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Prediction of Stability of Drugs. IV.[1] Prediction of Stability by Multilevel Nonisothermal Method[2]

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For prediction of stability of drugs upon storage attended by temperature change, the multilevel nonisothermal method that estimates stability from degradation ratio after a specific period in straight temperature increase process was proposed. The theoretical consideration for this method and the development of an apparatus were made and the graphical method was employed for calculation.

Several drugs were used to test this method. As a result, the values predicted by the graphic calculation were consistent with the values observed after storage in a warehouse. It is considered that the present method is a useful means for quality assurance of drugs.

Kinetic studies to predict the stability of drugs have been conducted by many workers. In almost all of these studies, drugs are preserved under an isothermal condition. However, drugs stored in pharmacies and warehouses for extended period of time are exposed to a wide range of temperatures. The most important point, consequently, is to predict the stability of drugs preserved in actual environment which depends on an atmospheric temperature cycle. That is, accuracy of the prediction depends on environmental conditions of storage. The prediction of stability of drugs under the condition of room temperature cycle is the most unadvanced field with many problems yet to be solved and only a few reports[4] refer to this problem. Therefore, establishment of a method for the prediction of stability of drugs preserved at room temperature has long been desired from the standpoint of appropriate quality assurance.

The prediction method proposed in the present paper is as follows. Heating rates are set up at multilevels and degradation ratio at each level is determined after a specified period. Then the degradation ratio after storage is estimated by a graphic calculation. This method is termed the multilevel nonisothermal method. In order to confirm the validity of this method, predicted values of degradation ratio of the drugs preserved in a specific warehouse were compared with observed values. Since the result showed a good agreement between the predicted and observed values, application of this multilevel nonisothermal method is expected to be useful for quality assurance.

Simulation of Annual Room Temperature Cycle

The annual minimum, maximum and average temperatures differ greatly for each geographical location in Japan according to different latitude or climate, therefore a great difficulty is inherent in a simulation for a storage temperature level. However, an actual simulation for a pattern of annual temperature cycle will be possible. Many of usual assurance period for stability are evaluated in yearly unit, and an actual simulation for annual temperature

1) Part III: N. Okusa, *Chem. Pharm. Bull.* (Tokyo), **23**, 794 (1975).
2) A part of this paper was presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, 1970.
3) Location: *No. 6–9, Narihira 5 chome, Sumida-ku, Tokyo.*
4) M. Terao, K. Aoki, and Y. Ueki, Abstract of Paopers, 84th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1964; S. Egawa, "Study on Stability of Liquid Preparations," Thesis for the degree of Ph. D. (Tokyo Univ.), 1964.

cycle would involve a pattern of changing monthly average temperatures. Monthly average temperatures, rather than daily periodicities or daily average temperatures, are used because the typical storage situation prevents the product from changing temperatures rapidly.[5]

The relation of the difference between the monthly average atmospheric temperature and annual average atmospheric temperature according to the meteorological statistics[6] obtained from 80 meteorological stations in Japan is shown in Fig. 1.

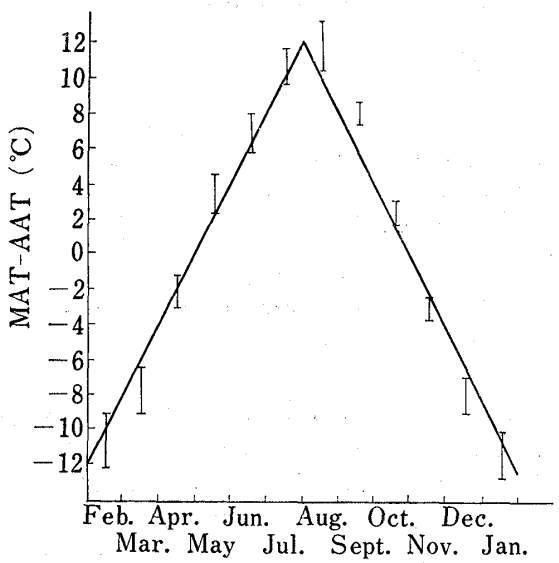

Fig. 1. Annual Periodicity of the Monthly Average Atmospheric Temperature of Various Locations in Japan

MAT: monthly average temperature (1931—1960)
AAT: annual average temperature (1931—1960)

