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New heating controller and computation for linear heating stability experiment

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Abstract

A digital linear heating controller with pulse counter and a new computation with optimization and Simpson integration for linear heating experiments have been introduced. This controller is simple, reliable and inexpensive. Its temperature range is 0–97°C for the water bath or 0–200°C for the oven. The accuracy and precision of temperature are ≤ 0.5°C at 0–100°C or $\leq 1\%$ at 100–200°C; the resolution is ± 0.1°C; the fluctuation is ± 0.1°C for the water bath or ≤ 0.5°C for the oven; and time is accurate to ≤ 5 s per month. Comparison of new and conventional computations is discussed. The results indicate that there is no approximation in the new computation and, therefore, that the deficiencies of the conventional computation have been overcome.

Keywords: Linear heating; Pulse counter; Optimization; Simpson integration

1. Introduction

Studies of the stability of drugs with linear heating experiments began in the 1960s (Okusa and Kinuno, 1968). In comparison with classic isothermal experiments, linear heating experiments can save time, labor and drugs. However, there were limitations in conventional computation in linear heating experiments which reduced the accuracy of the experimental results. Moreover, in the conventional programmed heating controller (Eriksen and Bird, 1965), the accuracy and regulation of temperature could not be expected to be very satisfactory owing to its use of the motor, gears, cam and mercury thermoregulator. These limitations make the application of linear heating experiments in stability studies of drugs rather difficult.

In our study, a digital linear heating controller was used for conducting the linear heating experiment. In the controller, an IC thermal sensor was used for temperature measurement; a quartz oscillator, a pulse counter and a D/A converter were applied to yield a linearly increased standard voltage, which was amplified and then used to control an common thermostat through a solid-state relay (SSR) in order to achieve a linear temperature increase. There is no motor, gear, cam, mercury thermoregulator or mechanical relay as in other known programmed heating controllers. Therefore, our controller is simple,

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reliable and inexpensive. Its temperature range is 0–97°C for the water bath or 0–200°C for the oven. The accuracy and precision of temperature are ≤ 0.5°C at 0–100°C or $\leq 1\%$ at 100–200°C; the resolution is ± 0.1°C; the fluctuation is ± 0.1°C for the water bath or ≤ 0.5°C for the oven; and time is accurate to ≤ 5 s per month.

The stability of a vitamin C tablet was studied and its shelf-life was predicted from the linear heating experiment. The surface reflectance of the vitamin C tablet was measured via diffuse reflectance spectrophotometry to evaluate the degradation of the tablet.

Through our study, a new computation with optimization and Simpson integration for linear heating experiments has been introduced. Comparison of the new and conventional computation is discussed; the results indicate that there is no approximation in the new computation. Therefore, the limitations of the conventional computation have been overcome.

2. Experimental

2.1. Drugs and reagents

Vitamin C tablets (100 mg per tablet) were prepared by our department. $BaSO_4$ was A.R. grade.

2.2. Instruments and devices

The following apparatus was used: a UV spectrophotometer with integrating sphere assembly (UV-240, Shimadzu Co., Japan), digital linear heating controller, and a nitrogen filled mercury thermometer (0–100°C, graduation 0.1°C, used as temperature standard; Arthur H. Thomas Co., U.S.A.).

2.3. Principles of temperature controlling

The assembly of the linear heating controller is shown in Fig. 1. The principle of the controller is explained as follows.

In the heating controller, a quartz oscillator was used to yield a continuous and highly accurate pulse signal; the pulse was divided by a variable frequency divider and then counted by a pulse counter. As a result, a uniformly increased digital number was sent to the counter. A D/A converter was used to convert the number into an increased analogue step voltage, the standard voltage in our heating controller. If the number of the steps is large enough ($2^{12} = 4096$ in our heating controller), the step size will be smaller than the resolution of temperature. Therefore, this step voltage can be thought of as a linearly increased voltage. The rate of temperature in-

