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Examination of a modified Arrhenius relationship for pharmaceutical stability prediction

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Summary

A modified Arrhenius relationship was derived and used to treat simulated accelerated stability data. The results obtained were compared to those when the same data were treated according to the traditional method. The modified method presented here is easy to apply and in many cases yields a narrower predicted room temperature stability interval than does application of the traditional Arrhenius method.

Introduction

Stability testing of pharmaceutical dosage forms usually begins during the early stages of their development, the main purpose being to establish a product shelf life. Because room-temperature shelf lives may range up to several years in duration, stability tests are often performed under exaggerated conditions (e.g. elevated temperatures) to accelerate the degradation process. Information about the room-temperature stability is then extrapolated from these accelerated data. The extrapolation is possible because of the so-called Arrhenius law, which relates the rate constant k of a process and the absolute temperature T at which the rate is measured. The Arrhenius law is expressed mathematically as:

$$k = Z \cdot \exp(-E_a/RT) \quad (1)$$

where R denotes the gas constant, E_a is the energy of activation, and Z is the preexponential or frequency factor.

Although the Arrhenius law holds reasonably well in most cases, there are instances when the use of a modified form of Eqn 1 is beneficial or necessary (Bentley, 1970; Carstensen, 1971; Scher, 1980; Nash, 1987). Chief among these is the situation where limited amounts of stability data are available, specifically, when data are generated at only a few temperatures (Garrett, 1962; Carstensen, 1971). The problem in this case is that the calculated confidence interval for an extrapolated degradation rate constant (and hence, the predicted stability interval) is often so wide that it is

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meaningless. Both nonlinear (King, 1984) and linear (Carstensen, 1978, 1981) modifications of Eqn 1 have been suggested which often yield narrower confidence intervals for extrapolated degradation rate constant values than the traditional Arrhenius method. Unfortunately, the nonlinear modification is cumbersome to use because it requires nonlinear parameter estimation. The linear modification is easier to apply; however, there is some evidence to suggest that its use is not statistically valid (Slater, 1979). The following work was undertaken in order to assess more fully the utility of the linear modification of the Arrhenius equation for treating accelerated stability data.

Theoretical

In the classical Arrhenius method, degradation rate constants calculated from accelerated stability data, along with the temperatures at which the data are generated, are plotted according to Eqn 1. The plot is then used to make predictions about the room-temperature stability of the product. Since the fitting of the original stability data to Eqn 1 is not performed directly, errors associated with the data are often ignored (King, 1984). In addition, the total number of data points used in the final construction is reduced, with a concomitant decrease in the number of degrees of freedom. It is advantageous, then, to derive a relationship which uses all of the original accelerated data to construct an Arrhenius-type plot. The following assumes that the Arrhenius law is followed over the temperature range studied. It is further assumed that degradation occurs via a single pathway and follows first-order kinetics.

For a first-order degradation process, the drug content at any time t is given by:

$$C = C_0 \cdot \exp(-kt) \tag{2}$$

where k is the first-order degradation rate constant at a particular temperature and C_0 and C represent the drug contents at time $t = 0$ and t', respectively. Rearrangement of Eqn 2 yields:

$$k = (1/t) \cdot \ln(C_0/C) \tag{3}$$

Taking the natural logarithm of both sides of Eqn 3 and combining with the linear form of Eqn 1 yields the final result:

$$\ln(k) = \ln\big((1/t) \cdot \ln(C_0/C)\big)$$

$$= -E_a/RT + \ln(Z) \tag{4}$$

Experimental

Three sets of error-free data were generated from the linear form of Eqn 1 using the slope ($-E_a/R$) and intercept ($\ln Z$) values in Table 1. Degradation rate constant values were calculated for each slope/intercept data pair at 35, 45 and 55 °C. The percentage of drug remaining after a given storage time was calculated using Eqn 2, assuming an initial assay value of 100%. Three accelerated stability data points were generated for each storage temperature. Thus, each error-free data set consisted of an initial data point plus nine accelerated data points.

Real accelerated data were simulated by assuming that each error-free value was the mean value of a normally distributed population of values from which a sample value was drawn at random. A total of 300 sets of random deviates (100 for each set of error-free data) from a normally distributed population were randomly chosen from a table (Natrella, 1966), multiplied by standard deviations of 0.25, 0.50, 0.75, or 1.00, and added to the error-free values. This yielded a total of 1200 data sets – 100 for each of the four population standard deviations times three error-free data sets. The maximum deviation of the simulated data (from the error-free values) ranged from −3.3 to +3.6%.

TABLE 1

Arrhenius plot parameters of the three error-free data sets used in this work

Data set	Slope	Intercept
1	−11550	32.20
2	−7599	20.07
3	−8095	21.45

Each simulated data set was treated by both the traditional and modified methods. Room-temperature (25 °C) degradation rate constant values were extrapolated from plots constructed according to Eqns 1 and 4, and 95% confidence intervals were calculated for the extrapolated points. The upper and lower confidence interval values were used to calculate the high and low stability values after 36 months of room-temperature storage. The success of each treatment was judged on the criterion of whether the calculated 36 month stability range contained the true value, which was calculated from the error-free data.

