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Computer-controlled heating system and new computation for reciprocal heating stability experiment

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Abstract

A computer-controlled heating system and a new computation with optimization for reciprocal heating experiment have been introduced. In the heating system, a pocket computer was used to control a common thermostat to obtain different heating models. This system 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 in the range 0–100°C or $\leq 1\%$ in the range 100–200°C; the resolution is 0.05°C; the fluctuation is 0.05°C for the water bath or ≤ 0.5°C for the oven; and time is accurate to ≤ 5 s per month. A comparison of the new and conventional computations is discussed. The results indicate that the deficiencies of the conventional computation have been overcome.

Keywords: Reciprocal heating; Optimization; Computation

1. Introduction

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

In recent years, computers have been widely used in many fields, however, they have been infrequently employed in temperature control for stability experiments. The present authors introduced a computer-controlled heating system and its simplified program flow diagram. In this system, a pocket computer is used to control a common thermostat to obtain different heating models. There is no motor, gear, cam, mercury thermoregulator or mechanical relay as in other known programmed heating controllers. There-

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fore, our system 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 in the range 0–100°C or $\leq 1\%$ in the range 100–200°C; the resolution is 0.05°C; the fluctuation is 0.05°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 based on the reciprocal 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 for the reciprocal heating experiment has been introduced. Comparison of the new and conventional computation is discussed; the results indicate that 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), pocket computer with digital assistant (PC-1500, Sharp Co. Japan), thermostat (CS-501, Chongqing, China), thermal sensor (a silicon transistor was used as the substitute), A/D converter (self-made with a CMOS integrated circuit ICL7109), photo-controlled triac (20 A, 600 V), 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. Computer-controlled heating system

2.3.1. Principle of temperature control

The assembly of the computer controlled heating system is shown in Fig. 1. The principle of the heating system is explained as follows.

A thermal sensor is sealed with epoxy resin and immersed into the thermostat to convert temperature to voltage. A very small non-linearity in the temperature-voltage conversion can be compensated in the computer programme. A CMOS A/D converting integrated circuit is used to convert the analog temperature voltage to digital and put it into the PC-1500 pocket computer.

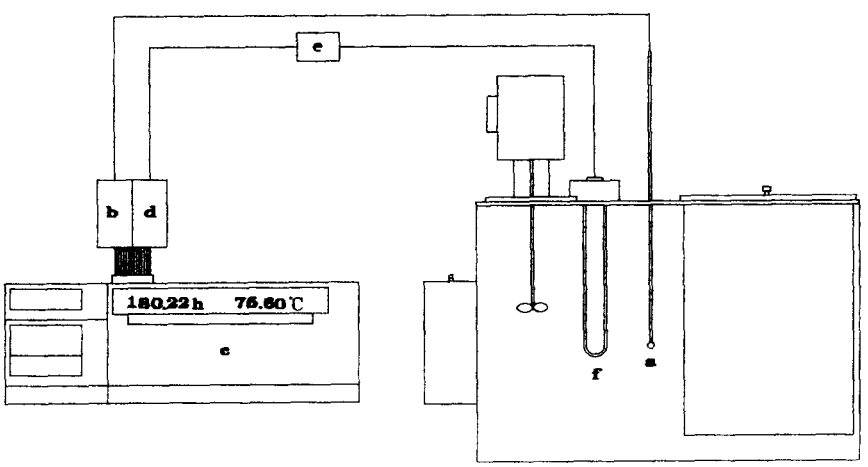

Fig. 1. Computer-controlled heating system. (a) Thermal sensor, (b) A/D converter, (c) computer, (d) D/A converter, (e) photo-controlled triac, (f) heater.

The computer is used to: (a) compensate the small non-linearity in the temperature-voltage conversion; (b) count time; (c) compute the temperature according to the heating model; (d) decide the heating power with the difference of the measured and computed temperature; (e) display time, computed temperature, measured temperature and a sign '*' to show whether or not the heater is working. A photo-controlled triac is used to conduct the heating power control.

2.3.2. Calibration of temperature

To compensate the small non-linearity in temperature voltage conversion, a temperature calibration is required when the system is first assembled or the thermal sensor is changed.

A nitrogen filled mercury thermometer, used as a temperature standard, is immersed into the bath close to the thermal sensor. Within the range 0–100°C and at an interval of about 5°C, the temperatures, measured with both the mercury thermometer and the computer, are read and put into the temperature control programme via data instruction. When running the programme, the computer can automatically compensate the small non-linearity according to the data of the temperature calibration.

