

PFAQ



PHARMACEUTICAL FORMULATION & QUALITY



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CAPSULE

Swedish scientist Svante Arrhenius provided the first kinetic model to interpret the effect of temperature on reaction rate. Since then, pharmaceutical scientists have often attempted to predict long-term chemical stability with insufficient understanding about the kinetic model, applying the practice in inappropriate situations. Understanding critical temperature relationships is the key to more accurately predicting long-term levels for a specific product.

HIGH-TEMPERATURE STABILITY

Do the Math for Shelf Life

Predict stability using data collected at higher temperatures

By Michelle Duncan, PhD, and Irene Zaretsky, MS

Pharmaceutical scientists routinely predict long-term chemical stability at a lower temperature using data generated at a higher temperature over a shorter time period. The use of 40 degrees C chemical data (e.g., assay and related substances) to predict levels over long-term 25 degrees C storage has become such common practice that the underlying theory is overlooked or was never learned.

There is disagreement about whether three months at 40 degrees C indicates expected 25 degrees C levels for 12 months or for 24 months because of insufficient understanding or information about the kinetic model. More importantly, without some theoretical understanding, the practice is inappropriately applied to situations that do not fit the kinetic model upon which it is based, resulting in erroneous predictions.

In addition to providing the background of how these kinetic predictions work, this paper will provide the key to understanding the temperature relationships and the ability to more accurately predict the expected long-term levels for a specific product.

Arrhenius Kinetics: Where This All Began

Swedish scientist Svante Arrhenius provided the first kinetic model to interpret the



effect of temperature on reaction rate given by Equation 1 (see info box).¹⁻³ The Arrhenius equation can be applied regardless of the order (zero-order, first-order, etc.) of the reaction kinetics.⁴ Equation 2 presents the linear form of the Arrhenius equation for graphical presentation ($y = mx + b$). For many reactions, a linear relationship can be obtained between the inverse of temperature (in degrees Kelvin) and the natural log (Ln) of the measured rate constant (k), as shown in Figure 1.

THE ARRHENIUS EQUATION

$$K = A \exp(-E_a/RT) \text{ (Equation 1)}$$

k = reaction rate constant

A = Arrhenius factor (y-intercept constant)

E_a = the energy of activation for the reaction, cal/mole (1000 cal = 1 kcal)

R = the ideal gas constant, 1.987 calories/deg mole

T = the absolute temperature (degrees Kelvin), for 25° C

T = 298° K and for 40° C T = 313° K

THIS EQUATION CAN BE WRITTEN IN SEVERAL EQUIVALENT FORMS AS FOLLOWS:

$$\ln k = -E_a/RT + \ln A \text{ (Equation 2, } y = mx + b)$$

$$\ln k_2/k_1 = -E_a/R * (1/T_2 - 1/T_1) \text{ (Equation 3)}$$

$$k_2 = k_1 * \exp[-E_a/R * (1/T_2 - 1/T_1)] \text{ (Equation 4)}$$

The constants k1 and k2 are the rate constants at temperature T1 and T2 (for example 25 degrees C and 40 degrees C), respectively.

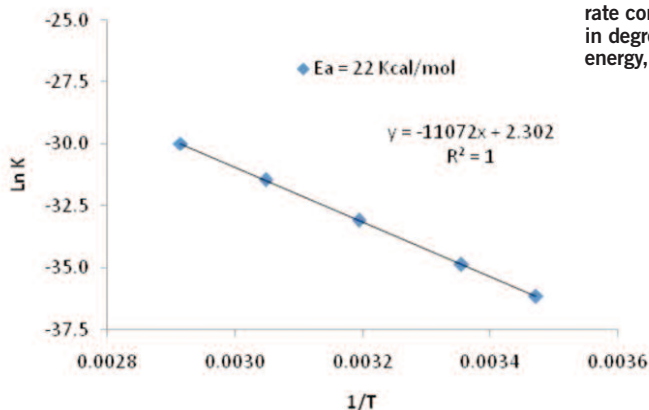
Equation 3 presents a simplified form for use with two temperatures. Equation 4 expresses the relationship between the reaction rates and the corresponding temperatures when the activation energy (E_a) of the reaction is known. Equation 4 allows for the calculation of a reaction rate constant at a lower temperature when the activation energy and the reaction rate at the higher temperature are known.

