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A NEW LINEAR MODEL FOR STABILITY PREDICTION

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ABSTRACT

Based upon Okusa's observation (Chem. Pharm. Bull. 1975) that the slopes of a linear plot of log·log fraction of active substance degraded vs log time for first order decay kinetics and a linear plot of log of drug remaining vs log time for a zero order decay kinetics are both unity, an algorithm has been developed to resolve both the energy of activation (E) and the rate constant (K_0 or L_0) at the desired shelf-life temperature (T_0) by analysis of the y-intercepts of parallel slopes at more than one elevated temperature (T).

Preliminary estimates of both E and either K_0 or L_0 are then substituted into a series of mathematical expressions based upon well known Arrhenius relationship:

$$k = A \cdot \exp -(E/1.987)\,(1/T-1/T_0) \quad \text{where } A = K_0 \text{ or } L_0$$

Using converging and interative techniques to treat elevated temperature data, the resulting mean loss rate (either K_0 or L_0) at the designated shelf-life temperature plus a residual error term thus obtained, is used to distinguish statistically between zero and first order treatments. A program called POTENCYLOSS, based upon the algorithm, has been written in business BASIC language for use with an IBM-PC micro-computer.

The program is ideally suited for use in preformulation studies or in assigning provisional expiration dating and overage requirements during the early stages of formulation development when there is limited potency stability test data available at accelerated, elevated temperature storage conditions.

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INTRODUCTION

Blythe of SKF (1) was the first to report on the use of accelerated, elevated temperature storage testing to determine the shelf-life stability of products such as pharmaceuticals. The use of the classical Arrhenius relationship (2) to predict (or extrapolate) shelf temperature rate constants for stability assessment was later refined by Free (3) and Garrett (4-7). Additional designs for accelerated, elevated temperature stability testing were next proposed separately by Tootill (8) and Kennon (9).

Nonisothermal (varying temperature) methods for stability prediction have also been reported separately by Ball (10) by Rogers (11) by Cole and Leadbeater (12) and by Tucker (13). Recently, Hempenstall et al (14) developed a computer program for use with this particular kinetic model. However, nonisothermal methods are not widely used in industrial applications.

Statistical techniques have been proposed in order to improve stability prediction using accelerated, elevated temperature data. Bentley (15) suggested the use of weighted least-squares analysis. Refinements in weighted least squares analysis have been provided separately by Davies and Hudson (16) and Yang (17, 18). Statistical analysis of nonlinear models have also been proposed separately by Davies and Hudson (16) and by King et al (19). In addition, the Weibull reliability model has been used by Ogden (20) for stability prediction. A simplified statistical method for studying stability has also been provided by Amirjahed (21).

A number of computer programs for stability prediction based upon the analysis of accelerated, elevated temperature data have been reported in the literature. Several of the earlier programs were reviewed by Hogg (22). DeTar (23) and Rey-Bellet (24) developed programs for use with the HP 97 programmable calculator. Company computerized, quality control stability systems have been reported separately by Stone and Slater (25) and Boudreau (26). Complete quality control computer software packages, which include a simple program for stability prediction, are currently available from J. A. Keane & Assocs. (27) and Scientific Software (28).

Although not extensively reviewed here, the Arrhenius model for stability prediction has been widely used by Labuza (29) in foods, by Thomas (30) in plastics and by others in paint and cosmetic systems. The purpose of this paper is to present a new linear model and information about a computer program for stability prediction.

NEW LINEAR MODEL FOR STABILITY PREDICTION

Based upon Okusa's observation (31) that the slopes of a linear plot of log·log fraction of active substance degraded vs log time for first order decay kinetics and a linear plot of log of active substance remaining vs log time for a zero order rate process are both unity (i.e. slope = 1.0) a new algorithm has been developed to resolve both the energy of activation (E) and the rate constant (K_0 or L_0) terms at the desired shelf temperature (T_0) by analysis of the y-intercepts of parallel slopes at more than one elevated temperature (T).

In the program, preliminary estimates of both E and either K_0 for first order or L_0 for zero order are then substituted into a series of mathematically related equations based upon the Arrhenius relationship:

$$k = A \cdot \exp{-(E/1.987)}\,(1/T-1/T_0) \quad \text{where } A = K_0 \text{ or } L_0$$

Using converging and interative techniques to treat accelerated, elevated temperature data, the resulting mean loss rate (either K_0 or L_0) plus a residual error term thus obtained, is used to distinguish statistically between zero and first order treatments.