2.3.3. Temperature control programme

The pocket computer is programmed in BASIC language. A simplified flow diagram of the temperature control programme is shown in Fig. 2. When the computer runs the programme, three kinds of heating model: (a) linear heating $T = T_0 + at$; (b) reciprocal heating $1/T_0 - 1/T = at$; and (c) logarithm heating $1/T_0 - 1/T = a\ \ln(1 + t)$ can be selected. It is also easy to put another heating model into the temperature control programme whenever it is needed. The time, computed temperature, measured temperature and

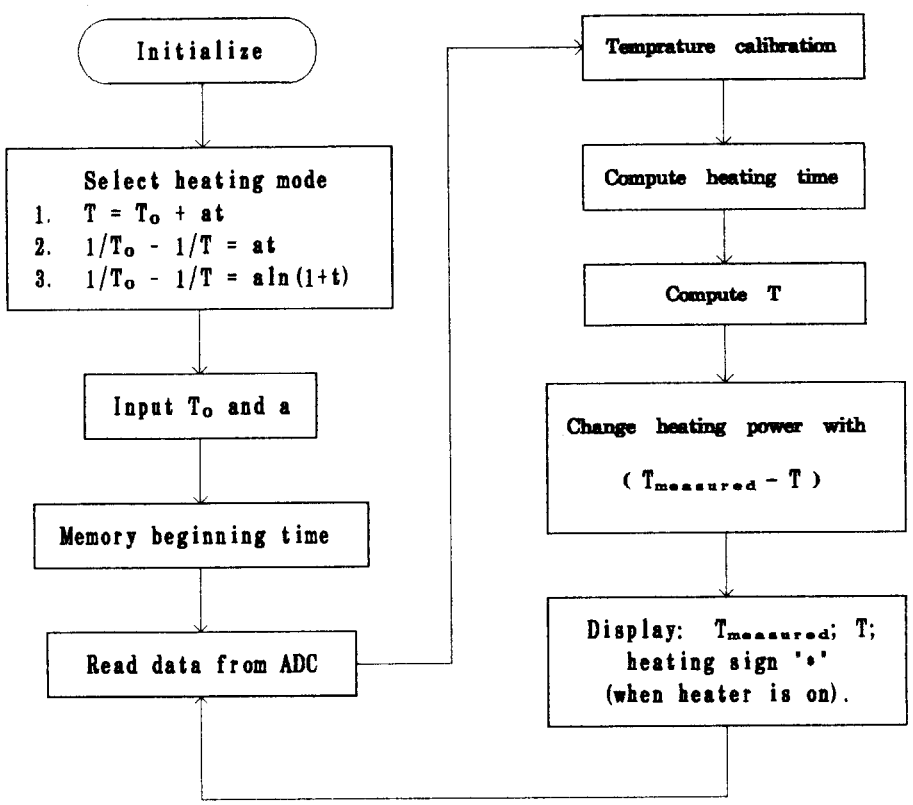

Fig. 2. Simplified flow diagram of the heat control program.

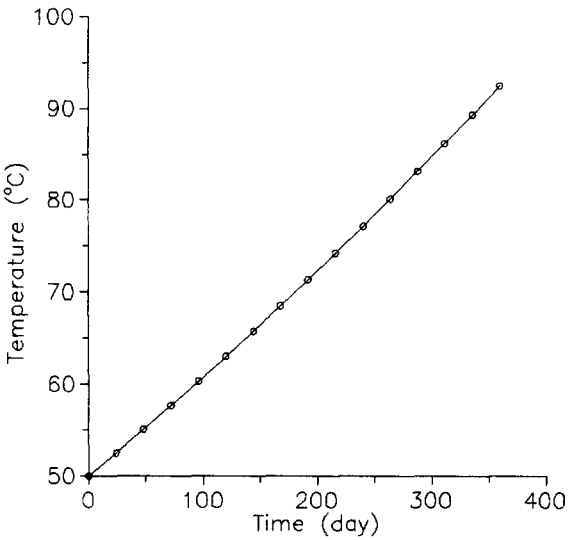

Fig. 3. Reciprocal heating curve. $1/T_0 - 1/T = at$; $T_0 = 323.15$ K; $a = 10^{-6}$ K^{-1} h^{-1}.

heating sign '*', showing whether or not the heater is working, will be shown on the liquid crystal panel of the computer. A self-consult subroutine in the programme can consult the troubles of the thermal sensor, A/D converter and their connections.

2.4. Experiment

The temperature curve and the reciprocal heating parameters are shown in Fig. 3.

10 vitamin C tablets were placed into an ampoule and sealed; the ampoules were placed into the reciprocal 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 the wavelength 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:

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

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 $k_{(T)} = k_0 \cdot \exp[(E/R) \cdot (1/T_0 - 1/T)]$ and the reciprocal temperature-time relationship $1/T_0 - 1/T = at$, yields:

$$f(c) = -\int_0^t k_0 \exp(Eat/R)\,dt + f(c_0) \qquad (2)$$

where c_0, T_0 and k_0 are the initial concentration, initial temperature and initial rate constant, respectively.