As shown by Figure 1, the Arrhenius model provides the ability to determine the reaction rate and, hence, predict stability at any temperature with knowledge of the activation energy (E_a) and the reaction rate at another temperature.

Limitations to Arrhenius' Model

The first requirement is a reaction (ongoing) where the reaction rate constant at

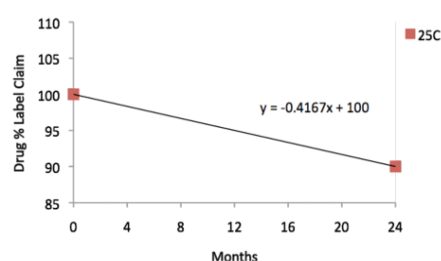
Figure 1.



Arrhenius plot of Ln K against 1/T. Slope = - E_a/R k = reaction rate constant, T = temperature in degrees Kelvin E_a = activation energy, R = ideal gas constant.

a given temperature can be determined. When monitoring the generation of a primary degradation product, the presence of a secondary degradation reaction can introduce error to the calculation of the primary rate constant and any attempted Arrhenius model predicted rates. Likewise, if a component is consumed to the extent that the reaction equilibrium changes, the reaction rate will not remain constant. The Arrhenius kinetic model requires a reaction rate constant (k).

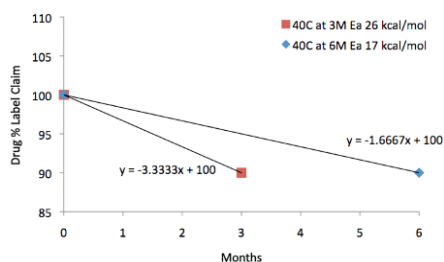
Figure 2.



The zero-order kinetic model for 10% drug loss over 24 months at 25 degrees C shown as the percent of drug remaining as a function of time at 25 degrees C.

The Arrhenius kinetic model can be utilized across the temperature range where a constant relationship between the effect of temperature on the reaction rate is maintained, where the graph is linear. The reaction mechanism should not change over the temperature range studied. Conformance to the model (linearity) is often lost when crossing a phase change, such as freezing and the glass-phase transition of proteins and peptides. Reactions where the rate is dependent upon oxygen, light (photochemical), diffusion, or microorganism-based decomposition may not demonstrate Arrhenius kinetics over any temperature range.

Figure 3.



Zero-order kinetic models for 10% drug loss over three months and over six months at 40 degrees C.

Table 1. Relationship of reaction rates at 40 degrees C and activation energy (E_a) for drug loss

Months at 40 degrees C to reach 10% drug loss	k_{40} (drug %label claim per month)	k_{25} (drug %label claim per month)	E_a (kcal/mole) activation energy
6	-1.6667	-0.4167	17
3	-3.3333	-0.4167	26

Finding E_a for the Reaction

The activation energy (E_a) for a reaction can be determined by conducting stability studies at several different temperatures and applying the Arrhenius kinetic model. The slope of the line formed with Equation 2 contains E_a , as demonstrated in Figure 1. Higher temperatures (e.g., 55 degrees C, 70 degrees C) and corresponding shorter times (e.g., weeks, days) can be employed for this determination provided the Arrhenius kinetic model remains valid (see Limitations to Using Arrhenius Kinetic Model). The E_a for drug decomposition will usually fall in the range of 12 to 24 kcal/mole, with a typical value of 19 to 20 kcal/mole.⁵ The activation energy can be approximated based upon prior knowledge of the drug decomposition kinetics. Once the E_a is known, it usually remains valid for use through small concentration changes or slight formulation changes.