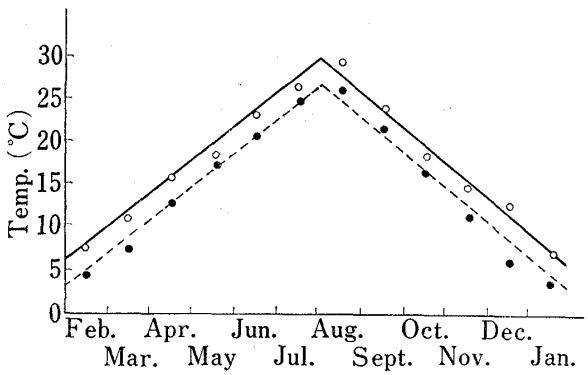

Fig. 2. Annual Periodicity of the Monthly Average Atmospheric and Room Temperature in a Warehouse (Reinforced Concrete Structure, without Air Conditioning) in Tokyo

●: monthly average atmospheric temp. (1968—1969)
○: monthly average room temp. (1968—1969)

It will been seen that the annual atmospheric temperature cycle of various geographical locations in Japan indicate a common pattern, and its pattern can be expressed approximately as a common, single straight line of temperature increase and decrease. It is also possible to simulate a common pattern of annual room temperature cycle, for various locations in Japan, similarly to that of annual atmospheric temperature cycle. As an example, the monthly average atmospheric temperature in Tokyo and the monthly average room temperature in a warehouse (reinforced concrete structure, without air conditioning) in Tokyo are shown in Fig. 2.

The example are seen to support the straight line model of temperature increase and decrease as mentioned above, for the annual cycle of atmospheric temperature and room temperature.

Theoretical

As mentioned above, a periodic model for room temperature was suggested, which might be regarded as a straight line model of temperature increase and decrease. If storage period is expressed by yearly unit, both the linear temperature increase and decrease period are the same and, consequently, since degradation ratio after each period also is equal, storage condition can be treated as a straight line of temperature increase.

5) J.D. Haynes, *J. Pharm. Sci.*, **60**, 927 (1971).
6) The Japan Meteorological Agency (ed.), "Climatic Table of Japan," Part 1, 1961.

In an isothermal process, eq. (3) for the relationship between degradation ratio α_c after a specified period t_c and absolute temperature T_c can be derived from eq. (1) and (2) described in the previous paper.[1)]

$$\ln\ln\left(\frac{1}{1-\alpha}\right) = \ln k + m \ln t \tag{1}$$

$$\ln k = \ln k_0 + \frac{mE}{\boldsymbol{R}}\left(\frac{1}{T_0}-\frac{1}{T_c}\right) \tag{2}$$

$$\ln\ln\left(\frac{1}{1-\alpha_c}\right) = \ln k_0 + m \ln t_c + \frac{mE}{\boldsymbol{R}}\left(\frac{1}{T_0}-\frac{1}{T_c}\right) \tag{3}$$

where E is the activation energy (cal. mole^{-1}), $\boldsymbol{R}$ is the universal gas constant, 1.987 cal. mole^{-1} degree^{-1}, and k_0 is the parameter corresponding to T_0.

On the other hand, eq. (5) for the relationship between degradation ratio α and absolute temperature T in nonisothermal process is derived from eq. (2) and eq. (4) differentiated to eq. (1).

$$\frac{d\alpha}{dt} = mkt^{m-1}(1-\alpha) \tag{4}$$

$$\frac{d\alpha}{dT}\cdot\frac{dT}{dt} = mk_0t^{m-1}(1-\alpha)\exp\left\{\frac{mE}{\boldsymbol{R}}\left(\frac{1}{T_0}-\frac{1}{T}\right)\right\} \tag{5}$$

If the nonisothermal process satisfies the conditions of linear process from the initial temperature T_0 to the final temperature T_r, eq. (6) is obtained

$$\left.\begin{aligned}\frac{dT}{dt} &= \phi = \frac{(T_r-T_0)}{t_c}\\ t &= \frac{(T-T_0)}{\phi}\end{aligned}\right\} \tag{6}$$

By integrating eq. (5) with respect to temperature, degradation ratio α_r after a specified time t_c is obtained from eq. (7) by substituting eq. (6) into eq. (5).