The k_0 is a constant and can be taken out of the integration. After integrating, Eq. 2 can be expressed as:

$$f(c) = k_0 \cdot R/(Ea) \cdot [1 - \exp(Eat/R)] + f(c_0) \qquad (3)$$

According to Eq. 3, a straight line can be obtained from a plot of the concentration function $f(c)$ vs $R/(Ea) \cdot [1 - \exp(Eat/R)]$ with intercept $f(c_0)$ and slope equal to k_0.

Since E, the observed activation energy, is unknown, we need to assume an E in a suitable range in order to carry out the regression.

If the E is assumed incorrectly, then k_0 will not be a constant and cannot be taken out of the integration and Eq. 3 will be untenable; 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. 3, 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 the real E. In addition, the initial rate constant k_0 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 the assumed E and the expected accuracy. If the range of the assumed E is 100 kJ/mol, the accuracy can be < 1 J/mol after 24 computation iterations. Since the computation is too com-

plex to be completed manually, a PC-1500 pocket computer is programmed to complete the whole computation automatically.

4. Data treatment and results

It was reported (Sun et al., 1992) 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 (440 nm) of the tablet, obeyed first-order kinetics $\ln R_t = -kt + \ln R_0$; in addition, when the R_t of the tablet was decreased to 70%, the absorbance (440 nm) of its solution was about 0.07, the expiration limit 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 (440 nm); 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 reciprocal heating experiments are listed in Table 1. The data in Table 1 were analyzed using Eq. 3. The maximum linear correlation coefficient r is 0.9981 when the assumed activation energy E is 94.35 kJ/mol. The linear relationship between $\ln R_t$ and $R/(Ea)\cdot[1-\exp(Eat/R)]$ under this condition is shown in Fig. 4. Within the E range of 50–150 kJ/mol, the relationship between the correlation coefficient r and the assumed activation energy E is shown in Fig. 5, in which a significant peak in the r-E curve can be seen.

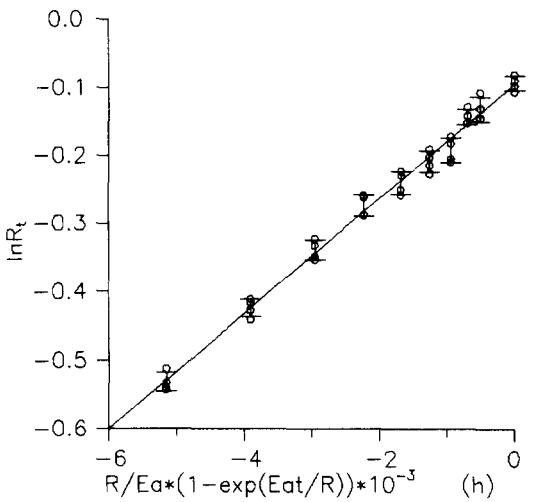

Fig. 4. Regression line of new computation of reciprocal heating accelerated experiment when $E = 94.35$ kJ/mol.

From the slope and intercept of the regression line in Fig. 4, $k_0 = (8.396 \pm 0.184) \times 10^{-5}$ h^{-1} (estimated value ± SD) and $\ln R_0 = -0.09592 \pm 0.00455$ (estimated value ± SD) were obtained, respectively.

The $k_{25°C}$ could be obtained from the Arrhenius equation:

$$k_{25°C} = \exp[\ln k_0 - (E/R) \cdot (1/298.15 - 1/323.15)] = 4.419 \times 10^{-6} h^{-1}$$

Table 1
Data from the reciprocal heating stability experiment ($E = 94.34$ kJ/mol)

Time (h)	Temperature (°C)	R_t (%)	$R/(Ea)\cdot[1-\exp(Eat/R)]$ (h)	$\ln R_t$
0	50.00	90.87 ± 0.95 [a]	0	−0.09574
168	68.55	87.61 ± 1.57	−504.8	−0.13228
192	71.38	86.68 ± 0.93	−690.4	−0.14295
216	74.25	82.51 ± 1.49	−934.2	−0.19225
240	77.17	81.19 ± 1.25	−1254.2	−0.20838
264	80.14	78.67 ± 1.31	−1674.3	−0.23991
288	83.16	76.06 ± 1.19	−2226.0	−0.27365
312	86.23	71.24 ± 1.02	−2950.5	−0.33912
336	89.36	65.50 ± 0.86	−3901.6	−0.42312
360	92.54	58.79 ± 0.82	−5150.5	−0.53120