Importance of E_a : Theoretical Model for Drug Loss

The following discussion demonstrates the relationship of drug degradation kinetics at 40 degrees C and 25 degrees C, where drug loss is the shelf life-determining parameter. For this illustration, acceptable product stability is based upon a lower limit of 90% label claim

and the expiration date set at exactly 90% label claim. For this exercise, a zero-order degradation kinetics model ($\Delta\text{drug}/\Delta\text{time} = -k$) is applied to determine the rate for 10% of drug loss occurrence over 24 months at 25 degrees C (Figure 2). The slope was calculated and is equal to -0.4167 drug %label claim/month, which is the reaction rate constant at 25 degrees C (k_{25}). Hence, for the drug to remain within acceptance criteria for 24 months at 25 degrees C, the rate of degradation at 25 degrees C must be less than 0.4167 drug %label claim/month.

In a similar manner, drug loss can be modeled at 40 degrees C accelerated temperature for the two scenarios of 10% drug loss occurring at three months and at six months (Figure 3). The slopes, which represent the reaction rate constant at 40 degrees C (k_{40}), were calculated to be -1.6667 drug %label claim/month for the six months limit scenario and -3.3333 drug %label claim/month for the three months limit scenario.

Using the Arrhenius equation (Equation 3) and the reaction rates at 25 degrees C and 40 degrees C, the E_a can be calculated as shown in Table 1. The Arrhenius equation can be applied regardless of the order of the reaction kinetics. For the kinetic model that assumes 10% drug loss at 24 months at 25 degrees C ($k_{25} = -0.4167$ drug %label

Table 2. Relationship of reaction rates at 40 degrees C and activation energy (E_a) for impurity generation

Months at 40 degrees C for impurity to reach 1%	k_{40} (%w/w impurity per month)	k_{25} (%w/w impurity per month)	E_a (kcal/mole) activation energy
6	0.1667	0.0417	17
3	0.3333	0.0417	26

Table 3. Relationship of rates and activation energy (Ea) for shelf-life stability when limit is reached after six months at 40 degrees C.

Months at 25 degrees C to reach 1.0% w/w degradant limit (kinetic shelf life)	k25 (%w/w per month) Rate of degradant growth at 25 degrees C through shelf life	k40 (%w/w per month) Rate of degradant growth at 40 degrees C when 1.0% w/w limit is reached at six months	Ea (kcal/mole) activation energy
24	0.0417	0.1667	17
18	0.0556	0.1667	14
12	0.0834	0.1667	9

claim/month) and 10% drug loss at three months at 40 degrees C ($k_{40} = -3.3333$ drug %label claim/month), the calculated Ea is 26 kcal/mole. For the model that assumes 10% drug loss at 24 months at 25 degrees C ($k_{25} = -0.4167$ drug %label claim/month) and 10% drug loss at six months at 40 degrees C ($k_{40} = -1.6667$ drug %label claim/month), the calculated Ea is 17 kcal/mole.

Knowledge of the Ea is key to the interpretation of accelerated data for predictions at lower temperatures. If the Ea is low (less than or equal to 17 kcal/mole), the accelerated 40 degrees C drug concentration must remain greater than 90% label claim for six months to achieve at least 90% label claim for a shelf life of 24

month at 25 degrees C. If the Ea is high (more than or equal to 26 kcal/mole), the accelerated 40 degrees C drug concentration must remain greater than 90% label claim for only three months (and be 80 %label claim at six months), and yet the product will remain at or above 90% label claim for a shelf life of 24 month at 25 degrees C. This application of Ea and Arrhenius kinetics to predict shelf life can be applied to any drug level (limit) specified.

