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A computer-controlled temperature recording system and a new computation system for flexible heating stability experiments

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Abstract

A computer-controlled temperature recording system and a new computation with optimization for flexible heating stability experiments are introduced. In the temperature recording system, a pocket computer was used to measure and record the temperature. This system is simple, reliable and inexpensive. Its temperature range is 0–97°C for a water bath or 0–200°C for an oven. The accuracy and precision of temperature is ≤ 0.5°C in the range 0–100°C or $\leq 1\%$ in the range 100–200°C; the resolution is 0.05°C; and the time is accurate to ≤ 5 s per month. A comparison of the new and conventional computations was discussed. Results indicate that the new computation is simple, clear and accurate. There is no approximation in the new computation; the deficiencies of conventional computation therefore are overcome. Both the temperature recording and the computation can be completed using an inexpensive pocket computer.

Keywords: Flexible heating experiment; Optimization

1. Introduction

Studies of drug stabilities with flexible heating experiments began in the 1970s (Maulding and Zoglio, 1970; Madsen et al., 1974). In comparison with the classic isothermal experiment or the programmed heating experiment, the most important advantage of the flexible heating experiment is that the temperature does not need to be controlled rigidly. Usually, drug stability experiments require days or months to be completed. If any trouble with the heating system or power failure happens during the long period of the experiments, all the previous efforts will be wasted. This kind of trouble is rather common in developing countries. In flexible heating experiments, the temperature is recorded instead of controlled, and neither heating trouble nor power failure can disturb the experiments provided the computer is battery operated. However, there have been limi-

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tations in the conventional computation in flexible heating experiments which reduced the accuracy of the experimental results. Besides, the reported flexible heating devices were too complicated and expensive. These limitations made the application of flexible heating experiments in drug stability studies rather difficult.

In our study, a pocket computer temperature recording system was used to conduct the flexible heating experiment. This system is simple, reliable and inexpensive. Its temperature recording range is 0–97°C for a water bath and 0–200°C for an oven. The accuracy and the precision of temperature are ≤ 0.5°C in the range 0–100°C and $\leq 1\%$ in the range 100–200°C; the temperature resolution is 0.05°C, and time is accurate to ≤ 5 s per month.

The stability of a vitamin C tablet was studied and its shelflife was predicted using the flexible heating experiment. The surface reflectance of the vitamin C tablet was measured via diffuse reflectance spectrophotometry to evaluate the degradation of the tablet.

In this study, a new computation with optimization for flexible heating experiments is introduced; a comparison of the new and conventional computation systems is discussed. The results indicate that the new system is simple, clear and accurate. There is no approximation in the new computation; therefore, the deficiencies of the conventional computation are overcome. Both temperature recording and computation can be completed using an inexpensive pocket computer.

2. Experimental

2.1. Drugs and reagents

Vitamin C tablets (100 mg per tablet, prepared by our department) and $BaSO_4$ (A.R.) were used for this study.

2.2. Instruments and devices

The equipment used in this study was: a UV-spectrophotometer with integrating sphere assembly (UV-240, Shimadzu Co., Japan); a pocket computer with digital assistance (PC-1500, Sharp Co. Japan); a thermostat (CS-501, Chongqing, China); a thermal sensor (a silicon transistor was used as a substitute); an A/D converter (self-made with a CMOS integrated circuit ICL7109); a nitrogen-filled mercury thermometer (0–100°C, graduation 0.1°C, used as temperature standard, Arthur H. Thomas Co., USA).

2.3. Temperature recording system

2.3.1. Principle

The assembly of the temperature recording system is shown in Fig. 1. The principle of the 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 for by the computer program. A CMOS A/D converting integrated circuit is used to convert the temperature-voltage analog into digital form and feed it into the PC-1500 pocket computer. The computer is used to: (a) compensate for the small non-linearity in the temperature-voltage conversion; (b) count time; (c) record temperature at definite time intervals; and (d) display the time, temperature and number of temperatures recorded.

