STABILITY OF PHARMACEUTICALS

Decomposition and Stabilization of Medicinal Agents

Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis, and these processes may affect the stability of drugs in liquid, solid, and semisolid products.

Examples of Martin physical pharmacy text book

- Example 1 In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$

The rate of reaction is

$$\text{Rate} = -\frac{d[(CH3CO)2O]}{dt}$$

$= k\,[(CH_3CO)_2O]\,[C_2H_5OH]^2$

What is the order of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction?

- If the alcohol, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer: The reaction appears to be first order with respect to acetic anhydride, second order with respect to ethyl alcohol, and overall third order. However, because alcohol is the solvent, its concentration remains essentially constant, and the rate expression can be written

$-d\,[(CH_3C0)_2O]/dt \;= k'[(CH_3CO)_2O]$

Kinetically the reaction is therefore a pseudo-first-order reaction.

Example .2

Shelf Life of an Aspirin Suspension-

A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is $4.5 \times 10^{-6}\ sec^{-1}$. Calculate the zero-order rate constant. Determine the shelf life, t_{90}, for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

Answer: $k_o = k \times$ [Aspirin in solution], from equation ($k\,[A] = k_0$). Thus,

$k_o = (4.5 \times 10^{-6}\ sec^{-1}) \times (0.33\ g/100\ mL)$

$k_o = 1.5 \times 10^{-6}\ g/100\ mL\ sec^{-1}$

$t_{90} = 0.10[A]_o / k_0 =$

$[(0.10 \times 6.5\ g/100\ mL)] / [(1.5 \times 10^{-6}\ g/100\ mL sec^{-1})]$

$= 4.3 \times 10^{5}\ sec = 5.0\ days$

EXAMPLE .3

Decomposition of Hydrogen Peroxide

- The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(a) Calculate k using equation ($k=\frac{2.303}{t}\log\frac{C0}{C}$).

(b) How much hydrogen peroxide remained undecomposed after 25 min?

(a)

$$k=\frac{2.303}{t}\log\frac{C0}{C}$$

$$k=\frac{2.303}{t}\log\frac{57.90}{9.60} \quad = 0.0277\ \text{min}^{-1}$$

(b)

$$0.0277 = \frac{2.303}{25}\log\frac{57.90}{C}$$

c = 29.01

EXAMPLE .4

First-Order Half-Life

- A solution of a drug contained 500 units/mL when prepared. It was analyzed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to one-half of its original concentration?

We have

$$k=\frac{2.303}{40}\log\frac{500}{300} = 0.0128\ \text{day}^{-1}$$

$$t=\frac{2.303}{0.0128}\log\frac{500}{250} = 54.3\ \text{days}$$

Example .5

Saponification of Ethyl Acetate

- Walker investigated the saponification of ethyl acetate at 25°C:

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 *M*. The change in concentration, *x*, of alkali during 20 min was 0.000566 mole/liter, therefore, (a - x) = 0.01000 - 0.00566 = 0.00434.

Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation

$$\frac{x}{a(a-x)} = Kt$$

or

$$k = \frac{1}{at}\left(\frac{x}{a-x}\right)$$

, we obtain

a=0.01

x=0.000566

a-x=0.009434

$$K = \frac{1}{0.01\times 20}\frac{0.000566}{0.009434} = 0.299 \text{ liter mole}^{-1}\text{min}^{-1}$$

(b) The half-life of a second-order reaction is

$$t1/2 = 1/ak$$

It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t_{1/2} = \frac{1}{0.01\times 0.299} = 334.44\text{min}$$

Example .6

- The rate constant k_1 for the decomposition of 5-HMF (5-hydroxymethylfurfural) at 120°C (393 K) is 1.173 hr^{-1} or 3.258 x 10^{-4} sec^{-1}, and k_2 at 140°C (413 K) is 4.860 hr^{-1}. What is the activation energy, Ea, in kcal/mole and the frequency factor, A, in sec^{-1} for the breakdown of 5-HMF within this temperature range?

We have

$$\log \frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

$$\log \frac{4.860}{1.173} = \frac{Ea}{2.303x1.987}\left(\frac{413-393}{413 \text{ x } 393}\right)$$

Ea = 23000 cal/mole

Ea = 23 kcal/mole

At 120°C, using equation

$\log K = \log A - \frac{Ea}{2.303R}\frac{1}{T}$

, we obtain

$\log (3.258 \text{ x } 10^{-4} \text{ sec}^{-1}) = \log A - \frac{23{,}000 \text{ cal}}{2.303x1.987}\frac{1}{393}$

A = 2 x 10^9 sec^{-1}

Example .7

Increased Shelf Life of Aspirin

- Aspirin is most stable at pH 2.5. At this pH the apparent fist-order rate constant is 5×10^{-7} sec^{-1} at 25°C. The shelf life of aspirin in solution under these conditions can be calculated as follows:

t_{90} = 0.105/(5×10^{-7})= 2.1×10^{5} sec

= 2 days

As one can see, aspirin is very unstable in aqueous solution.

- Would making a suspension increase the shelf life of aspirin?

The solubility of aspirin is 0.33g/100mL. At pH 2.5, the apparent zero- order rate constant for an aspirin suspension is

$ko = 5 \times 10^{-7}$ sec $^{-1}$ x 0.33 g/100 mL = 1.65×10^{-7} g/mL • sec

If one dose of aspirin at 650 mg per teaspoonful is administered, then one has 650 mg/5 mL = 13 g/100 mL. For this aspirin suspension,

t_{90} = [(0.1) (13)]/ [1.65×10^{-7}] = 7.9×10^{6} sec = 91 days

- The increase in the shelf-life of suspensions as compared to solutions is a result of the interplay between the solubility and the stability of the drug. In the case of aspirin, the solid form of the drug is stable, whereas when aspirin is in solution it is unstable. As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.