Theoretical Model for Impurity/Degradant Generation

The same approach can be used to understand and predict the generation of impurities/degradants. For this exercise, a

zero-order degradation kinetics model ($\Delta\text{Impurity}/\Delta\text{time} = -k$) is applied to determine the rates for an arbitrary 1% impurity growth at 25 degrees C and at 40 degrees C. The calculated slope for growth from 0 to 1.0% w/w over 24 months at 25 degrees C is equal to 0.0417% w/w per month, which is the impurity generation rate constant at 25 degrees C (k_{25}). In the same manner, the impurity generation rate at 40 degrees C can be calculated for reaching 1.0% w/w after three months (0.3333% w/w per month) and for reaching 1.0% w/w after six months storage (0.1667% w/w per month). Table 2 summarizes the corresponding rates and Eas:

Example calculation

Where:

$$\ln k_2/k_1 = -E_a/R \cdot (1/T_2 - 1/T_1) \text{ (Equation 3)}$$

$$\ln (k_{40}/k_{25}) = - [E_a/1.987 \cdot (1/313 - 1/298)]/1000 \text{ kcal/kcal}$$

$$k_{40} = 0.1667 \text{ w/w degradant/month}$$

$$k_{25} = 0.0417 \text{ w/w degradant/month}$$

Solving for Ea:

$$E_a = - [\ln (0.1667/0.0417) \cdot 1.987] / [(1/313 - 1/298) \cdot 1000]$$

$$E_a = 17 \text{ kcal/mole}$$

As the Ea increases, the reaction rate at 40 degrees C increases. The degradant level at six months at 40 degrees C is predictive of the degradant level to be reached after 24 months at 25 degrees C when the Ea is 17 kcal/mole. Degradants with reaction mechanisms with high activation energies (greater than 17 kcal/mole) can exhibit levels exceeding 1.0% w/w by six months at 40 degrees C, yet have 25 degrees C values below the 1.0% w/w limit.

Shelf Life, Rates, and Activation Energy

To demonstrate the importance of Ea in predicting long-term shelf life at 25 degrees C from 40 degrees C rates, the Arrhenius kinetic equation was used to demonstrate the relationship of reaction rates and Ea. The relationships are demonstrated in Table 3 for the scenario where the degradant reaches the 1.0% w/w limit at six months at 40 degrees C and the zero-order rate constant (k_{40}) is equal to 0.1667% w/w degradant/month.

Table 4 demonstrates these relationships for the scenario where the degradant reaches the 1.0% w/w limit at three months at 40 degrees C and the zero-order rate constant (k_{40}) is equal to 0.3333% w/w

Table 4. Relationship of rates and activation energy (Ea) for shelf-life stability when limit is reached after three months at 40 degrees C.

Months at 25 degrees C to reach 1.0% w/w degradant limit (kinetic shelf life)	k25 (%w/w per month) Rate of degradant growth at 25 degrees C through shelf life	k40 (%w/w per month) Rate of degradant growth at 40 degrees C when 1.0% w/w limit is reached at three months	Ea (kcal/mole) activation energy
24	0.0417	0.3333	26
18	0.0556	0.3333	22
12	0.0834	0.3333	17
9	0.1111	0.3333	14



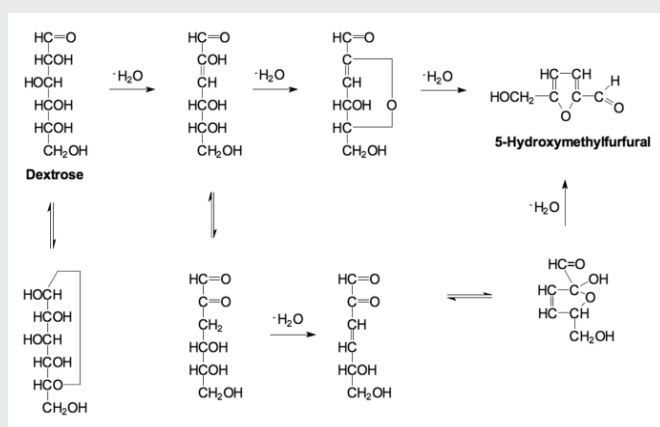
CASE STUDY

Predict Dextrose Degradation

It is widely reported that dextrose in solution degrades to form 5-hydroxymethylfurfural (5-HMF) during heating (terminal sterilization) and over time.⁶⁻⁸ According to the dextrose injection monograph in the USP, the limit for 5-HMF and related substances is not more than 0.25 absorbance units at 284 nm wavelength.⁹

The multiple pathway formation of 5-HMF by dehydration of dextrose is depicted in Figure A.¹⁰ The overall kinetic scheme, involving an intermediate,

Figure A.



