

STABILITY SYSTEM

ScienTek Software, Inc.

This short discussion is an excerpt from "A Crash Course on Chemical Kinetics and Statistical Data Treatment" that is part of the documentation for STABILITY SYSTEM program from ScienTek Software, Inc.

Arrhenius Equation: Effect of Temperature on Reaction

The theory of the temperature effect on the reaction rate originated from the temperature effect on the equilibrium constant. It is known that:

$$\frac{d \ln K}{d \frac{1}{T}} = -\frac{H}{R} \quad (1)$$

where K is an equilibrium constant, R is the gas constant, and H is the heat of reaction. The equilibrium constant is $K = \frac{k_1}{k_2}$, where k_1 and k_2 are the rate constants for the forward and reverse reactions respectively. Substituting the relationship into EQ(1), we obtain:

$$\frac{d \ln k_1}{d \frac{1}{T}} - \frac{d \ln k_2}{d \frac{1}{T}} = -\frac{H}{R} \quad (2)$$

Arrhenius [S. Arrhenius, *Z. Phys. Chem.*, 4, 226(1889)] recognized that EQ(2) could be conveniently divided into two parts, each having the form of:

$$\frac{d \ln k}{d \frac{1}{T}} = -\frac{E}{R} \quad (3)$$

where E is referred by Arrhenius as representing the energy difference between the reactants and an activated species. The term E is therefore called the *activation energy*.

Taking E as a constant, EQ(3) can be integrated to yield:

$$\ln k = \ln A - \frac{E}{RT} \quad (4)$$

where $\ln A$ is the constant of integration. EQ(4) can be converted to:

$$k = Ae^{-\frac{E}{RT}} \quad (5)$$

which is the most widely adopted form of the Arrhenius equation. The term A is the *pre-exponential factor*. This is related to the frequency of molecular collisions in the collision theory and to the entropy term in the transition state theory.

The activation energy is the energy barrier that the reactants must surmount in order to react. Therefore the activation energy is viewed as an energetic threshold for a fruitful reaction.

Application of the Arrhenius equation in pharmaceutical stability testing is straightforward. In the isothermal method, the system to be investigated is stored

under several high temperatures with all other conditions fixed. Excess thermal exposure accelerates the degradation and thus allows the rate constants to be determined in a shorter time period.

The rate constant at each temperature is determined. The logarithm of the rate constant is linearly related to $\frac{1}{T}$ as shown in EQ(4). Although it is possible to calculate A and E with the Arrhenius equation by just using rate constants at two temperatures, it would be more realistic and reliable to use at least three rate constants (preferably more) at three different temperatures and determine A and E using a statistical method. This statistical method will be discussed in Chapter 2.

Having determined the values of A and E , it is then possible to use the Arrhenius equation to project the rate constant at any temperature. This process is graphically represented in Figure 4.

What we have just discussed is a straightforward application of the Arrhenius equation and is probably one of the most important tools that a formulator possesses in the product development process.

Figure 4: Application of Arrhenius equation in accelerated stability testing

