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Nonisothermal Kinetics Using a Microcomputer: A Derivative Approach to the Prediction of the Stability of Penicillin Formulations

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Abstract □ A procedure is described for the determination of the shelf-life of pharmaceutical preparations using nonisothermal kinetics. A BASIC computer program, which enables the data analysis to be undertaken rapidly and automatically on a microcomputer, is presented.

Keyphrases □ Kinetics, nonisothermal—derivative approach to the prediction of the stability of penicillin formulations using a microcomputer □ Stability—nonisothermal kinetics using a microcomputer, a derivative approach to the prediction, penicillin formulations □ Penicillin—nonisothermal kinetics using a microcomputer, a derivative approach to the prediction of stability in formulations □ Formulations—penicillin, nonisothermal kinetics using a microcomputer, a derivative approach to the prediction of stability

Nonisothermal methods for the prediction of the shelf-life of pharmaceutical preparations are an attractive alternative to traditional isothermal accelerated storage tests. A nonisothermal study involves a temperature change throughout the reaction and enables a full stability–temperature profile to be determined from one experiment. This procedure offers a considerable reduction in effort for the estimation of shelf-life and has received much attention. Early methods (1, 2) were extended to pharmaceuticals by Rogers (3) who used a defined temperature rise profile to simplify data handling. The validity of this approach, using various heating programs, has been confirmed (4–8), but theoretical and practical limitations have been discussed (9, 10). Greater freedom in experimental design is available if a predetermined temperature–time profile is not demanded. Methodology has therefore been extended to allow the rate of temperature increase to be determined by experimental, rather than theoretical, expedience (11, 12). Nonisothermal–isothermal methods have also been reported (13, 14), and many important applications of nonisothermal kinetics to solid-state degradations have appeared (15, 16). The estimation of the errors involved in these procedures has also received attention (12, 17).

Despite the success of these methods, few applications to formulated products have appeared (18). In this study a general method for the determination of nonisothermal kinetic profiles is described, and a BASIC computer program (NONISO) is presented, which can be implemented on a microcomputer, to undertake the calculations automatically. The procedures are shown to be comparable to methods requiring large computing facilities (12) and prove satisfactory for formulated products.

THEORETICAL

Degradation Rates—The rate of degradation of a drug can be represented by:

$$\frac{-dC_t}{dt} = k_T C_t^n \qquad \text{(Eq. 1)}$$

where C_t is the concentration at time t, k_T is the specific rate constant at temperature T, and n is the order of reaction. For a first order reaction ($n = 1$) this can be written as:

$$C_t = C_0 e^{-k_T t} \qquad \text{(Eq. 2)}$$

In logarithmic form this is:

$$\ln C_t = \ln C_0 - k_T t \qquad \text{(Eq. 3)}$$

and the negative slope of the plot k *versus* $\ln C_t$ yields the rate constant.

When the temperature is continually increased throughout the reaction, the degradation rate progressively increases. The isothermal rate constant is now approximated by:

$$k_T = -\left[\frac{\ln C_t - ln C_{t-\delta t}}{\delta t}\right] \qquad \text{(Eq. 4)}$$

where δt is a small increment of time, over which period the temperature may be considered constant. For an infinitesimal increase in time and temperature, the specific rate constant is given by:

$$k_T = -\frac{d(\ln C_t)}{dt} \qquad \text{(Eq. 5)}$$

The slope of the tangent at a point for the plot of t *versus* $\ln C_t$ for nonisothermal data yields the specific rate constant at the temperature observed.

If other orders of reaction are followed the appropriate equations are:

