the packaged tablets, the individual K values were estimated with the 95% confidence limits.[5c,7] For example, the individual K value, under the condition of $T=293$ °C and $m=3.90\%$, was estimated to lie between 0.00135 d^{-1} and 0.00269 d^{-1}, while the most probable value was 0.00190 d^{-1}.

Moisture Sorption Isotherm

The relative humidity in equilibrium with the moisture content of the tablets, RH_2, was obtained as a polynomial in the form:

$$RH_2 = 180.836 - 149.696 \cdot m + 47.583 \cdot m^2 - 4.315 \cdot m^3 \quad (2.50\% \leqq m \leqq 5.00\%) \qquad (4)$$

The mean value of the moisture content was adopted as the moisture content for a j-th interval, $m_{a\cdot j}$,[5] and a correction procedure for the moisture content was involved in order to prevent excessive in creses or decrease in the moisture content as described in detail before.[5]

Moisture Permeability of Packaging Materials

The moisture permeability constants of the packaging materials, P, for the SP and the HDPE pouch were expressed in the following forms, respectively:[5]

$$P = 1.47\times10^{6}\cdot\exp(-4.39\times10^{3}/T) \quad (5)$$

$$P = 6.70\times10\cdot\exp(-1.66\times10^{3}/T) \quad (6)$$

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

Storage Tests on Packaged Tablets

Predictions were performed through an iterative calculation procedure over a time interval of several days, Δt, by means of Eq. 2 as follows; *i.e.*, the retardation of the dissolution rates for a j-th interval, Δk_j, could be estimated by using the k value at the $(j-1)$-th interval, k_{j-1}, and the K value at the j-th interval, K_j, in the form:

$$\Delta k_j = -K_j\cdot k_{j-1}\cdot\Delta t \quad (7)$$

Thus, the k value at the j-th interval, k_j, could be obtained:

$$k_j = k_{j-1} + \Delta k_j = k_{j-1}\cdot(1-K_j\cdot\Delta t) \quad (8)$$

The confidence interval of the K value estimated with 95% probability was involved in the prediction calculations for the purpose of obtaining the confidence interval of the k value.[5c,7]

Figure 3 shows the results obtained for the packaged tablets kept under the severe condition of 90% RH at 40 °C, with the values predicted for Δt=1 d with a confidence level of 95%. The predicted k values were in good agreement with the observed data. There was a large difference between the k value of the tablets in the SP overwrapped with the HDPE pouch and that of the tablets in the glass bottles owing to the difference of moisture contents between them. It was found that the moisture content of the tablets in the SP overwrapped with the HDPE pouch rapidly reached a value in equilibrium with the outer relative humidity on account of the high temperature and humidity, *i.e.*, 90% RH at 40 °C.

The observed data for the samples kept in the storechouse for two years are illustrated in Fig. 4 with the predicted values (Δt=30 d) and the 95% confidence intervals. There was a good agreement between the actual data and the predicted values. Prednisolone in the tablets was stable, and the tablet disintegration time was found to be 1 min in the SP cverwrapped with the HDPE pouch after two years. These findings were in accordance with those obtained in experiments for determining the dependence of the dissolution rate on moisture and heat. There appeared to be no relation between the dissolution rate and the tablet disintegration time, since the dissolution rate decreased while the tablet disintegration rate increased.

It was very difficult to find a general relationship between the data obtained under an accelerated condition and those obtained under ordinary conditions, because the changes in these values were dependent on the moisture content and the ambient temperature; the retardation of the dissolution for the samples in the bottles kept under 90% RH at 40 °C was observed to be about twice that of the samples kept in the storehouse, while that of samples in the SP overwrapped with the HDPE pouch under 90% RH at 40 °C was found to be about six times that of the samples in the storehouse, as shown in Fig. 3 and Fig. 4. If it is assumed that the point where the time required for 60% of the prednisolone content in the tablets to dissolve in the test solution exceeds 20 min denotes the shelf-life, the limit of the k value is estimated to be 0.0458 min^{-1}. Thus, the prediction procedure studied here estimated the shelflife of prednisolone tablets in the SP overwrapped with the HDPE pouch to be two years at the 95% confidence level, and the shelf-life of the tablets in the bottles to be more than four years.