2.3.2. Temperature calibration

To compensate for 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 temperature standard, is immersed into the bath adjacent to the thermal sensor. Within the temperature range 0–100°C, at intervals of about 5°C, the temperatures, measured with both the mercury thermometer and the computer, are read and input to the temperature recording program via DATA instruction. When running the program, the computer can automatically compensate for the small non-linearity according to the data of the temperature calibration.

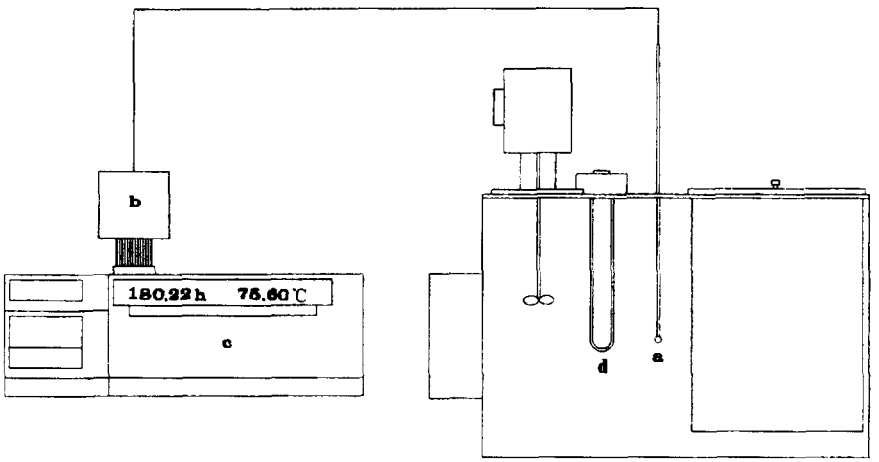

Fig. 1. The temperature recording system. (a) Thermal sensor; (b) A/D converter; (c) computer; (d) heater.

2.4. Experiment

Ten vitamin C tablets were placed into an ampule and sealed; the ampules were placed into a flexible heating water bath at the beginning of the experiment. The temperature was gradually increased from about 50 to 95°C over 15 days. The power to the thermostat was deliberately turned off twice to simulate a power failure (the computer was battery operated). During the experiment, a total of 4321 temperature values were recorded (at 5-min intervals) by the computer. The temperature-time curve is shown in Fig. 2. Four ampules were taken out of the water bath at each suitable interval. The surface reflectance of the tablet was measured at wavelength 440 nm using 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:

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

where k is the observed rate constant, t is 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, $k_{(T)} = k_{25°C}\cdot\exp[(E/R)(1/298.15 - 1/T)]$, yields:

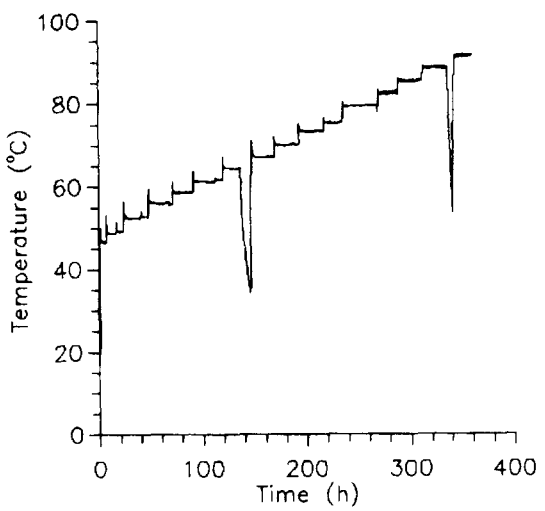

Fig. 2. The flexible temperature rising curve.

$$f(c) = -\int_0^t k_{25°C}\exp[(E\ R)(1\ 298.15 - 1\ T)]dt + f(c_0)$$

It is difficult to accurately express the temperature-time relationship in the flexible heating experiment with a 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 within a suitable range in order to carry out the integration.