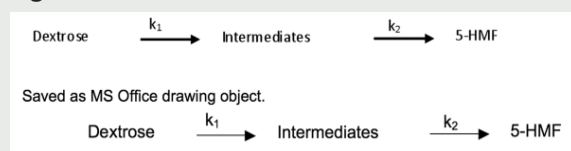
Possible mechanism of 5-HMF formation in dextrose solutions (reference 10).

with definable rate constants for formation and reaction, has been published by at least three groups.¹¹ The *E_a*s for *k*₁ and *k*₂ of the reaction scheme shown in Figure B, as determined by Sturgeon and colleagues, are 32.6 kcal/mole and 12.3 kcal/mole, respectively. Previously, Heimlich and Martin determined the *E_a* for 5-HMF formation from dextrose to be 31.2 kcal/mole and 31.8 kcal/mole, dependent upon the method used to determine the first-order rate constant.¹¹

Before appreciable formation of 5-HMF can occur, a reasonably high steady state level of the intermediate must first be established. Thus, the overall generation of 5-HMF will be dependent upon the *k*₁ with an activation energy of 32.6 kcal/mole. Using Table 5 and the *E_a* of 31 kcal/mole listing, the last column indicates that 5-HMF levels measured after two months at 40 degrees C will be predictive of 24 months at 25 degrees C. The production of 5-HMF is proceeding at least 12 times faster at 40 degrees C than at 25 degrees C. The level of 5-HMF after six months at 40 degrees C will be three times higher than the level reached at 24 months at 25 degrees C.

The U.S. Food and Drug Administration/International Conference on Harmonisation Guidance for Industry, Q1A(R2), Stability Testing of New Drug

Figure B.



Simplified reaction scheme for 5-HMF formation.

Substances and Products, requires long-term testing over 12 months at room temperature (25 degrees C or 30 degrees C) and over six months at accelerated conditions of 40 degrees C at the time of submission. The document's Objections of the Guidance section states: "The guidance exemplifies the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons."¹²

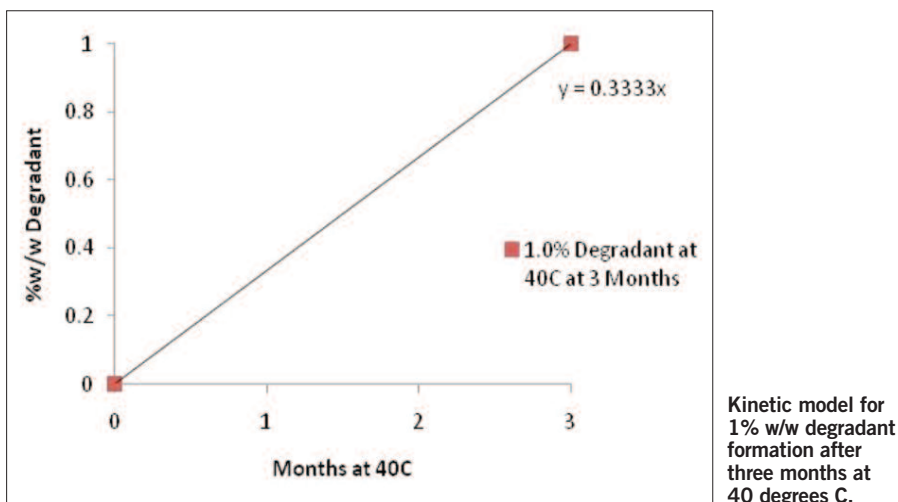
The known chemistry of dextrose degradation to 5-HMF as presented here represents a justifiable reason for submitting a shorter time period of accelerated data. The kinetic model with known activation energy indicates that submission of two months at 40 degrees C data is sufficient and more appropriate than six months at 40 degrees C data to estimate the level of 5-HMF at 25 degrees C and to support a requested 24 months at 25 degrees C expiration dating period. ■

Table 5.