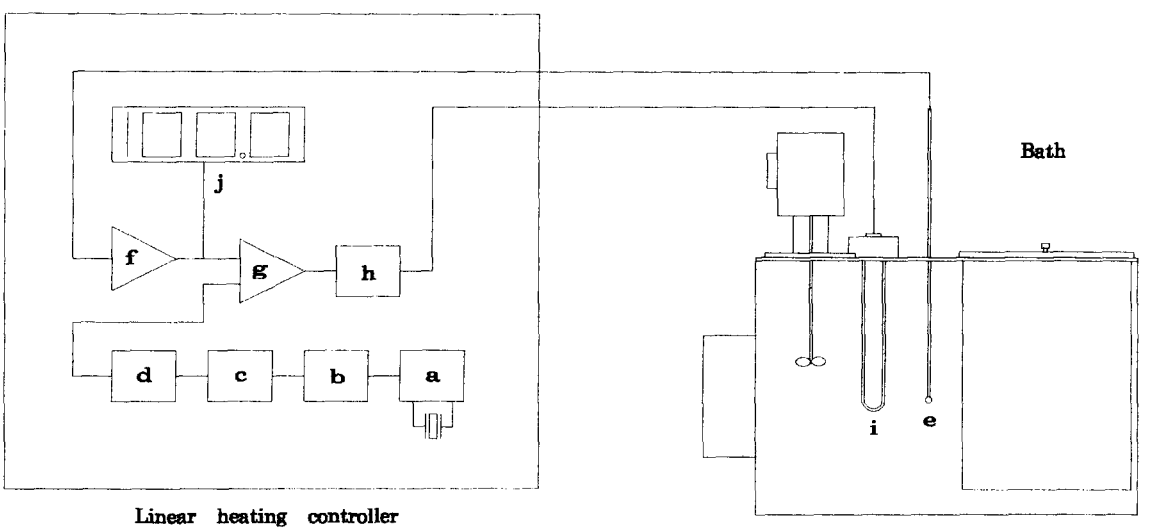

Fig. 1. Assembly of the linear heating controller. (a) Quartz oscillator, (b) frequency divider, (c) pulse counter, (d) D/A converter, (e) thermal sensor, (f) amplifier, (g) comparator, (h) solid-state relay, (i) heater, (j) temperature display.

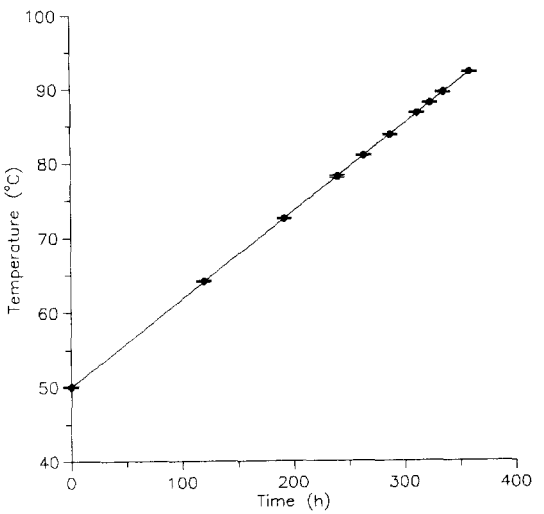

Fig. 2. Temperature line of linear heating accelerated experiment. $T = T_0 + at$; $T_0 = 323.15$ K; $a = 0.1171875$ K/h.

crease can be changed by altering the frequency dividing times and the initial temperature can be modified by changing a preset number in the pulse counter.

An IC temperature sensor was sealed with epoxy resin and immersed into the thermostat to linearly convert temperature to voltage. The temperature voltage was amplified by an amplifier and then compared with the linearly increased standard voltage in a comparator. The heater in the common thermostat (either the water bath or the oven) was controlled by a solid-state relay (SSR) in accordance with the result obtained from the comparison. Therefore, the temperature could be linearly increased according to the precisely linearly increased standard voltage. A digital voltmeter was used to measure the amplified temperature voltage and display the temperature.

2.4. Experiment

The temperature curve and heating parameters are depicted in Fig. 2.

10 vitamin C tablets were placed in an ampoule and sealed. The ampoules were placed in the linear heating water bath at the beginning of the experiment. Four ampoules were taken out of the water bath at each suitable interval. The surface reflectance of the tablet was measured at a wavelength of 440 nm via diffuse reflectance spectrophotometry to evaluate the degradation of the tablet (Sun et al., 1992).

3. Computation

A nonfractional order chemical reaction can be described by some form of the general equation:

$$f(c) = -\int_0^t k \, dt + f(c_0) \tag{1}$$

where k is the observed rate constant, t denotes the time, and $f(c)$ is the concentration function, which depends on the reaction order. For zero-, first- and second-order reactions, $f(c)$ is c, $\ln c$ and $1/c$ or $[1/(c_{B,0} - c_{A,0})] \cdot \ln[c_{B,0}c_A/(c_{A,0}c_B)]$, respectively.

Combining Eq. 1 with the Arrhenius equation $k_{(T)} = k_{298.15} \cdot \exp[(E/R) \cdot (1/298.15 - 1/T)]$ and the linear temperature-time relationship $T = T_0 + at$, yields:

$$f(c) = -\int_0^t k_{298.15} \exp\{(E/R)[1/298.15 - 1/(T_0 + at)]\} \, dt + f(c_0) \tag{2}$$

The integral function on the right-hand side of the above equation can be proved to be a non-integratable function. Therefore, Simpson integration is applied to compute the integral. Since the function to be integrated contains an unknown E, observed activation energy, we need to assume an E in a suitable range in order to carry out the integration. If the E is assumed correctly, then $k_{298.15}$ will be a constant and can be taken out of the integration, which then yields:

$$f(c) = -k_{298.15}\int_0^t \exp\{(E/R)[1/298.15 - 1/(T_0 + at)]\} \, dt + f(c_0) \tag{3}$$

According to Eq. 2, A straight regression line can be obtained from a plot of the concentration function $f(c)$ vs the integration $-\int_0^t \exp\{(E/R) \cdot [1/298.15 - 1/(T_0 + at)]\} \, dt$ with intercept $f(c_0)$ and slope equal to $k_{298.15}$.