$$\ln\ln\left(\frac{1}{1-\alpha_r}\right) = \ln m + \ln k_0 + m\ln t_c - m\ln(T_r-T_0) + \left(\frac{mE}{\boldsymbol{R}T_0}\right) + \ln\int_{T_0}^{T_r}(T-T_0)^{m-1}\exp\left(\frac{-mE}{\boldsymbol{R}T}\right)dT \tag{7}$$

When the values of degradation ratio α_c and α_r after a specified time t_c are equal, eq. (8) for the relationship between T_c and T_r is derived by eliminating common terms in eq. (3) and (7).

$$\left(\frac{1}{T_0}-\frac{1}{T_c}\right) = \frac{1}{T_0} + \frac{\boldsymbol{R}}{mE}\left[\ln\left\{\frac{m}{(T_r-T_0)^m}\right\}\int_{T_0}^{T_r}(T-T_0)^{m-1}\exp\left(\frac{-mE}{\boldsymbol{R}T}\right)dT\right] \tag{8}$$

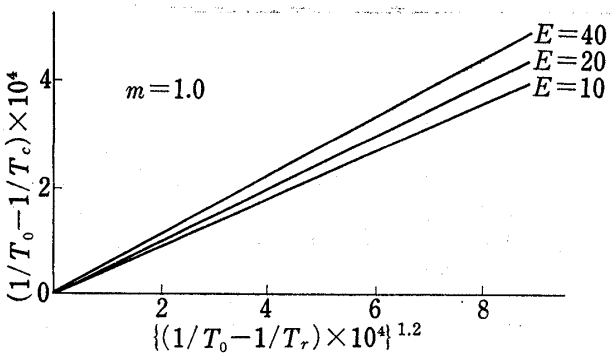

Fig. 3. Relationship between T_c (Isothermal) and T_r (Nonisothermal) after t_c is influenced by Value of Activation Energy (E) (kcal/mole)

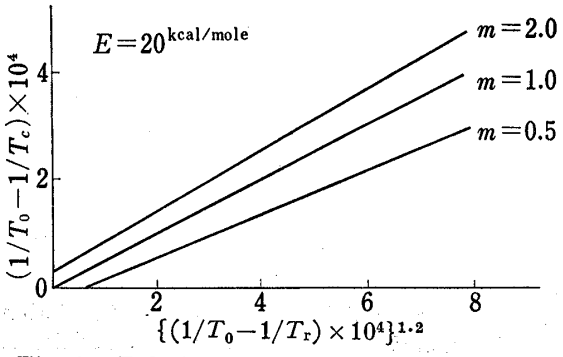

Fig. 4. Relationship between T_c (Isothermal) and T_r (Nonisothermal) after t_c is influenced by m Value

The solution of eq. (8) is computed by numerical integration, namely, the value of $(1/T_0-1/T_c)$ is determined by numerical integration giving the values of T_0, T_r, m, and E beforehand. The result is as follows: $(1/T_0-1/T_c)$ *vs.* $(1/T_0-1/T_r)^{1.2}$ showed a linear relationship even if the values of m and E were varied, and such a linear relationship should hold when T_0 and T_r are within the range of 0—100°. Typical examples of the linear relationship are shown in Fig. 3 and 4. Equation (8) is rearranged to eq. (9)

$$\left(\frac{1}{T_0}-\frac{1}{T_c}\right)=\theta\left(\frac{1}{T_0}-\frac{1}{T_r}\right)^{1.2}+w \tag{9}$$

where θ is the parameter depending on activation energy and w is the parameter depending on m.

The relationship between degradation ratio α_r after a specified time t_c and final absolute temperature T_r is obtained by substituting the right side of eq. (9) into $(1/T_0-1/T_c)$ of eq. (3), and eq. (3) is rearranged as eq. (10)

$$\ln\ln\left(\frac{1}{1-\alpha_r}\right)=\ln k_0+m\ln t_c+\left(\frac{wmE}{R}\right)+\left(\frac{\theta mE}{R}\right)\left(\frac{1}{T_0}-\frac{1}{T_r}\right)^{1.2} \tag{10}$$

When the degradation ratio of eq. (10) is fixed and its time t and final temperature T_r are varied, eq. (10) can be transformed into eq. (11). Therefore, $(1/T_0-1/T_r)^{1.2}$ *vs.* $\ln t$ is shown as a linear relationship with a gradient of $R/\theta E$

$$\left(\frac{1}{T_0}-\frac{1}{T_r}\right)^{1.2}=\left(\frac{R}{\theta mE}\right)\left\{\ln\ln\left(\frac{1}{1-\alpha_r}\right)-\ln k_0\right\}-\left(\frac{w}{\theta}\right)-\left(\frac{R}{\theta E}\right)\ln t \tag{11}$$

The stability of drugs can be predicted by the multilevel nonisothermal method by using the correlation of eq. (10) and (11).