$$\text{zero order:} \quad k_T = -d(C_t)/dt \qquad \text{(Eq. 6)}$$

$$\text{2nd order (a = b):} \quad k_T = d(1/C_t)/dt \qquad \text{(Eq. 7)}$$

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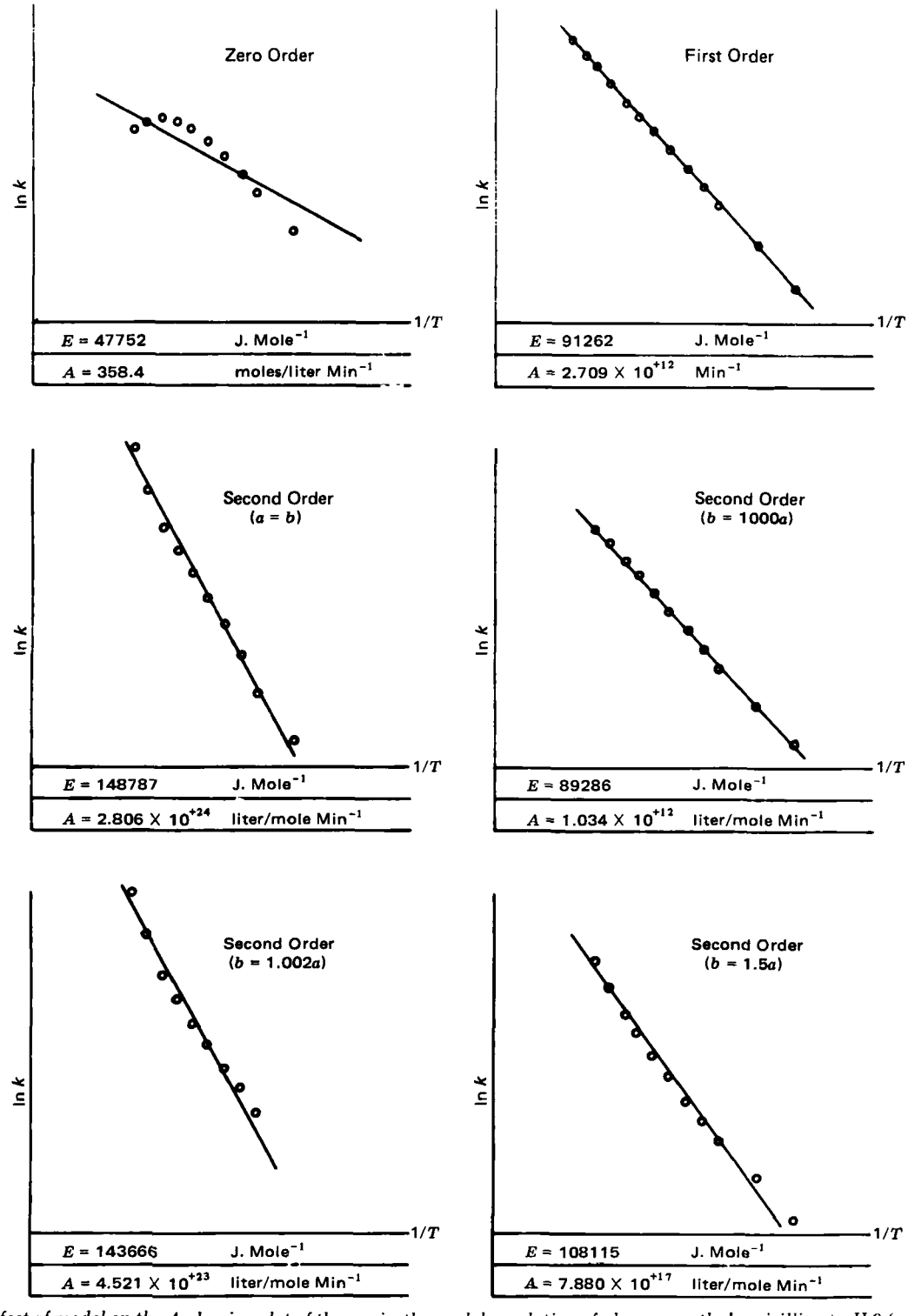


Figure 1—*The effect of model on the Arrhenius plot of the nonisothermal degradation of phenoxymethylpenicillin at pH 9* (a *and* b *refer to the initial concentrations of penicillin and hydroxide in second-order reactions).*

$$\text{2nd order (a} \neq \text{ b):} \quad k_T = \frac{d\left[\left(\frac{1}{B_0 - C_0}\right) \ln \frac{(B_0 - C_0 + C_t)C_0}{C_t B_0}\right]}{dt} \qquad \text{(Eq. 8)}$$

where C_t is the concentration (moles/liter), at time t, of the monitored drug of initial concentration C_0. B_0 is the initial concentration (moles/liter) of the excess reagent in a second-order reaction when the initial concentrations of the two reactants (a,b) are not identical.