If E is assumed incorrectly, then $k_{298.15}$ will not be a constant and cannot be taken out of the integration; thus, the line will be curved and the correlation coefficient r will be reduced.

If a group of different assumed Es within a definite range are evaluated using Eq. 2, a group of regression lines with different correlation coefficients r can be obtained. The higher the correlation coefficient r is, the closer the assumed E will be to the real E. Therefore, the E which gives the highest r is the best estimate of real E. In addition, the rate constant $k_{298.15}$ can be obtained from the slope of this regression. To reduce the computation times, optimization is applied. The computation times depend on the range of assumed E and the expected accuracy. If the range of assumed E is 100 kJ/mol, the accuracy can be < 1 J/mol after 24 computation iterations. Since the computation is too complex to be completed manually, a PC-1500 pocket computer was programmed to complete the whole computation automatically.

4. Data treatment and results

The experiment showed that during the degradation of vitamin C tablets, the color of the tablet changed significantly more than the concentration of vitamin C; the discoloration of the tablet, evaluated with the change of the surface reflectance R_t of the tablet, obeyed first-order kinetics $\ln R_t = -kt + \ln R_0$ (Sun et al., 1992); in addition, when the R_t of the tablet was decreased to 70%, the absorbance of its solution would be about 0.07, the limitation of expiration of the tablet according to the Chinese Pharmacopoeia (1990). Therefore, in our experiment, the degradation of the vitamin C tablet was evaluated based on the surface reflectance R_t; the concentration function was $\ln R_t$; and the shelf-life of the tablet was determined using $R_t = 70\%$ as the expiration limit.

The results of the linear heating experiment are listed in Table 1. The data in Table 1 were analyzed using Eq. 3. The maximum linear correlation coefficient r was 0.9988 when the assumed activation energy E was 94.91 kJ/mol. The linear relationship between $\ln R_t$ and $-\int_0^t \exp\{(E/R)[1/298.15 - 1/(T_0 + at)]\}\,dt$ under these conditions is shown in Fig. 3. Within the E range of 50–150 kJ/mol, the relationship between the correlation coefficient r and the assumed E is shown in Fig. 4, in which a significant peak in the $r - E$ curve can be seen.

From the slope and the intercept of the regression line in Fig. 3, $k_{298.15} = (4.307 \pm 0.074) \times 10^{-6}$ h^{-1} (estimated value $\pm$ SD) and $\ln R_0 = -0.09601 \pm 0.0043$ (estimated value $\pm$ SD) were

Table 1
Data from linear heating accelerated experiment ($E = 94.91$ kJ/mol)

Time (h)	Temperature (°C)	R_t (%)	$-\int_0^t \exp\{(E/R)\cdot[1.298.15 - 1/(T_0 + at)]\}\,dt$ (h)	$\ln R_t$
0	50.0 ± 0.1 [a]	90.87 ± 0.95 [b]	0	−0.09754
120	64.1 ± 0.1	89.14 ± 0.57	−5350	−0.11496
192	72.5 ± 0.1	84.77 ± 0.93	−14824	−0.16523
240	78.1 ± 0.1	80.55 ± 1.49	−27033	−0.21629
264	80.9 ± 0.1	78.27 ± 1.25	−35990	−0.24501
288	83.7 ± 0.1	73.28 ± 1.31	−47561	−0.31088
312	86.6 ± 0.1	70.39 ± 1.19	−62447	−0.35112
324	88.0 ± 0.1	67.10 ± 1.02	−71399	−0.39899
336	89.4 ± 0.1	63.32 ± 0.86	−81524	−0.45697
360	92.2 ± 0.1	57.60 ± 0.80	−105877	−0.55165

[a] Mean ± fluctuation range.
[b] Mean ± SD of four experiments.