Results and Discussion

The difference between the classical Arrhenius method (Eqn 1) and the modified procedure (Eqn 4) is best illustrated by example. A randomly chosen set of error-free accelerated stability data calculated using the parameters in Table 1 is shown in Table 2. The room-temperature degradation rate constant value extrapolated from a traditional Arrhenius plot constructed from these data is 0.0014 months^{-1}. The 36 month potency at this temperature is thus 95%. Because the data in Table 2 are error-free, this value is the true potency after 36 months of room-temperature storage.

Simulated accelerated data generated from the error-free data in Table 2 are listed in Table 3.

TABLE 2

Error-free stability values calculated using the data set 1 Arrhenius plot parameters

Temperature (°C)	Time (months)	Assay (%)
–	0	100.0
35	4	98.0
35	8	96.0
35	12	94.1
45	2	96.9
45	4	93.8
45	6	90.8
55	2	90.5
55	3	86.1
55	4	81.9

TABLE 3

Simulated accelerated stability data generated by adding random normal deviates [a] to the values in Table 2

Temperature (°C)	Time (months)	Assay (%)
–	0	99.8
35	4	98.5
35	8	95.9
35	12	93.7
45	2	96.7
45	4	93.1
45	6	87.8
55	2	89.5
55	3	84.2
55	4	81.8

[a] A population standard deviation of 1.0 was assumed.

Treating these data according to the traditional method yields an extrapolated room-temperature rate constant of 0.0017 months^{-1}, with a 95% confidence range from 5.6×10^{-5} to 0.047 months^{-1}. A degradation rate constant confidence range from 0.00039 to 0.0018 months^{-1} is obtained when the same data are treated by Eqn 4. The confidence values calculated via each method were used to construct the room-temperature stability curves shown in Figs 1 and 2. Although both methods yield 36 month stability intervals that contain the true value, the attractiveness of the modified method is apparent when the interval widths are compared.

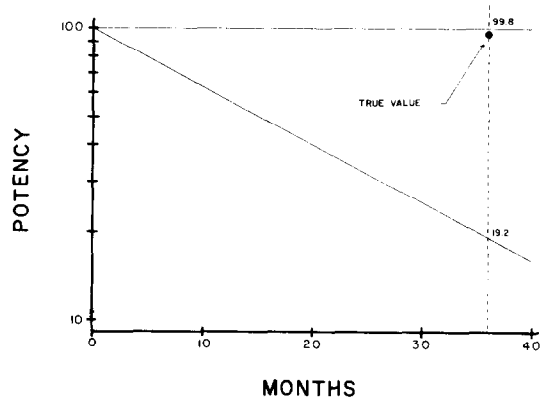

Fig. 1. Room-temperature stability plot generated using the best and worst degradation rate constant values obtained from a traditional plot (Eqn 1) of the data in Table 3. The high and low 36 month stability values are indicated.

TABLE 4

Summary of the results obtained when the simulated data sets were treated by the traditional Arrhenius method (Eqn 1) and the modified method (Eqn 4)

Normal deviate population standard deviation	Percentage of intervals containing the true value	
	Eqn 1	Eqn 4
0.25 (1) [a]	95	81
0.25 (2)	100	74
0.25 (3)	99	86
0.50 (1)	95	78
0.50 (2)	87	75
0.50 (3)	99	85
0.75 (1)	93	78
0.75 (2)	90	78
0.75 (3)	98	89
1.0 (1)	89	77
1.0 (2)	90	78
1.0 (3)	98	88

[a] Number in parentheses is the error-free data set used to generate the simulated data.

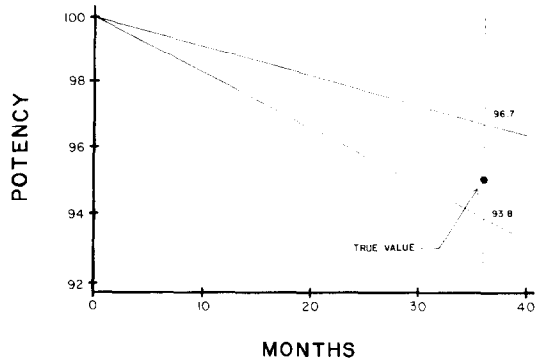

Fig. 2. Room-temperature stability plot generated using the best and worst degradation rate constant values obtained from a modified plot (Eqn 4) of the data in Table 3. The high and low 36 month stability values are indicated.

The results obtained by treating all of the simulated data sets according to Eqns 1 and 4 are summarized in Table 4. For either method to be reliable, the 36 month stability interval should contain the true value at least 95% of the time, since the interval is calculated from the 95% confidence limits of the degradation rate constant. In all cases, the nontraditional method fails a greater number of times than expected. This finding is consistent with results obtained previously by Slater et al. (1979). It should be noted that the classical method also fails to provide reliable results in several cases.