The values of k_T are calculated by fitting a polynomial to the transformed data as a function of time. For the first-order case this is:

$$\ln C_t = a_0 + a_1 t + a_2 t^2 \ldots a_n t^n \qquad \text{(Eq. 9)}$$

Differentiation at the experimental points yields the corresponding rate constants:

$$\frac{d(\ln C_t)}{dt} = -k_T = a_1 + 2a_2 t + 3a_3 t^2 \ldots n a_n t^{n-1} \qquad \text{(Eq. 10)}$$

The rate constants at the experimentally measured temperatures are then used to compute the activation energy (E) and pre-exponential factor (A) in the Arrhenius Equation:

$$k_T = Ae^{-E/RT}$$

These data enable the calculation of rate constants at storage temperatures and the prediction of shelf-life ($t_{90\%}$) and half-life ($t_{1/2}$) to be made.

Table I—Input Data and Isothermal Rate Constants[a] for the Degradation of Phenoxymethylpenicillin at pH 9

Minutes	Concentration, %	Temperature, °	Rate Constant, 1/min
0	100.00	28.3	6.75997 E-05
9	99.60	32.8	7.16944 E-04
19	98.50	39.4	1.55624 E-03
29	96.40	45.8	3.07291 E-03
39	92.10	52.0	5.83865 E-03
44	89.10	54.8	7.85191 E-03
49	85.20	57.5	1.03574 E-02
52	82.50	59.0	1.21146 E-02
55	79.40	60.6	1.40709 E-02
58	75.90	62.1	1.62312 E-02
61	71.80	63.6	1.85985 E-02
64	67.90	64.9	2.11736 E-02
67	63.40	66.2	2.39550 E-02
70	58.40	67.5	2.69387 E-02
73	53.90	68.6	3.01181 E-02
76	48.80	69.8	3.34838 E-02
79	43.80	70.8	3.70232 E-02
82	39.00	71.8	4.07210 E-02
85	34.40	72.7	4.45581 E-02
88	30.00	73.6	4.85123 E-02
91	26.00	74.5	5.25574 E-02
94	22.00	75.3	5.66638 E-02
97	18.40	76.0	6.07977 E-02
100	15.10	76.7	6.49210 E-02
103	12.50	77.4	6.89917 E-02
106	10.00	78.0	7.29629 E-02
109	7.90	78.5	7.67834 E-02
112	6.40	79.0	8.03970 E-02

[a] Polynomial coefficients are: 4.60496, -6.75179×10^{-5}, -4.09094×10^{-5}, 6.03266×10^{-7}, -1.93521×10^{-8}, -1.08408×10^{-10}, and 9.47380×10^{-13} (a_0 term first).

EXPERIMENTAL

Nonisothermal Kinetics—*At pH 9*—A borate buffer (500 ml) containing boric acid (5.17 g), sodium hydroxide (1.67 g), and hydrochloric acid (5 *M*, 1.9 ml) was placed in a three-necked round-bottomed flask suspended in a thermostated water-bath (20-liter capacity, 1 kW). A thermometer, graduated to 0.1°, was placed into the buffer solution through one neck, a polytef sampling-tube was fitted through the second neck, and a stirrer rotated at 200 rpm was positioned through the third neck. When the buffer had reached thermal equilibrium, potassium phenoxymethylpenicillin [potassium (2*s*, 5*R*, 6*R*)-3-3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (250 mg) was rapidly added to the buffer. When solution was complete (2 min), the water-bath heater was set at 100° (providing a temperature increase to 80° in 2 hr). A sample (5 ml) was immediately withdrawn and two 2-ml volumes were accurately measured. To each was added a solution of phenol (2 ml, 0.02% w/v in a phosphate buffer containing 0.9073% KH_2PO_4 adjusted to pH 5) as internal standard. This gave a final solution pH of 7: a more stable value for the penicillin (19). The initial penicillin concentration was determined in duplicate by high-performance liquid chromatographic (HPLC) analysis through interpolation onto a calibration curve prepared similarly over a penicillin concentration range of 0–50 mg/100 ml ($r = 0.999$). At frequent intervals throughout the run, samples (3 ml) were removed and a 2-ml aliquot was assayed. Time and precise temperature were also noted.