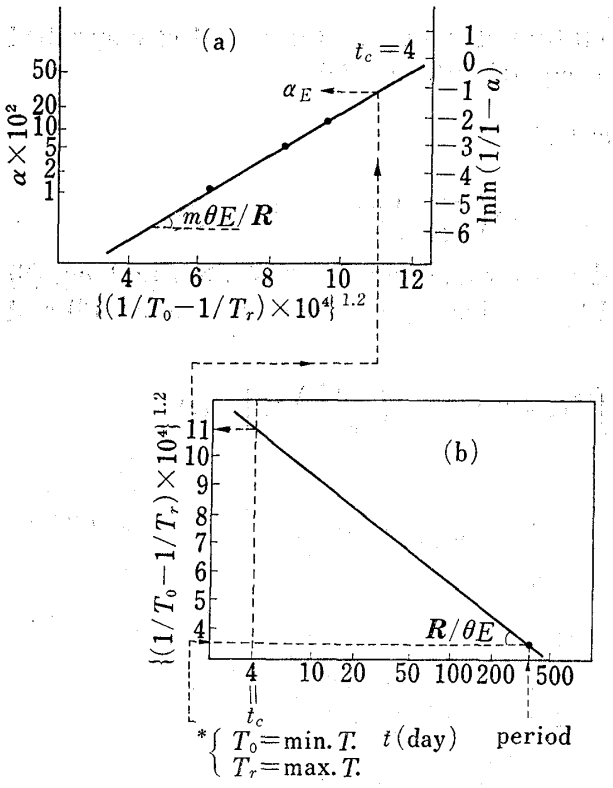

Fig. 5. Graphic Calculation for the Prediction of Degradation Ratio (α_E) by the Multilevel Nonisothermal Method

* T_0: minimum temp. in storage period
T_r: maximum temp. in storage period

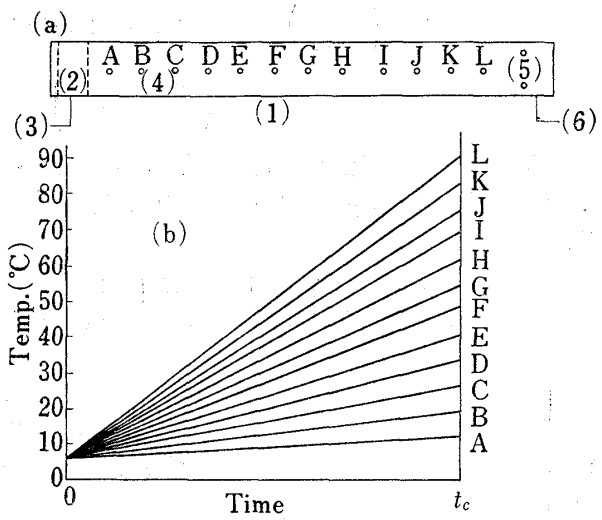

Fig. 6. (a) Scheme of the Multilevel Temperature Gradient Apparatus (b) An Example of Temperature Rise in Each Sample Hole

(1) aluminium block
(2) cooling water tank
(3) refrigerator
(4) holes (A, B, C, ···)
(5) heater
(6) program controller

Procedure of Graphic Solution

Graphic solution for prediction of the stability of drugs by the multilevel nonisothermal method can be explained by the example shown in Fig. 5, (a) and (b). The relationship of eq. (10) is illustrated in Fig. 5(a), and that of eq. (11) in (b). When the minimum temperature T_0 in storage period is given as the intial temperature, a straight regression line is obtained by plotting $(1/T_0-1/T_r)^{1.2}$ *vs.* degradation ratio after a specified time t_c. An example of the regression line is shown in Fig. 5(a).