The program called POTENCYLOSS*, based upon the algorithm, has been written in business BASIC language for use with an IBM-PC microcomputer. The features of the new linear model for stability prediction are summarized as follows:

1. The program enables the user to make a preliminary estimate of product stability with not less than two potency-time points (initial potency at time zero plus one additional potency-time point) at two elevated temperatures, one of which may be room temperature (25°C). The program calculates a provisional energy of activation (E) from which a provisional loss rate (K_0 or L_0) can be assigned.

2. Programming is accomplished with the use of linear equations without the need to use weighted least squares analysis of individual data points nor the need to use nonlinear curve fitting techniques.

3. As additional potency-time points are generated at two or more elevated temperatures, these data are fed into a series consisting of three consecutive mathematical expressions, which feature converging and iterative techniques. The resulting mean loss rates are determined at a desired, designated temperature (T_0) plus a residual error term that can be used to distinguish between two basic kinetic treatments (zero and first order).

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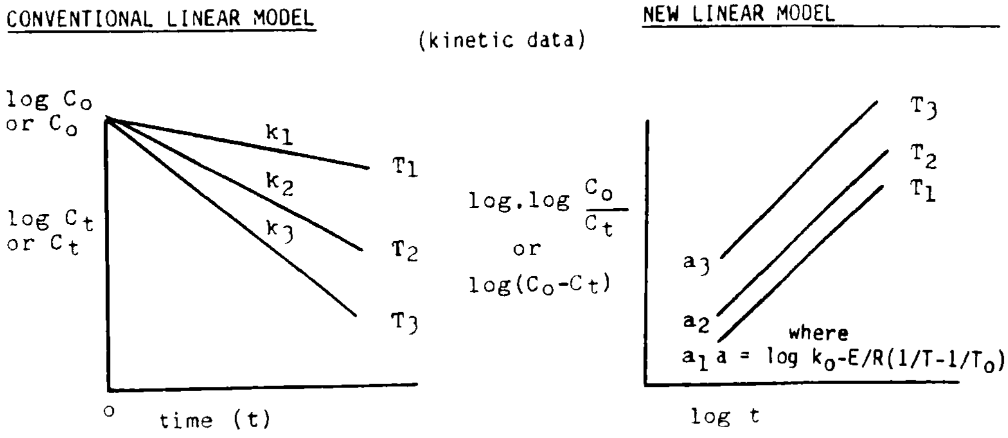
*POTENCYLOSS, is available by writing to Ranco Programs, Inc., P.O. Box 257, Pearl River, New York 10965, USA.

Figure 1. ARRHENIUS MODEL FOR STABILITY PREDICTION

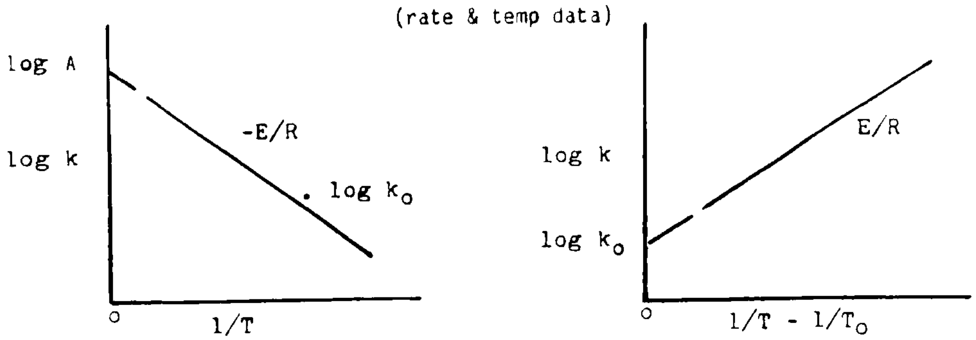


Disadvantages

1. Negative slopes should be fitted through origin (log C_o or C_o)
2. Negative slopes (k values) are variable.

Advantages

1. Parallel slopes are positive and equal 1.0
2. The alpha expression, which is common to both 0th & 1st order, contains k_o & E terms.



Disadvantages

1. Converges to log A
2. Negative slope

Advantages

1. Converges to log k_o (rate at shelf-life temperature)
2. Positive slope

The advantages of the new linear model for stability prediction are summarized by referring to information presented in connection with figure 1.

4. The program then calculates expiration dating periods with concomitant overage requirements for both zero and first order cases based upon 95% confidence limits.