Stability predictions based upon the ratio of rates (*E_a*) at 40 degrees C and 25 degrees C.

<i>E_a</i> (kcal/mole) activation energy	Ratio (R) <i>k</i> ₄₀ to <i>k</i> ₂₅ (<i>k</i> ₄₀ = <i>R</i> * <i>k</i> ₂₅)	Required months at 40 degrees C to reach level equivalent to 12 months at 25 degrees C	Required months at 40 degrees C to reach level equivalent to 18 months at 25 degrees C	Required months at 40 degrees C to reach level equivalent to 24 months at 25 degrees C
9	2	6	9	12
14	3	4	6	8
17	4	3	4.5	6
20	5	2.5	3.6	5
22	6	2	3	4
26	8	1.5	2.25	3
31	12	1	1.5	2

Figure 4.

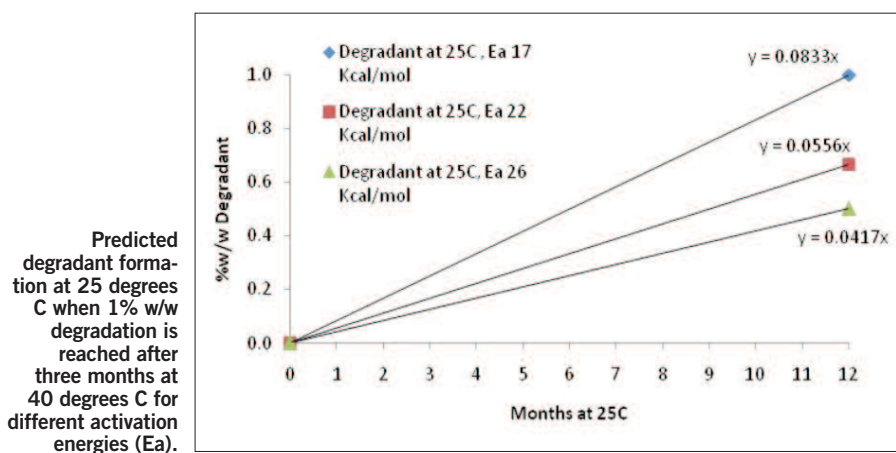


degradant/month. The zero-order degradant generation rates at 25 degrees C (k_{25}) are calculated for reaching 1.0% w/w at different expiry time intervals: 12, 18, and 24 months (Tables 3 and 4). For these examples, the initial time zero starting level is set to 0% w/w. As shown in Tables 3 and 4, each of these different shelf-life scenarios has a reaction mechanism with a different Ea.

As the Ea decreases, the reaction rate at 25 degrees C increases relative to the rate at 40 degrees C. The temperature sensitivity of the reaction decreases with decreased activation energy, as indicated by the decreased proportionality between the rates ($k_{40} \propto k_{25}$). When the activation energy is 9 kcal/mole (very low), even when remaining within the limit of 1.0% w/w degradation through six months at 40 degrees C, a maximum of 12 months at 25 degrees C shelf life can be projected.