On the other hand, minimum and maximum daily average room temperatures for a storage period were designated previously as the storage conditions. An example of these conditions is illustrated in Fig. 5(b). A line was drawn through a fixed point satisfying the given conditions and its gradient is given as the product of m value and the reciprocal of the gradient mE/R shown in Fig. 5(a). By taking a specified time t_c on the abscissa, the value of $(1/T_0-1/T_r)^{1.2}$ on the ordinate corresponding to t_c was read from the straight line in Fig. 5(b). The value read on the ordinate in Fig. 5(b) is given on the abscissa in Fig. 5(a), and the degradation ratio corresponding to the given value on the abscissa can be read from the straight regression line of $(1/T_0-1/T_r)^{1.2}$ *vs.* lnln $(1/1-\alpha_r)$. The degradation ratio obtained from the graphic solution shows the predicted value which satisfies the given storage conditions.

Experimental

Materials——The drugs used for the accelerated isothermal storage test in the previous work were also used in the present experiments; as follows: Acetylsalicylic acid solution, ascorbic acid solution, ascorbic acid-mannitol powder, and pyridoxal phosphate solution. Preparation and determination of these drugs were the same as reported in the previous paper.[1]

Experiment on Multilevel Nonisothermal Method——For the present experiment, an apparatus characterized by producing different temperature gradients simultaneously was devised. This apparatus is illustrated in Fig. 6(a).

It is made of a block of metallic material (aluminium) which has a good heat conductivity. One end of the long axis of the block is maintained at the minimum daily average room temperature and the other end is raised by heating at a constant temperature gradient. Several sample holes are bored at definite intervals along the long axis of the block as shown in Fig. 6(a). Sample holes should indicate different temperature gradients at the same time, as shown in Fig. 6(b).

First, designated straight heating line was previously programmed by the program controller. Next, ampules containing the test material were inserted in respective sample holes whose temperature was adjusted to the initial temperature, and then respective sample holes were continuously heated following the programmed straight heating line for a given period. After the time t_c, samples were removed from the holes and immediately in a refrigerator. The samples were then assayed by the same procedure as in the accelerated isothermal storage test described in the previous paper.

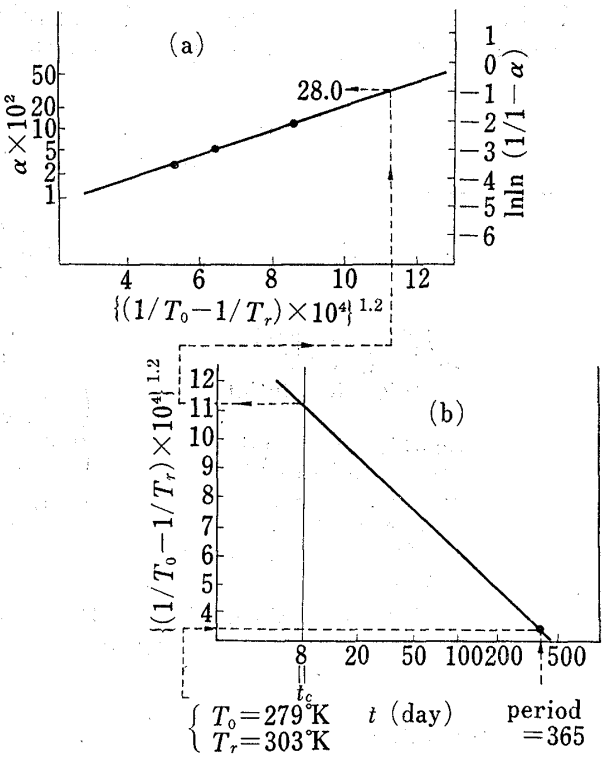

Fig. 7. Graphic Calculation for the Prediction of Degradation Ratio of Ascorbic Acid in Solution Preserved in Room Temperature Cycle

Results

The degradation ratio of respective drugs after a specified period at each level of temperature increase is shown in Table I.