Table II—Arrhenius Parameter Estimates for the Nonisothermal Degradation of Phenoxymethylpenicillin at pH 9

All Data Points[a]

Parameter	Value	Range	Units
E	103044	95431–110657	J/Mole
A	1.7066 E + 14	1.1225 *E* + 13–2.5945 *E* + 15	/Min

Omission of 28.3° Point[b]

Parameter	Value	Range	Units
E	91262	90862–91663	J/mole
A	2.7090 *E* + 12	2.3491 *E* + 12–3.1241 *E* + 12	/Min

[a] Slope −12393.6 ± 915.7 (p = 95%), intercept 32.771 ± 2.722 (p = 95%), r = 0.98367. [b] Slope −10976.6 ± 48.2 (p = 95%), intercept 28.628 ± 0.143 (p = 95%), r = 0.99994.

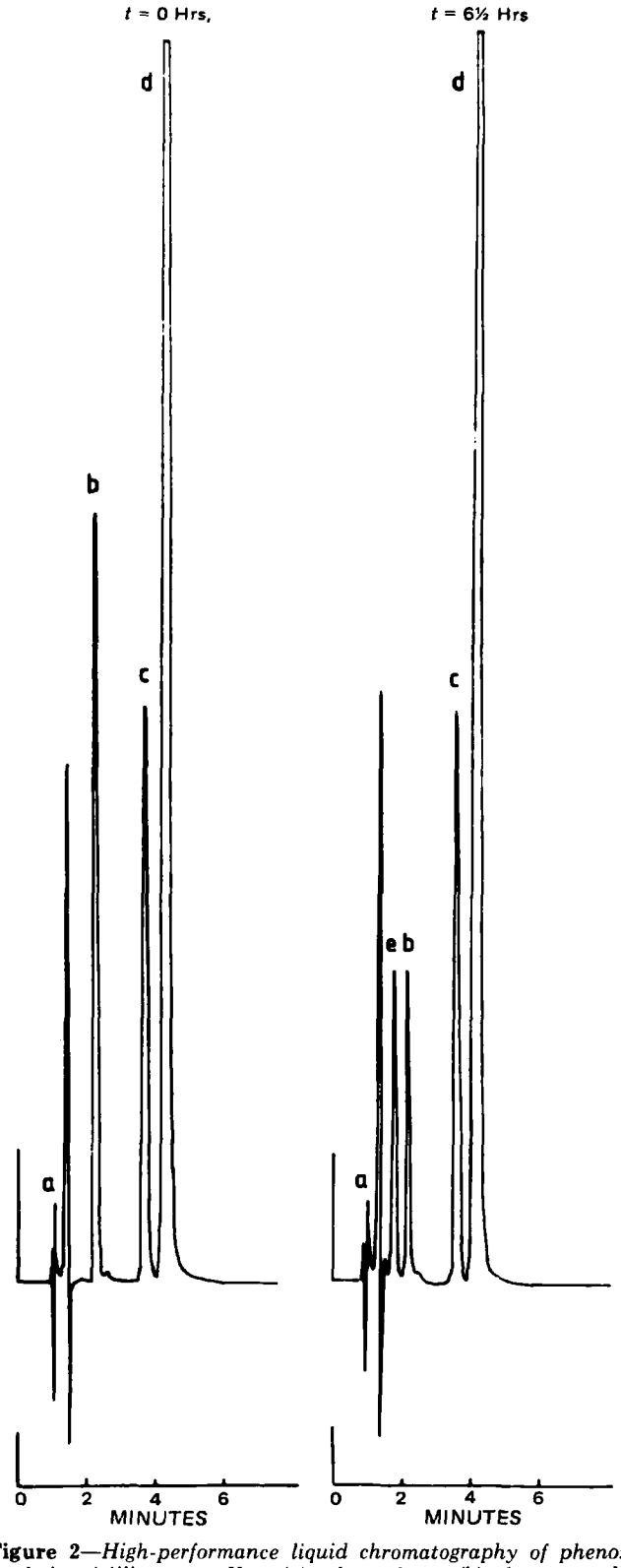


Figure 2—*High-performance liquid chromatography of phenoxymethylpenicillin syrup. Key: (a) solvent front; (b) phenoxymethylpenicillin; (c) phenol (internal standard); (d) methyl paraben; (e) degradation product.*

At pH 6—A citrate buffer (140 ml) containing citric acid (1.76 g) and sodium hydroxide (0.90 g) were placed in a medicine bottle fitted with a thermometer and sampling port. When temperature equilibrium was reached potassium phenoxymethylpenicillin (70 mg) was added, samples were removed, and the temperature program was initiated.