5. The program also provides important thermodynamic terms, such as entropy (S) and free energy (G) factors in order to assess the mechanism of thermal degradation.

6. The program features two special mathematical expressions that permit the calculation of the "t" statistic and the loss rate in percent for a first order rate expression at any time (t), where loss rate in percent per unit time equals 100 (1-exp-kt).

7. The program is user-interactive so that estimates can be made for potency values at any temperature and future time period, based upon the selection of either a zero or first order rate process for analysis.

The following mathematical expressions are used to predict potency loss rate constant (L_o) at the desired temperature (To) for a zero order rate process.

Basic equations for a zero order rate process are listed below, where C_t = potency remaining at any time (t), Co= initial potency at t_o (100% at zero time), N= number of data points at any temperature (T) in °C. Arrhenius relationship relates loss rate constant L_T and temperature T (273.16 + °C), where E= energy of activation, L_o = loss rate constant at desired temperature (To), A = frequency factor and e = exponential (2.71828).

$C_t = Co - L_T \cdot t$

$\Sigma C_t = 100 N - L_T \cdot \Sigma t$

$L_T = (100 - \Sigma C_t/N)/\Sigma t/N$

But L_T also equals the Arrhenius relationship:

$L_T = A \cdot e^{(-E/1.987)(1/T-To)}$

sign is minus when $T > To$ then $L_T = A \cdot e^{(E/1.987)(1/T-1/To)}$

When $1/T-1/To = 0$, $e^0 = 1$ thus $L_T = A = L_o$

Solving the following simultaneous equations for L_o and E:

$\Sigma \ln L_T = N \cdot \ln L_o + (E/1.987)\, \Sigma\, (1/T-1/To)$

$\Sigma \ln L_T\, (1/T-1/To) = \ln L_o\, \Sigma\, (1/T-1/To) + (E/1.987)\, \Sigma\, (1/T-1/To)^2$

Combining 1st and 4th equations above and taking logs of both sides of the resulting expression, the following is obtained:

$\ln (Co-C_t) = \ln L_o \cdot t - (E/1.987)(1/T-1/To)$

At a fixed time, t the following simultaneous eqns. are again solved for L_0 and E:

$$\Sigma \ \ln(Co-Ct) = N \cdot \ln L_0 \cdot t + (E/1.987)(1/T-1/To)$$

$$\Sigma \ln(Co-C_t)\ (1/T-1/To) = \ln L_0 \cdot t\, \Sigma\ (1/T-1/To) + (E/1.987)\, \Sigma\ (1/T-1/To)^2$$

The values for each set of L_0 and E are then fed into the two series of simultaneous equations using iteration technique until they converge on the best mean values for L_0 and E. Since the simultaneous equations were developed based upon statistical least squares treatment of these linear equations, mean L_0 and E terms are obtained with an appropriate standard deviation term for each value.

The following mathematical expressions are used to predict potency loss rate constant (K_0) at the desired temperature (To) for a first order rate process.

Basic equations for a first order rate process are listed below, where C_t = potency remaining at any time (t), Co = initial potency at t = 0, 4.6052 = ln 100%, N = number of data points at any temp. T in ^{0}C and k_T = loss rate constant at T in ^{0}C. Arrhenius relationship relates loss rate constant k_T and Temp. T (273.16 + ^{0}C), where E = energy of activation, Ko = loss rate constant at desired temp.(To), A = frequency factor and e = exponential (2.71828).

$$\ln C_t = \ln Co - k_T \cdot t$$

$$\Sigma \ \ln C_t = 4.6052\ N - k_T \cdot \Sigma\ t$$

$$k_T = (4.6052 - \Sigma\ \ln C_t/N)/\ \Sigma t/N$$

But K_T also equals the Arrhenius relationship

$$k_T = A \cdot e^{(-E/1.987)\ (1/T-1/To)}$$

sign is minus when T > To then $k_T = A \cdot e^{(E/1.987)\ (1/T-To)}$

When 1/T - 1/To = 0, $e^0 = 1$ thus $k_T = A = Ko$

Solving the following simultaneous equations for ko and E:

$$\Sigma\ \ln k_T = N \cdot \ln Ko + (E/1.987)\Sigma\ (1/T-1To)$$

$$\Sigma\ \ln k_T\ (1/T-1/To) = \ln Ko\, \Sigma\ (1/T-1/To) + (E/.1987)\, \Sigma\ (1/T-1/To)^2$$