Table I. Degradation Ratio of Respective Drugs by the Multilevel Nonisothermal Programs

Preparation	m[a]	Period (t_c) (day)	Final temp. (T_r-273)	$\{(1/T_0{}^{b)}-1/T_r)\times 10^4\}^{1.2}$	Degradation ratio (%)
Acetylsalicylic acid solution (pH 2.6)	1.0	1	41	5.26	9.5
			48	6.39	15.0
			62	8.57	32.2
Ascorbic acid solution	0.8	8	41	5.26	2.8
			48	6.39	4.4
			62	8.57	10.3
Ascorbic acid-mannitol powder (moisture 2%)	0.5	8	41	5.26	3.5
			48	6.39	4.5
			62	8.57	7.3
Pyridoxal phosphate solution (pH 9.5)	0.9	8	48	6.39	2.4
			62	8.57	5.8
			69	9.63	9.0

a) cited from Table VI of the previous paper[1]
b) $T_0=279°K$

For analysis in the present work, m value obtained in the previous work and storage conditions, such as storage period, and minimum and maximum daily average room temperature of this period, must be given previously. For example, the storage conditions in a warehouse in Tokyo were designated by room temperature cycle, which was already given as the model in Fig. 2. The storage period, and minimum and maximum daily average room temperatures of the storage period of respective drugs are shown in Table II.

Table II. Storage Conditions of Respective Drugs preserved in a Warehouse (Tokyo)

Preparation	Preserved date and period	Min. daily av. room temp. (°C)	Max. daily av. room temp. (°C)
Acetylsalicylic acid solution (pH 2.6)	Feb. 1—Mar. 2 30 days	6	10
Ascorbic acid solution	(Oct. 1—Oct. 1 1 year)	6	30
Ascorbic acid-mannitol powder (moisture 2%)	(Feb. 1—Feb. 1 2 years)	6	30
Pyridoxal phosphate solution (pH 9.5)	(Oct. 1—Oct. 1 1 year)	6	30

Table III. Comparisons of Predicted and Observed Degradation Ratio of Respective Drugs preserved in Room Temperature Cycle

Preparation	Preserved period	Predicted degradation ratio (%)	Observed degradation ratio (%)	Predicted degradation ratio (25°)[a] (%)
Acetylsalicylic acid solution (pH 2.6)	30 days (Feb.)	24.5	25.7	82.6
Ascorbic acid solution	1 year	28.0	28.4	30.4
Ascorbic acid-mannitol powder (moisture 2%)	2 years	16.0	16.7	22.9
Pyridoxal phosphate solution (pH 9.5)	1 year	19.0	21.3	26.5

a) cited from Table VII of the previous paper[1]

From the data in Table I, predicted values of degradation ratio under the storage conditions shown in Table II were determined by graphic calculation according to the procedure of the multilevel nonisothermal method described in the preceding section. For example, graphic calculation and the solution for ascorbic acid solution are shown in Fig. 7.

The values predicted by graphic calculation and the values observed after storage for the same period in a warehouse in Tokyo were in good agreement as shown in Table III. The values predicted at 25° are cited from the previous paper[1] and shown in Table III.

Discussion

From the analysis of meteorological statistics in Japan, atmospheric temperature and room temperature model in a warehouse were obtained. Since these models can be expressed as a straight temperature increase and decrease process, the multilevel nonisothermal method for the prediction of stability of drugs described in the present paper applies by assuming that degradation ratio under the condition of the room temperature cycle is equivalent to the one under the condition of the straight temperature increase process.

The remarkable feature of kinetic analysis in the present paper consists in that kinetics in both nonisothermal and isothermal processes can be approximately combined by eq. (9). Advantages of the present multilevel nonisothermal method are as follows:

(1) It is possible to predict stability of materials preserved at room temperature cycle.

(2) Stability of drugs that shows various degradation types can be predicted by using a rate equation suggested in the previous paper.

(3) Predicted values can be obtained by graphic calculation.

(4) Different temperature gradient can be obtained simultaneously by a newly devised apparatus.

On the other hand, disadvantages are as follows:

(1) Establishment of models for room temperature cycle is difficult due to the difference in atmospheric conditions peculiar to each location, kind of construction of buildings, and room conditions (presence or absence of air conditioning).

(2) In the graphic calculation, large errors may be produced by how a regression line is drawn or by the length of storage period.

(3) The storage period for prediction of stability is limited to yearly unit.

In order to estimate the stability of drugs in actual environmental condition, the trial described in the present paper is expected to be applied widely as a practical and useful means for quality assurance of drugs.

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