In these experiments the water-bath was programmed to rise from 60 to 95° over a 6-hr period. This was achieved by using a motorized syringe-drive unit to continuously adjust the thermostat. At frequent in-

tervals through the run, samples (3 ml) were removed and a phenol solution (2 ml, 0.02% w/v in water) as internal standard was added to an aliquot (2 ml). HPLC analysis was undertaken through interpolation onto a calibration curve prepared similarly over a penicillin concentration range of 0–50 mg/100 ml (r = 0.999). Time and precise temperatures were noted for each assay point.

Formulated Products—Syrups were reconstituted as directed by the manufacturer. Typically, this involved addition of 70 ml of water to the product (in the case of Syrup 1) and shaking vigorously to facilitate dissolving granules. The reconstituted product of nominal concentration (62.5 mg/5 ml and pH 5.8) was then transferred to a 150-ml clear bottle fitted with a sampling tube and a thermometer.

The stability of the syrups was monitored from 60 to 95° for the pH 6 samples. The HPLC assay was undertaken by adding phenol solution (2 ml, 0.25% w/v in water) to aliquots (1 ml), which were then diluted to 50 ml with water.

Isothermal Kinetics—Isothermal degradation was undertaken as described for the nonisothermal runs except that the selected temperature was held constant throughout the experiment. A series of temperatures within the range of those in the corresponding nonisothermal program was used.

HPLC—The stationary phase[1] was 5 μm in a 10-cm column with a 4.6 mm i.d. The mobile phase was acetonitrile (28% v/v) in phosphate buffer (0.132% $Na_2HPO_4 \cdot 2H_2O$, 0.807% KH_2PO_4; pH 6) pumped[2] at 1 ml min^{-1} under a pressure of ~600 psi. The UV detector[3] was operated at 271 nm with a sensitivity of 0.16 AUFS. Samples (20 μl) were injected onto the column by means of a loop injector[4]. Under these conditions phenoxymethylpenicillin had a retention time of 2.2 min and phenol 3.6 min.

Calculations were undertaken on a computer[5] using a BASIC version (see *Appendix*) of NONISO or by means of a FORTRAN integral nonisothermal kinetics program (12) implemented on a main frame system[6].

RESULTS AND DISCUSSION

Typical results for the nonisothermal degradation of phenoxymethylpenicillin (penicillin V) are shown in Table I. The transformed concentration–time polynomial coefficients for a first-order model and the isothermal rate constants attained by differentiation at the experimental points are also shown. The Arrhenius parameter estimates for these data are presented in Table II. The limits of error about the estimates are rather wide and the poor nature of the fit is further revealed by the correlation coefficient (r = 0.984), the coefficient of variation (CV = 10.52%), and the chi-squared statistic (6.37×10^{-3}; 26 degrees of freedom). Examination of the plotted data reveals that almost all of the variation arises from the first point (28.3°). This is due to the small amount of degradation that occurs over this initial temperature range. The true polynomial gradient is small, and the estimated rate constant is significantly affected by experimental error. The removal of this one point from the data set has a dramatic effect on the quality of the fit (Table II). The activation energy is now estimated to $<\pm 0.5\%$ (p = 95%). The rate constants calculated from these estimates are available for scrutiny and the predicted shelf-lives are shown in Table III. The output from the plotting routine is depicted in Fig. 1, which shows the effect of the chosen model on the Arrhenius plot. This rapid visualization of the data immediately reveals problems in the fit. When the reaction order is unknown, each model can be examined sequentially, and the best-fitting data (low χ^2, CV; high r) can be used for the shelf-life estimates.

To establish the validity of the NONISO approach a series of experiments were undertaken to establish the reproducibility of the method. The results were calculated using NONISO and the FORTRAN program described in an earlier study (12). These data, and those from a traditional isothermal study, are recorded in Table IV. Also included are the results reported previously (12) for riboflavin which have been recalculated using NONISO. Data taken from a graphical presentation in a previous report (8) on the nonisothermal degradation of p-acetamidophenol and procainamide have also been recalculated using NONISO and the integral approach. Parameter estimates from these calculations are also reported in Table IV. The agreement between these various estimates confirms the validity of the NONISO approach reported here.