Combining the 1st and 4th eqns. and taking logs of both sides of the resulting expression, the following equation is obtained:

$$\ln(\ln Co/C_t) = \ln Ko \cdot t - (E/1.987)\ (1/T-1/To)$$

At a fixed time, t the following simultaneous equations are again solved for Ko and E:

$$\Sigma\ \ln(\ln Co/C_t) = N \cdot \ln Ko \cdot t + (E/1.987)\ (1/T-1/To)$$

$$\Sigma \ln(\ln Co/Ct)\,(1/T-1/To)=\ln Ko\cdot t\Sigma\,(1/T-1/To)$$
$$+(E/1.987)\,\Sigma\,(1/T-\ 1/To)^2$$

The values for each set of Ko and E are then fed into the two series of simultaneous equations using iteration techniques until they converge on the best mean values for Ko and E. Since the simultaneous equations were developed based upon statistical least squares treatment mean Ko and E terms are obtained with an appropriate standard deviation term for each value.

LIMITATION OF KINETIC MODELS AND POTENCYLOSS

The limitations of most kinetic models and the present computer program are summarized as follows:

1. Most decomposition reactions in aqueous solution or suspension may be described by either a zero order, first order or pseudo first order rate process (32). Many of these processes include hydrolysis, oxidation and rearrangement reactions. In the case of more complicated thermal degradations in the solid state, the initial loss rate of the active substance will often follow either zero or first order kinetics. In the case of complex systems such as reversible, parallel or consecutive reactions, the initial phase of these decompositions as well can be described by either a first or pseudo first order rate process. In situations such as acid or base catalysis, where pH and/or buffer concentration is held constant, stability predictions from accelerated, elevated temperature storage data can be made at a given set of experimental conditions using the present computer program. Thus in most situations cited above, zero or first order treatments are most likely to describe the kinetics of the reaction.

2. Since in the new linear model, both potency and time data are transformed logarithmically and the resulting parallel slopes at the several temperatures for analysis are equal to 1.0, there is little need to consider weighting techniques, as described by Bentley and others. In fact, logarithmic transformations may be considered to be a weighting process by itself. The linear least squares analytical procedures supplied with POTENCYLOSS are sufficient to provide data (means and standard deviations) for statistical treatment.

3. In a number of systems at high temperatures, (say greater than 40°C or more) the Arrhenius relationship (log reaction rate constant vs reciprocal of absolute temperature) may deviate from linearity. In such cases, nonlinear models, such as those described by Davies and Hudson (16) and by King et al (19) have been employed for stability prediction (or extrapolation) based upon data at elevated temperatures. Such nonlinear curve fitting techniques, if based upon inaccurate input potency data may, like linear models such as POTENCYLOSS, lead to false estimates of rate constants at the desired shelf temperature. In both situations, greater reliance with respect to stability prediction, must be placed on data obtained at lower elevated temperatures where linearity of the Arrhenius model is often observed. In this respect, the use of the present program should provide a better choice of models.

4. The calculation of thermodynamic parameters such as, entropy of activation, free energy of activation, etc. in the program are

based upon equations described by Martin, Swarbrick and Cammarata (33). In the case of decompositions in solutions, where concentration of degrading substances may not be equivalent to its chemical activity or in the case of suspensions or solids, the thermodynamic parameters thus calculated by the present program should be considered to be apparent values.

5. The present computer program can also be applied to numerical data, other than potency values, that exhibit decay in accordance with the Arrhenius model. However, the expiration dating period and overage requirements thus calculated may lose their usual significance.

6. The ability of the program to accurately estimate desired shelf temperature stability ultimately depends upon the quality of the input potency data, the time of exposure and the various elevated temperatures at which the system or samples of the system have been stored. Data variability will often reflect the precision, accuracy and selectivity of the assay method employed in generating potency data. In this connection, modern chromatographic techniques in the hands of competent and experienced analysts will significantly reduce assay variability and thereby provide good input data. In addition, the use of well-controlled temperature storage stations and appropriate packaging components will insure the reliability of the stability data thus generated. The oft repeated phrase, "garbage-in results in garbage-out" applies as well to the operation of the present computer program.

CONCLUSIONS

A new linear model for stability prediction, based upon the Arrhenius relationship, has been presented for use in assigning provisional expiration dating and overage requirements during the early stages of product formulation development, when the potency data required for such assignments are often limited. A computer program called POTENCYLOSS, based upon the new linear model, has been written for use with the IBM PC miro-computer. The advantages and limitations of both the model and the computer program have been described in the present article.

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