If the E is assumed correctly, then $k_{25°C}$ will be a constant and can be taken out of the integration, which then yields:

$$f(c) = -k_{25°C}\int_0^t \exp[(E\ R)(1\ 298.15 - 1\ T)]dt + f(c_0) \quad (2)$$

According to Eq. (2), a straight regression line can be obtained from a plot of the concentration function $f(c)$ versus the integration $-\int_0^t \exp[(E\ R)(1\ 298.15 - 1\ T)]dt$ with intercept $f(c_0)$ and slope equals $k_{(25°C)}$.

If E is assumed incorrectly, then $k_{(25°C)}$ 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 E values 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 $k_{25°C}$ can be obtained from the slope of this regression.

To reduce 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 computation automatically.

Table 1
Data from flexible heating stability experiment ($E = 96.64$ kJ mol)

Time (h)	R_t (%)	$f(t)^a$ (h)	$\ln R_t$
0	90.87 ± 0.95[b]	0	−0.09574
120	89.10 ± 1.57	−5090	−0.11541
192	86.03 ± 0.93	−13675	−0.15047
240	82.13 ± 1.49	−26446	−0.19687
264	78.70 ± 1.25	−36403	−0.23953
288	75.45 ± 1.31	−48849	−0.28170
312	70.20 ± 1.19	−65889	−0.35382
324	67.94 ± 1.02	−77238	−0.38655
336	64.32 ± 0.86	−88731	−0.44130
348	63.11 ± 0.80	−97058	−0.46029
360	58.83 ± 0.97	−111672	−0.53052

[a] $f(t) = -\int_0^t \exp[(E\ R)\cdot(1\ 298.15 - 1\ T)]dt$.
[b] Mean ± S.D. of four experiments.

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 would be about 0.07, the expiration limit of the tablet allowed by the Chinese Pharmacopoeia (1990). Therefore, in our experiment, the degradation of the vitamin C tablet was evaluated by the surface reflectance R_t (440nm); the concentration function was $\ln R_t$; and the shelflife of the tablet was determined using $R_t = 70\%$ as the expiration limit.

The results of the flexible heating experiment are shown in Table 1. These data were analyzed using Eq. (2). The maximum linear correlation coefficient r was 0.9995 when the assumed activation energy E was 96.64 kJ mol. The linear relationship between $\ln R_t$ and $-\int_0^t \exp[(E\ R)(1\ 298.15 - 1\ T)]dt$ 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.

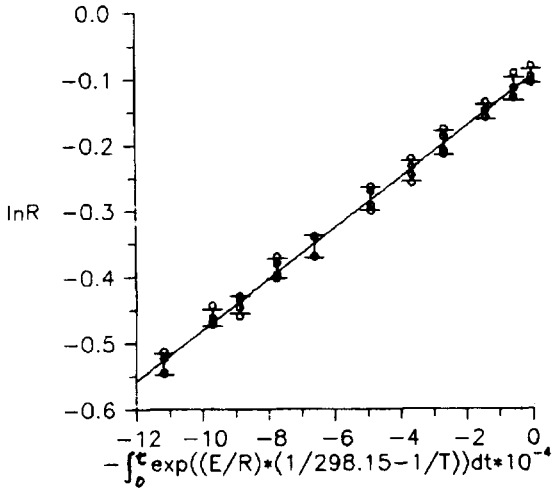

Fig. 3. Regression line of flexible heating stability experiment when E = 96.64 kJ mol.