[a] Mean ± SD of four experiments

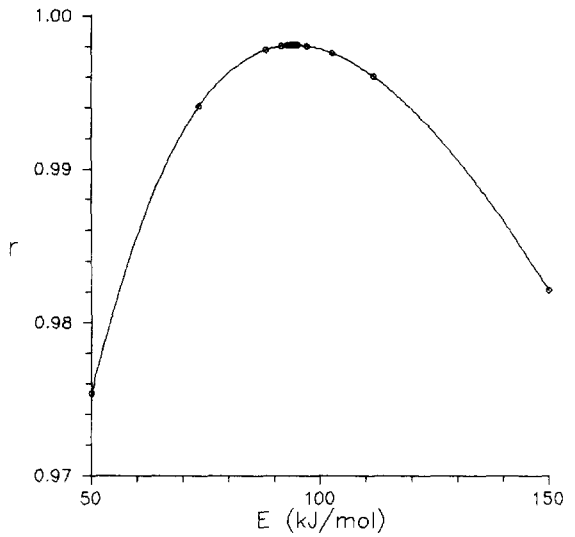

Fig. 5. Relationship between correlation coefficient and assumed activation energy.

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

$$t_{0.7} = (\ln R_0 - \ln 0.7)/k_{25°C}$$
$$= 59003 \text{ h} = 6.74 \text{ years}$$

In comparison, the activation energy of the vitamin C tablet was determined to be 94.9, 95.1 and 96.6 kJ/mol, and the shelf-life was predicted to be 6.9, 7.1 and 7.7 years using linear heating (Zhan et al., 1995), logarithmic heating (Zhan et al., unpublished data) and flexible heating (Zhan et al., unpublished data) experiments, respectively. These results are comparable to those of our reciprocal heating experiment. Moreover, all the predicted results of the above experiments are also comparable to those of long-term storage testing.

5. Discussion

In the conventional computation of reciprocal heating (Eriksen and Stelmach, 1965), in order to facilitate Eq. 3 carrying out the regression (there were some positive and negative sign mistakes in this and some of the succeeding equations in the original article, which have been corrected in the present paper), it was rearranged as:

$$f(c_t) - f(c_{t+\Delta t}) = [k_0 R/(Ea)] \cdot \exp(Eat/R) \cdot [\exp(Ea\Delta t/R) - 1]$$

or

$$\ln[f(c_t) - f(c_{t+\Delta t})] = Eat/R + \ln\{[k_0 R/(Ea)] \cdot [\exp(Ea\Delta t/R) - 1]\}$$

This equation represents a straight line for plots of $\ln[f(c_t) - f(c_{t+\Delta t})]$ vs time t provided a constant time interval (Δt) is maintained. The slope and intercept are Ea/R and $\ln\{[k_0 R/(Ea)] \cdot [\exp(Ea\Delta t/R) - 1]\}$, respectively. In our experiment, $f(c_0)$ and $f(c_t)$ are ln R_0 and ln R_t, respectively.

The deficiencies of the conventional computation method for reciprocal heating experiment are that a constant time interval (Δt) must be maintained and the concentration functions should be arranged as the differences, $[f(c_t) - f(c_{t+\Delta t})]$, between the adjacent time t and $t + \Delta t$. Usually, in drug stability studies, the entire experiment is in the initial stage of the degradation. If a large number of the experimental points are arranged in this stage, the time interval will be very small and the concentration data will be very close together, especially at the beginning of the experiment while the temperature is low. Therefore, the relative error of the concentration function difference will be very large even if the measurements of the concentrations are quite accurate. That will reduce the correlativity of the data and the correlation coefficient r of the straight line. It is difficult to improve the accuracy simply by increasing the interval because very few of the experimental points can be arranged in the initial stage if the interval becomes large.

As a comparison, the data in Table 1 were treated with the conventional computation, the result being shown in Fig. 6. The observed activation energy and the shelf-life at room temperature of the vitamin C tablet can be determined as $E = 95.44$ kJ/mol and $t_{0.7} = 7.48$ years, respectively. This result is comparable to that of our new computation; however, it is much less reli-

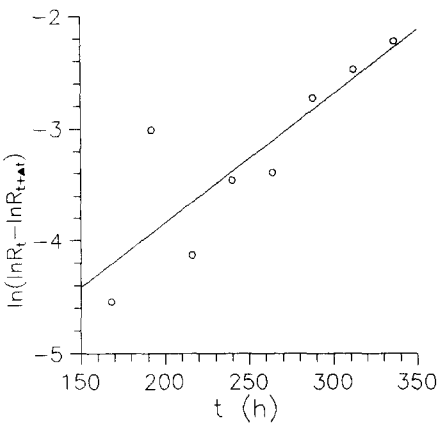

Fig. 6. Regression line of ordinary computation of reciprocal heating accelerated experiment.

able than that of our new computation because of its low correlativity of data and low correlation coefficient ($r = 0.8439$).

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