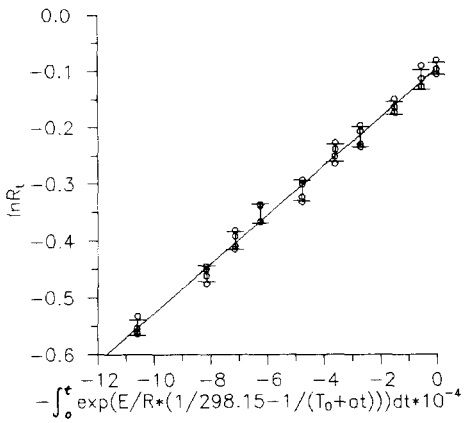

Fig. 3. Regression line of new computation of linear heating accelerated experiment when $E = 94.91$ kJ/mol.

obtained respectively. The shelf-life of the vitamin C tablet could be predicted as:

$$t_{0.7} = (\ln R_0 - \ln 0.7)/k_{298.15} = 60\,523 \text{ h}$$
$$= 6.9 \text{ years}$$

In comparison, the activation energy of the vitamin C tablet was determined to be 94.4 and 95.1 kJ/mol and the shelf-life was predicted to be 6.7 and 7.1 years using reciprocal heating (Zhan et al., 1995) and logarithmic heating experiments, respectively. These results are comparable to those of our linear heating experiment. Moreover, all the predicted results of the above experiments are also comparable to those of long-term storage testing.

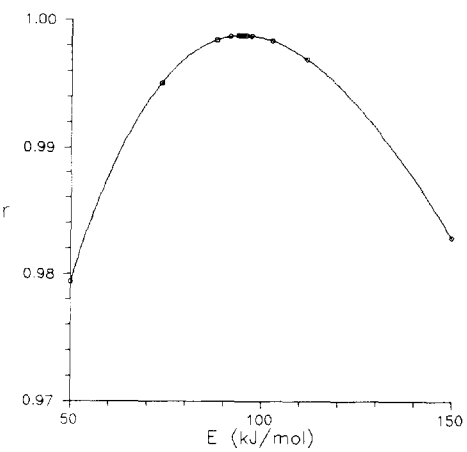

Fig. 4. Relationship between correlation coefficient and assumed activation energy.

5. Discussion

In the conventional computation of linear heating (Okusa and Kinuno, 1968), the temperature-time relationship, $T = T_0 + at$, could be approximately substituted by $1/T_0 - 1/T = a' \ln(1 + bt)$. In addition, the restriction $k_t \gg k_0$ led to the following equation:

$$f(c) = -k_0 \int_0^t \exp\{(E/R)[1/T_0 - 1/(T_0 + at)]\}\, dt + f(c_0)$$

which can be solved easily, and can then be rearranged as:

$$\ln[f(c_0) - f(c_t)] = (1 + Ea'/R) \ln(1 + bt) + \ln k_0 - \ln[b(1 + Ea'/R)]$$

where the constant a' is $1/T_0$, and the constant b can be determined by using a mean temperature T and the corresponding time t in the equation $1/T_0 - 1/T = a' \ln(1 + bt)$. The above equation represents a straight line for plots of $\ln[f(c_0) - f(c_t)]$ vs $\ln(1 + bt)$, the slope and the intercept of which are $(1 + Ea'/R)$ and $\ln k_0 - \ln[b(1 + Ea'/R)]$, respectively. Also, in our experiment, $f(c_0)$ and $f(c_t)$ were $\ln R_0$ and $\ln R_t$, respectively.

The deficiencies of the conventional computation method for linear heating experiments are that all the restrictions and approximations expressed above are untenable when the temperature is low at the beginning of the experiment. Therefore, the regression line will be curved. For this reason, some data at the beginning of the experiment should be abandoned, and the result of the computation thus depends on the time of abandonment.

As a comparison, the data in Table 1 were treated with the conventional computation of linear heating experiment, the regression line being shown in Fig. 5. When the first datum of the

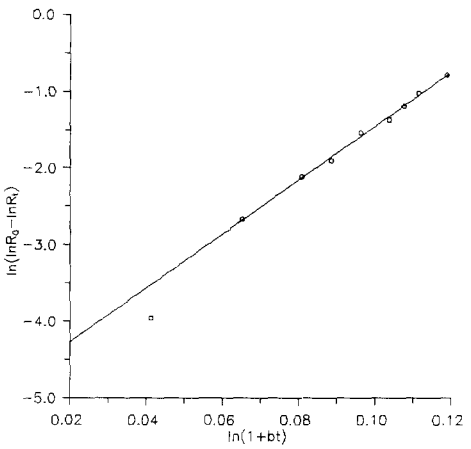

Fig. 5. Regression line of ordinary computation of linear heating accelerated experiment.

experiment was abandoned, the shelf-life at room temperature was 6.1 years. However, when all the data were kept, the shelf-life was 12.1 years, almost twice as much as above.

In our new computation with optimization and Simpson integration for linear heating experiments, there is no approximation. Therefore, the deficiencies of the conventional computation are overcome and the result is more accurate and reliable. When a computer is used, the large amount of computing work required by the new computation becomes manageable.

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