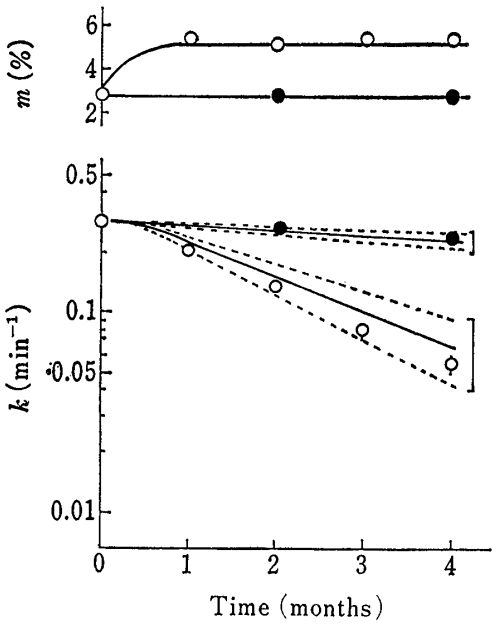

Fig. 3. Comparison of Predicted Values with Observed Data of Dissolution Rate Constant (k) and Moisture Content (m) for Packaged Prednisolone Tablets Kept under 90% RH at 40 °C

○, the observed data for the tablets in the strip pack;[a] ●, the observed data for the tablets in the glass bottle; —, the most probable predicted value; ---, the upper and lowerlimits predicted at the confidence level of 95%.

a) Each point represe nts the mean value of three tablets and vertical lines show the ranges.

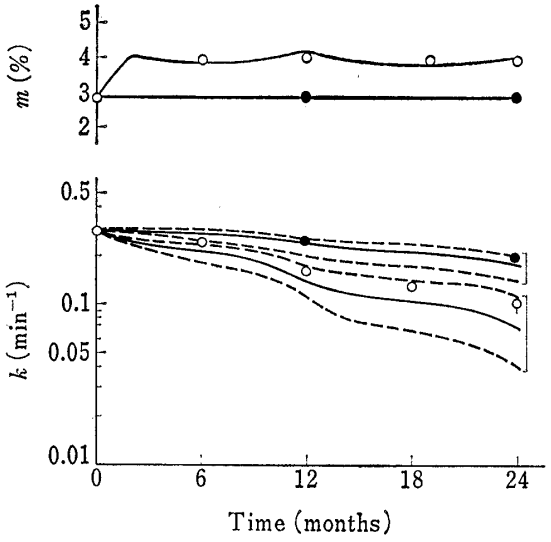

Fig. 4. Comparison of Predicted Values with Observed Date of Dissolution Rate Constant (k) and Moisture Content (m) for Packaged Prednisolone Tablets in a Storehouse

○, the observed data for the tablets in the strip pack;[a] ●, the observed data for the tablets in the glass bottle; —, the most probable predicted value; ---, the upper and lower limits predicted at the confidence level of 95%.

a) Each point represents the mean value of three tablets and vertical lines show the ranges.

It was concluded that the effects of moisture and heat on the dissolution rates for the predn-isolone tablets studied here could be analyzed by a multiple regression technique, and that the shelf lives of the tablets in moisture-semipermeable packages colud be reliably predicted by an iterative calculation through a mathematical model including the multiple regression function in part. Thus, through the prediction procedure in this paper, it should be possible to estimate the physico-chemical stabilities of packaged solid dosage forms as well as the chemical stabilities of these packaged solid dosage forms, if a kinetic model can be obtained.

References and Notes

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