In comparison, when activation energy is 17 kcal/mole with 1.0% w/w degradation through six months at 40 degrees C, 24 months elapses before the same 1.0% w/w degradant level is reached at 25 degrees C. If the Ea is known to be 17 kcal/mole or greater, then 40 degrees C values at six months of 1.0% w/w (or less) can kinetically support a shelf life, for this degradant limit, of 24 months at 25 degrees C. (This article does not address data accuracy—variability of the analytical methodology and/or the product samples—or the use of confidence intervals,

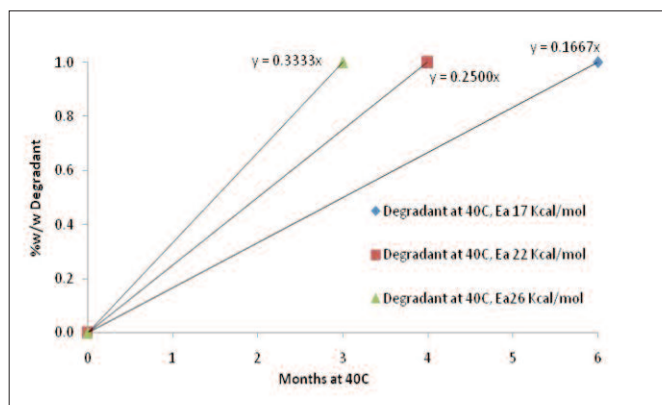
Figure 5.



Editor's Choice

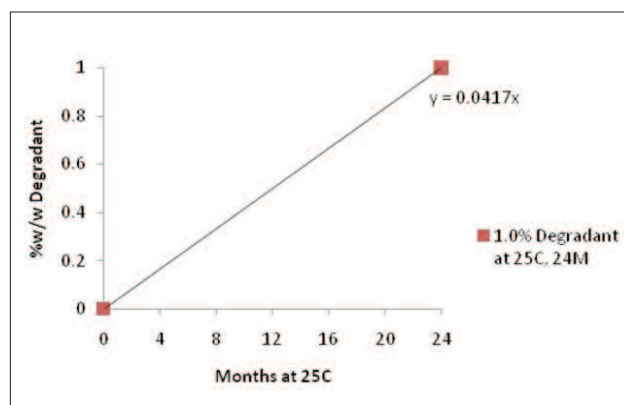
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Figure 6.



Degradant reached 1%w/w at 40 degrees C; each model predicts the same level at 25 degrees C.

Figure 7.



Degradant level at 25 degrees C for the three activation energy models in Figure 6.

which should also be incorporated when establishing product shelf life.)

Because many drugs demonstrate Eas of 19-20 kcal/mole, this is the basis for the practice of comparing six month 40 degrees C values against the specification limit as a predictor of meeting that specification through a shelf life of 24 months at 25 degrees C. The proportionality of six months storage at 40 degrees C as predictive of 24 months at 25 degrees C is predicated upon an activation energy of at least 17 kcal/mole.

Some reactions proceed relatively fast at higher temperatures, as demonstrated in Table 4 and Figure 4. In this example, the degradant growth at 40 degrees C reaches the product limit (assigned here as 1.0% w/w) after three months storage ($k_{40} = 0.3333\% \text{ w/w degradant per month}$). The usual response is to assume that only a 12-month shelf life at 25 degrees C can be achieved. In reality, the levels of degradant reached at 25 degrees C are dependent upon the Ea of the reaction as shown in Figure 5.

The proportionality of the level measured after three months at 40 degrees C as predictive of the level for 12 months at 25 degrees C is valid only for an Ea of 17 kcal/mole. If the activation energy is known to be 22 kcal/mole or greater, then 40 degrees C values at three months up to 1.0% w/w can kinetically support a shelf life, for this degradant limit, of 18 months at 25 degrees C. This application of Ea and Arrhenius kinetics to the prediction of shelf life can be applied to any degradant level specified.

Stability Prediction Made Easy

Now that the relationship of reaction rates to Ea is understood, it becomes easier to predict values over longer time periods at lower storage temperatures, like 25 degrees C, from values obtained at higher (accelerated degradation) temperatures, such as 40 degrees C.