From the slope and the intercept of the regression line in Fig. 3, $k_{25°C} = (3.837 \pm 0.039) \cdot 10^{-6}$ h^{-1} (estimated value ± S.D.) and $\ln R_0 = -0.09647 \pm 0.0025$ (estimated value ± S.D.) were obtained, respectively. The shelflife of the vitamin C tablet could be predicted as:

$$t_{0.7} = (\ln R_0 - \ln_{0.7})\ k_{(25°C)} = 67817h \approx 7.7 years$$

By comparison, the activation energy of the vitamin C tablet was determined to be 94.35 and 94.91 kJ/mol, and the shelflife was predicted to be 6.7 and 6.9 years, using reciprocal heating (Zhan et al., 1995a) and linear heating (Zhan et al., 1995b) experiments, respectively. These results are comparable to those of our flexible heating experiment. Moreover, all the predicted results of the above experiments are also comparable to the results of long-term storage testing.

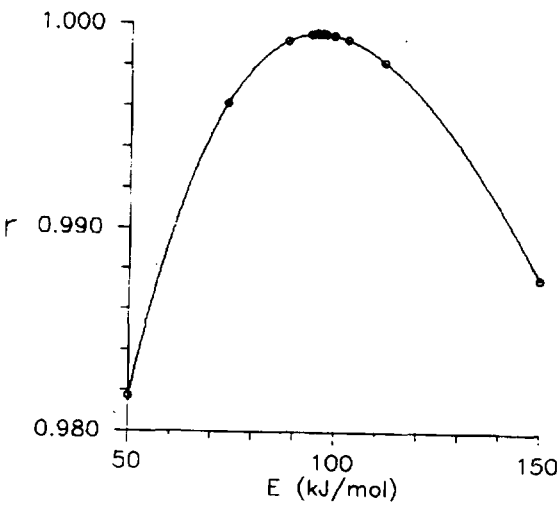

Fig. 4. Relationship between correlation coefficient and assumed activation energy.

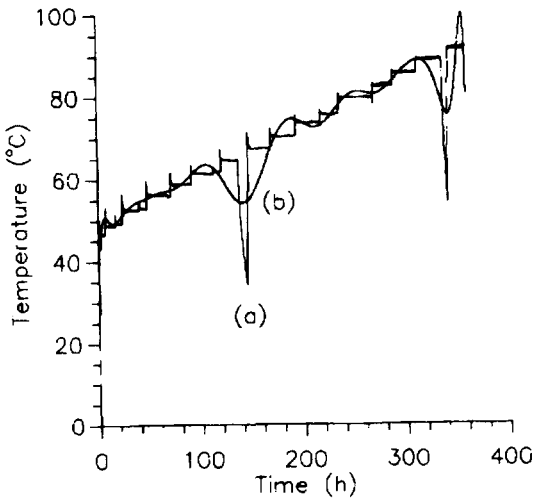

Fig. 5. The flexible temperature rising curve (a) and its curve fit of polynomial with order of 18 (b).

5. Discussion

In the reported computations (Maulding and Zoglio, 1970; Madsen et al., 1974) of flexible heating experiment, curve fit of polynomial was used in order to carry out the integration. Theoretically, high order polynomial equations can fit any curve within a definite range. However, because of the limitation of significant digits of the computer (16 significant digits are used in the following computation), too high an order polynomial does not make any sense. For comparison, the curve fit of polynomial with orders of 5, 10, 14, 18 or 22 were used to fit the temperature-time relationship. The curve fit with an order of 18 is shown in Fig. 5. The shelflife values of the vitamin C tablet, predicted with above polynomial curve

fits, were 26.0, 14.6, 11.7, 10.8 or 14.5 years, respectively. It shows that the polynomial curve cannot fit the temperature-time relationship satisfactorily, even if the order is as high as 22; the result of conventional computation depends on the order of the polynomial curve fit, and is neither comparable to that of other experiments (Zhan et al., 1995a,b) nor to that of long-term storage tests.

Since there is neither any approximation or curve fit, our new computation is simple, clear and accurate. The deficiencies of conventional computation are overcome. Both temperature recording and computation can be completed using an inexpensive pocket computer.

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