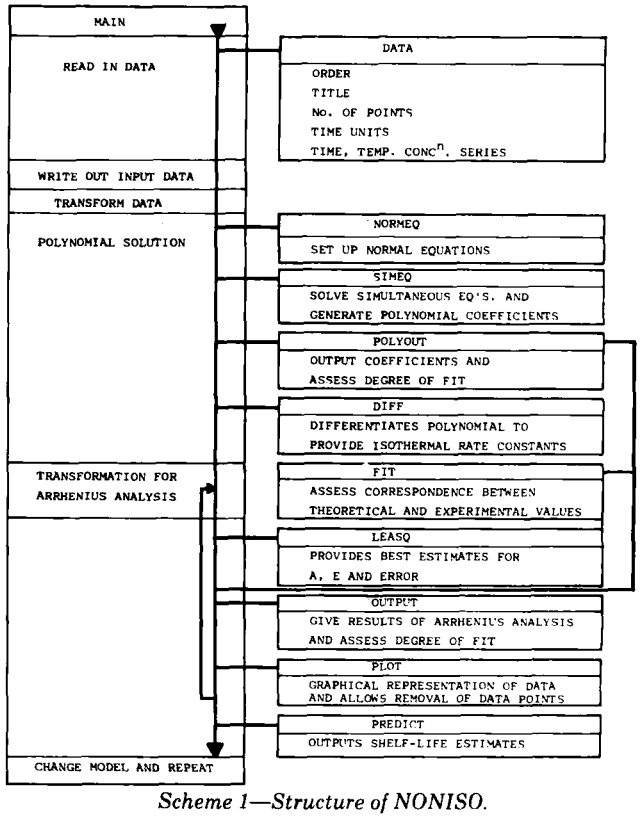
[1] Hypersil ODS Shandon Scientific.
[2] Model 100A, Altex Corp.
[3] LC3, Pye Unichem Ltd.
[4] Rheodyne 7120.
[5] North Star Horizon.
[6] ICL 1904S.

Table III—Shelf-life Predictions for Phenoxymethylpenicillin at pH 9

Temperature, °	Shelf-life Predictions $t_{1/2}$	First Order Model $t_{90\%}$
5	24.44 days	3.72 days
10	12.18 days	1.85 days
15	149.12 hr	22.67 hr
20	77.87 hr	11.84 hr
25	41.56 hr	6.31 hr
30	22.64 hr	3.44 hr

When all experimental points are used in the computation (typically 25–30) the major source of error occurs in the calculation of rate constants at the temperature range extremes. Inspection of the graphical presentation reveals any deviation, and recalculation with the omission of ill-fitting data dramatically increases the validity of the parameter estimates. For this reason, points that correspond to degradation in excess of 95% for a first-order process or in excess of 80% for the zero- or second-order models are automatically eliminated from the data set. The elimination of points determined in the initial stages of the degradation is left to the operator's discretion. Usually few points require attention so that, providing a reasonably complete data set has been collected, sufficient points remain to establish a valid analysis. In the case of phenoxymethylpenicillin (pH 9) 33 points were collected, 28 were used in the initial calculation (Table I), and the final parameter estimates were derived from 27 observations (Tables II and III). The reduced data set may be recalculated in part, *via* the Arrhenius subroutines, or in total, through the generation of a new polynomial expression. The first option is satisfactory if analytical error is small and has been adopted in all calculations reported here. However, if less precise assay results are available it is more effective to generate a new polynomial equation. The two approaches are compared in Table V. This records the effect of a ±2% random error incorporated into the concentration values and reveals that polynomial regeneration is more effective in providing an acceptable solution with this degree of error. To reduce the effect of analytical error it is advisable to design the nonisothermal temperature program to cover a range not less than 25° and to monitor the degradation over a period of at least one half-life.

Figure 2 is a typical chromatogram from a phenoxymethylpenicillin syrup and shows that excipients and degradation products are detectable but do not interfere with the analysis. The results of the nonisothermal



Scheme 1—Structure of NONISO.