The Ea is the proportionality factor between reaction rates at different temperatures ($k_{40} \propto k_{25}$). The Arrhenius equation (Equation 4) can be solved for the exact relationship between reaction rates at 40 degrees C and 25 degrees C for any activation energy Ea. This proportionality can be used to predict levels and shelf life, as presented in Table 5. When the activation energy is 17 kcal/mole, the same degradant limit is reached at six months at 40 degrees C and at 24 months at 25 degrees C.

Table 5 can be used as a guide to interpret 40 degrees C kinetic prediction of 25 degrees C shelf life. As data is collected over time at 40 degrees C, the results at each test interval can be used to predict the level and, hence, the shelf life at 25 degrees C. When the activation energy is greater than 17 kcal/mole, samples stored at 40 degrees C and tested at six months will exhibit levels greater than what will be actually reached over 24 months at 25 degrees C. If the activation energy is 26 kcal/mole, the level measured at three months at 40 degrees C represents the expected level for 24 months at 25 degrees C, and the level measured at six months at 40 degrees C will actually represent twice the expected

level for 24 months at 25 degrees C.

The concept presented in Table 5 is shown in Figures 6 and 7. Figure 6 shows three different rate scenarios for the months at 40 degrees C to reach 1% w/w degradant. When the Ea for the reaction is 26 kcal/mole or greater, although the 1% w/w level is reached by three months at 40 degrees C ($k_{40} = 0.3333\% \text{ w/w degradant/month}$), the degradant growth at 25 degrees C will not reach 1%w/w until 24 months or beyond, as represented in Figure 7.

When the Ea for the reaction is 22 kcal/mole and at four months at 40 degrees C the 1% w/w level is reached ($k_{40} = 0.2500\% \text{ w/w degradant/month}$), the degradant growth at 25 degrees C will again not reach 1%w/w until 24 months, as represented in Figure 7. An Ea of 17 kcal/mole and a six months 40 degrees C degradant level of 1% w/w ($k_{40} = 0.1667\% \text{ w/w degradant/month}$) likewise corresponds to a projection of 24 months at 25 degrees C to reach 1% w/w. Thus, as demonstrated, different rates at 40 degrees C can project to the same or similar stability at 25 degrees C.

Additionally, as indicated in Table 5, for the same activation energy of 17 kcal/mole, when the degradation rate at 40 degrees C is faster, reaching 1% w/w by three months ($k_{40} = 0.3333\% \text{ w/w degradant/month}$), the 1%w/w level is projected to be reached by 12 months at 25 degrees C (Figures 4 and 5). A shelf life of 12 months is kinetically supported. Consequently, if the activation energy is lower than 17 kcal/mole for this same k_{40} rate of reaching 1% w/w

by three months ($k_{40} = 0.3333\%$ w/w degradant/ month), levels at 25 degrees C will reach 1% w/w before 12 months, and a shelf life of 12 months is not kinetically supported. The information in Table 5 can be used to estimate shelf life based upon the E_a and stability at 40 degrees C.

The practice of predicting long-term chemical stability at a lower temperature using data generated at a higher temperature over a shorter time period is based upon application of the Arrhenius kinetic model. The Arrhenius equation can be applied regardless of the order of the reaction kinetics. By using the E_a with the experimental level of drug or degradant obtained at a higher temperature (40 degrees C), the expected level of drug or degradant over long-term storage at a lower temperature (25 degrees C) can be more accurately predicted and the kinetic shelf life estimated. The proportionality of six months storage at 40 degrees C as predictive of 12 months at 25 degrees C is predicated upon an activation energy of 9 kcal/mole. The proportionality of six months storage at 40 degrees C as predictive of 24 months at 25 degrees C is predicated upon an activation energy of 17 kcal/mole. As the activation energy increases, the temperature sensitivity of the reaction increases, resulting in a greater difference in the rates at different temperatures. The information in Table 5 can also be used to estimate shelf life at 25 degrees C based upon the activation

energy and the stability at 40 degrees C. As presented, the Arrhenius kinetic model can be applied to specific drug chemistry to scientifically justify appropriate months at accelerated 40 degrees C condition for submission. ■

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