A possible reason for the high failure rate of the nontraditional method is that it depends heavily on the initial assay value. This dependence is decreased if the initial assay is treated as an unknown, the value of which is determined iteratively, or simply assumed to be 100% (Carstensen, 1981). The former is accomplished by multiple regression following rearrangement of Eqn 4 to obtain:

$$\ln(\ln(C_0/C)) = \ln(t) - E_a/RT + \ln(Z) \qquad (5)$$

Using iterated values for C_0 decreased the residual sums of squares obtained when the simulated data sets were fitted to Eqn 4; however, the number of data sets whose 36 month stability interval contained the true value decreased. This is

TABLE 5

Comparison of slopes and stability intervals calculated from Eqn 4 using the original and iterated initial assay values

Data Set	Original initial value		Iterated initial value	
	Slope	Stability interval	Slope	Stability interval
A	−12014 (0.0795) [a]	96.1 − 94.5	−11344 (0.0373) [a]	94.6 − 93.7
B	−11483 (0.0610)	95.6 − 94.4	−12002 (0.0460)	96.3 − 95.5
C	−10833 (0.2270)	96.3 − 90.3	−9947 (0.1786)	94.0 − 87.4
D	−11297 (0.1168)	95.6 − 92.8	−12244 (0.0920)	96.7 − 95.2

[a] Number in parentheses is the residual sum of squares.

TABLE 6

Comparison of slopes and stability intervals calculated from Eqn 4 using the original initial assay value and an assumed initial value of 100 (The simulated data sets are the same as those in Table 5.)

Data set	Original initial value		Initial value = 100	
	Slope	Stability Interval	Slope	Stability Interval
A	−12014 (0.0795) [a]	96.1 − 94.5	−11911 (0.0703) [a]	95.9 − 94.4
B	−11483 (0.0610)	95.6 − 94.4	−11183 (0.0797)	95.3 − 93.4
C	−10833 (0.2270)	96.3 − 90.3	−11158 (0.2616)	97.0 − 90.8
D	−11297 (0.1168)	95.6 − 92.8	−11853 (0.0972)	96.3 − 94.4

[a] Number in parentheses is the residual sum of squares.

apparently due to changes in the the stability interval width and the slope of the line fitted to the data, which determines the extrapolated value about which the stability interval is constructed. Examples of how the C_0 value affects the slope and stability interval width are shown in Table 5. Decreasing the residual sum of squares (which results in a narrower stability interval) is not necessarily beneficial, especially if the change in the slope is such that it yields an extrapolated stability that is further removed from the true value.

Setting $C_0 = 100\%$ in Eqn 4 also produced changes in the stability interval width and the slope of the line fitted to the data (Table 6), but these variations were not as great as when iterated C_0 values were used. The modified method yielded reliable results in all cases when an initial assay of 100% was assumed (Table 7). Furthermore, the average stability interval width obtained using the modified method was much less than that given by the traditional method.

Eqn 4 cannot be applied when assay values at times $t > 0$ exceed the initial assay value, since the quantity $\ln[(1/t) \cdot \ln(C_0/C)]$ is not defined. This problem may arise in situations where the degradation rate constant is very small and/or the

TABLE 7

Summary of the results obtained when the simulated data sets were treated using the traditional Arrhenius method (Eqn 1) and the modified method (Eqn 4) (An initial assay value of 100% was assumed in all calculations)

Normal deviate population standard deviation [a]	Percentage of intervals containing the true value		Mean 25° stability interval width [b] ($n = 100$)	
	Eqn. 1	Eqn. 4	Eqn. 1	Eqn. 4
0.25 (1)	95	97	6.0 (0.521)	1.2 (0.004)
0.25 (2)	99	98	11.0 (0.089)	2.0 (0.007)
0.25 (3)	99	96	13.9 (0.103)	2.2 (0.007)
0.50 (1)	95	95	13.5 (0.140)	2.4 (0.009)
0.50 (2)	93	95	20.6 (0.189)	3.9 (0.014)
0.50 (3)	97	97	25.3 (0.214)	4.3 (0.014)
0.75 (1)	99	95	23.7 (0.239)	3.8 (0.167)
0.75 (2)	92	96	31.2 (0.280)	5.9 (0.022)
0.75 (3)	100	96	37.7 (0.309)	6.5 (0.022)
1.0 (1)	96	96	35.1 (0.313)	5.5 (0.046)
1.0 (2)	92	96	40.4 (0.331)	7.9 (0.030)
1.0 (3)	99	97	47.0 (0.351)	8.8 (0.032)

[a] Number in parentheses is the error-free data set used to generate the simulated values.
[b] Number in parentheses is the standard deviation of the mean.

sample storage times are relatively short. The problem could be handled by simply omitting the offending data point(s). Realistically, the initial assay should reflect the maximum drug content. A more prudent solution, therefore, is to design the stability study to ensure that adequate degradation takes place in the accelerated samples.

Conclusion

A modified Arrhenius method was derived and tested on simulated accelarated stability data sets. The results indicate that it is valid to use this method provided an initial assay value of 100% is assumed. The modified method presented here is advantageous because it is easier to apply than some previously proposed procedures. Furthermore, this method will, in many cases, yield a narrower predicted stability interval for a given set of accelerated stability data than the traditional Arrhenius method.

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