Table IV—Comparison of Differential and Integral Calculations of Nonisothermal Degradation Data [a]

Run	Temperature Range	Differential (NONISO) E (J/mole)	A ($\times 10^{-14}$ hr^{-1})	Predicted K ($\times 10^2$ hr^{-1}) 25°	50°	Integral (Anderson) E (J/mole)	A ($\times 10^{-14}$ hr^{-1})	Predicted K ($\times 10^2$ hr^{-1}) 25°	50°
Nonisothermal (Phenoxymethylpenicillin pH 9)									
1	28°–81°	91024 (413)[a]	1.496 (0.205)[a]	1.697	29.07	91209 (43)[b]	1.588 (0.024)[b]	1.673	28.81
2	31°–78°	90966 (1125)[a]	1.345 (0.444)[a]	1.562	26.71	90076 (71)[b]	0.977 (0.025)[b]	1.625	27.02
3	31°–60°	89496 (2305)[a]	0.809 (0.464)[a]	1.700	27.76	94494 (157)[b]	5.045 (0.028)[b]	1.412	26.95
Isothermal (Phenoxymethylpenicillin pH 9)	3°–72°	86485 (2282)[a]	0.261 (0.152)[a]	1.848	27.46				
Nonisothermal Riboflavin (12)	21°–70.5°	82552 (2420)[a]	0.1075 (0.064)[a]	3.718	48.89	84888 (242)[b]	0.2558 (0.0221)[b]	3.448	48.77
p-Acetamidophenol (8) (Nonisothermal)	34.9°–83°	67245 (4632)[a] 71128(8)[c]	5.282×10^{-7} (4.244×10^{-7})	8.745×10^{-3}	7.131×10^{-2}	68810 (3284)[b]	9.2316×10^{-7} (9.606×10^{-7})	8.129×10^{-3}	6.961×10^{-2}
Procainamide HCl (8) (Nonisothermal)	34.9°–82.6°	129513 (9232)[a] 121336(8)[c]	4.57×10^3 (4.39×10^3)	9.328×10^{-4}	5.311×10^{-2}	120967 (3396)[b]	2.3383×10^2 (2.363×10^2)	1.500×10^{-3}	6.539×10^{-2}

[a] Confidence interval 95%. [b] Standard deviation units. [c] Literature values.

Table V—Effect of ±2% Random Error in Concentration on E from Nonisothermal Degradation of Phenoxymethylpenicillin (pH = 9)

Source	Run 1	2	3	4	5	Result Mean	CV, %
Arrhenius Recalculated	111674	94420	90161	93714	85814	95157	10.3
Polynomial Regenerated	91655	86647	90850	88772	88662	89317	2.2

degradation of formulated products are illustrated in Table VI. A high degree of similarity is observed between shelf-life estimates from NONISO and those obtained using the integral method of Anderson *et al.* (12). The estimates compare well with those predicted from isothermal accelerated tests and with shelf-lives measured at the storage temperature. The advantages of this approach include the availability of a full kinetic profile with no more effort than is required by a single isothermal rate determination. Zero-, first-, and second-order (a = b; a ≠ b) and first-order equilibrium reactions may be handled. A set temperature program is not required and the heating rate can be adjusted readily to suit the stability of the formulation. Only simple apparatus is required, and degradation in the final dispensing container is easily monitored. In addition, the use of an analytical rather than an iterative solution to the kinetic equations requires a relatively short processing time. This allows effective use of a BASIC program, which can be run on inexpensive microcomputers rather than requiring main-frame computing facilities. The use of this approach should enable nonisothermal kinetic procedures to be available on a routine basis.

APPENDIX

NONISO, a BASIC computer program, has been written for implementation on a Z80-based microcomputer with 64K RAM[5] and requires ~22K for the fully labeled version. A listing of the program is available on request, from the authors. Scheme I illustrates the structure of this program. Individual operations have, as far as possible, been incorporated into separate subroutines to allow modification or extension to be easily achieved. Although BASIC does not allow subroutine names, these are used in the discussion for purposes of clarity. DATA (lines 3940–4300) are written into the program before computation. This records the proposed order of reaction, an identifying label for the experiment, the number of data points, and the time units used. This is followed by time, temperature, and residual concentration measurements for each experimental point beginning with time zero.

The segment MAIN (lines 470–1080) sets dimensions, reads in the input data, and transforms the concentration values (compare Eqs. 4–7) so that differentiation of the polynomial yields k_T values. Subsequent calls to the major subroutines follow.

The NORMEQ (lines 1150–1270) routine sets up the normal equations for the solution of the transformed concentration data in terms of a time polynomial. The normal equations take the form:

$$\sum_{i=1}^{N} (\ln C_{t_i}) = a_0 N + a_1 \Sigma t_i + a_2 \Sigma t_i^2 + \ldots + a_n \Sigma t_i^n$$

$$\sum_{i=1}^{N} t_i (\ln C_{t_i}) = a_0 \Sigma t_i + a_1 \Sigma t_i^2 + a_2 \Sigma t_i^3 + \ldots + a_n \Sigma t_i^{n+1} \quad \text{(Eq. 11)}$$

$$\sum_{i=1}^{N} t_i^2 (\ln C_{t_i}) = a_0 \Sigma t_i^2 + a_1 \Sigma t_i^3 + a_2 \Sigma t_i^4 + \ldots a_n \Sigma t_i^{n+2}$$

$$\sum_{i=1}^{N} t_i^n (\ln C_{t_i}) = a_0 \Sigma t_i^n + a_1 \Sigma t_i^{n+1} + a_2 \Sigma t_i^{n+2} + \ldots a_n \Sigma t_i^{2n}$$

where n is the order of the polynomial and N is the number of data points; the program is able to generate polynomials up to the tenth order. The maximum available order, however, is dictated by the word length of the computer used. Values in excess of Σt_i^{2n} are generated and overflow errors may occur. In practice, a sixth-order polynomial was found satisfactory, with higher orders giving no improvement.

The subroutine SIMEQ (lines 1280–1700) solves up to 10 simultaneous equations by the Gauss Elimination Method (20). A typical execution time for 30 points is 90 sec.

POLYOUT (lines 1710–1930) presents the coefficients for the polynomial and the calculated values are compared with the observed transformations. Subroutine FIT (lines 1940–2100) is also called to calculate a determination coefficient, the coefficient of variation, and the chi-squared value.

DIFF (lines 2110–2330) differentiates the polynomial expression and the result is solved for the experimental points to yield the isothermal rate constants throughout the run. The experimental data are modeled well but extrapolation beyond this range rapidly introduces unacceptable error. Transformation for the Arrhenius analysis ($k_T \rightarrow \ln k_T$; $T \rightarrow 1/T$) is thus undertaken, and the parameters (A,E) are estimated by LEASQ (lines 2340–2540), which undertakes a linear least-squares analysis of the data.

The parameter estimates and correlation coefficients are printed by OUTPUT (lines 2550–2780) which also provides 95% error limits for the estimates. The isothermal rate constants predicted by the model are compared with the experimental values, and the degree of correspondence is again assessed by subroutine FIT.

PLOT (lines 3000–3750) is a subroutine that displays the theoretical regression line together with the experimental points, thus allowing a visual assessment of the significance of the fit. Options are available to remove wildly deviating points: in practice, if this is necessary, these are

Table VI—Parameter Estimates for Formulated Products [a]

Run	Temperature Range	Differential (NONISO) E (J/mole)	A ($\times 10^{-12}$ hr^{-1})	Predicted $t_{90\%}$ 25° (days)	50° (hr)	Integral (Anderson) E (J/mole)	A ($\times 10^{-2}$ hr^{-1})	Predicted $t_{90\%}$ 25° (days)	50° (hr)
Syrup 1									
Nonisothermal	60°–94°	82717 (967)[a]	0.251 (0.070)[a]	5.4	9.8	86951 (789)[b]	1.040 (0.263)[b]	7.2	11.5
Isothermal	25°–50°	80250	0.1067	4.70	9.2				
Syrup 2		83945	0.557	4.0	7.0	83992	0.560	4.0	8.9
Nonisothermal	61–95°	(±1788)[a]	(±0.254)[a]			(356)[b]	(0.066)[b]		
		85840 (2169)[a]	1.115 (0.579)[a]	4.3	7.1	87091 (254)[b]	1.684 (0.142)[b]	4.7	7.5
Solution (pH 6)									
Nonisothermal	60°–95°	92610 (6804)[a]	2.639 (2.37)[a]	27.9	37.2	92169 (5470)[b]	2.251 (3.719)[b]	27.4	37.0

[a] Confidence interval. [b] Standard deviation units.

the initial data points when the concentration is changing slowly and is thus subject to more error. The regression calculations are then repeated on the reduced data set.

When a satisfactory model is obtained, the subroutine PREDICT (2790–2990) calculates the $t_{90\%}$ and $t_{1/2}$ values at typical storage temperatures to assess the shelf-life of the formulation. The model can then be changed by the use of the appropriate code [line 3940; 0—zero-order, 1—first-order, 2—second-order ($a = b$), 3—second-order ($a \neq b$)] and the calculations are repeated.

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