CHAPTER II

REVIEW OF LITERATURE

Chemical Kinetics (Carstensen, 1990).

Kinetic principles are always of great importance in stability programs. Optimization of a dosage from design are often based on, for instance, a pH-rate profile, and hence the kinetics leading to the pH-rate profile must be established. The goal of chemical kinetics is to elucidate reaction mechanisms. It is therefore important to lay the proper kinetic foundation before discussing the phenomena encountered in actual dosage forms.

The fundamental principles are mostly conveniently described by solution kinetics which are best elucidated. First, it is necessary to develop a stability-indicating assay. In a stability indicating assay methodology, it is usual to deliberately decompose the drug in a solution so as to challenge the assay and ensure its capability of separating the parent drug from decomposition products. It is also desired to establish the kinetic order of the decomposition.

1. Rate of Reactions (Connors, Amidon and Kennon, 1979).

The rate of a reaction can be expressed either as the decrease in concentration per unit time of any of the reacting substances, or as the increase in concentration per unit time of one of the products. The rate of a reaction may be written as $-d[D]/dt$ or $d[P]/dt$where D is a drug molecule and P is a product molecule.

2. Order of Reactions (Connors, Amidon and Kennon, 1979).

The order of a chemical reaction determines the shape of the concentration-time profile of a drug or drug products, whereas the rate constant determines its slope. The order of a reaction with respect to a single reactant is equal to the power to which the concentration term of the reactant is raised in the experimental rate equation. An example of a chemical reaction can be expressed as :

$$uA + vB + wC \xrightarrow{k} \text{products} \qquad (1)$$

and if its reaction rate is

$$\text{rate} = k [A]^{u} [B]^{v} [C]^{w} \qquad (2)$$

where A, B and C are the reactants and k is a rate constant; u, v and w will be the order of reaction with respect to A, B and C, respectively. If u, v, and w have values of 2, 1 and 0, respectively, it is said to be second-order with respect to A, first-order in B and zero-order in C. The overall order of the reaction is the sum of the power of the concentration terms affecting the experimentally determined rate. In the above example, the reaction would be third-order overall.

3. Determination of Order (Martin, Swarbrick and Cammarata, 1983).

The order of a reaction may be determined by several methods.

3.1 Substitution Method.

The data accumulated in a kinetic study may be substituted in the integrated form of the equations that describe the various orders. When the equation of which the calculated k values remain constant within the limits of experimental variation is found, the reaction is considered to be of that order.

3.2 Graphic Method.

A plot of the data in the form of a graph as shown in Figure (1) may also be used to ascertain the order. If a straight line results when concentration is plotted against *t*, the reaction kinetics is said to be zero-order. The reation kinetics is first-order if log (concentration) versus *t* yields a straight line; and it is second-order if 1/(concentration) versus *t* gives a straight line (in the case in which the initial concentration are equal). When a plot of $1/(\text{concentration})^2$ against *t* produces a straight line, with all reactants at the same initial concentration, the reaction kinetics is third-order.

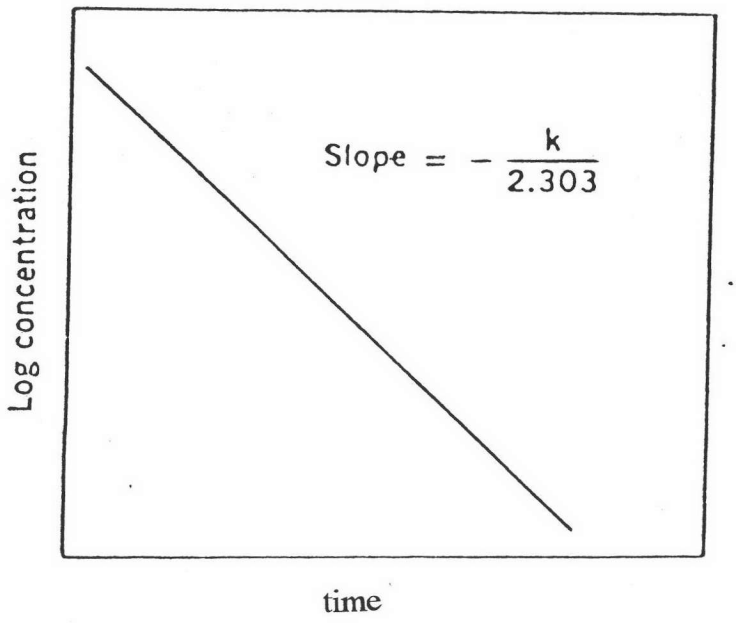

Figure 1: A linear plot of log C versus time for a first-order reaction.

3.3 Half-Life Method.

In a zero-order reaction, the half-life ($t_{1/2}$) is proportional to the initial concentration *a*. The half-life of a first-order reaction is independent of *a*; $t_{1/2}$ for a second-order reaction, in which *a=b*, is proportional to $1/a$. In a third-order reaction, in which *a=b=c*, $t_{1/2}$ is proportional to $1/a^2$. The relationship between these results shows that, in general, the half-life of a reaction in which the initial concentrations of all reactants are identical is

$$t_{1/2} = \frac{1}{a^{n-1}} \qquad (3)$$

in which a, b, c and n are the initial concentrations of reactant A, B, C and order of reaction, respectively.

4. Kinetic pH Profile.

4.1 Specific Acid-Base Catalysis (Martin, Swarbrick and Cammarata, 1983).

Solutions of a number of drugs undergo accelerated decomposition upon an addition of an acid or a base. In the case of specific acid catalysis, the reactant is catalyzed by solvated protons, that is, by the hydronium ion in an aqueous solution. While the drug is catalyzed by hydroxide ions in an aqueous solution in the case of specific base catalysis.

The pH dependence for the hydrolysis of an ester is an example of specific acid-base catalysis. In an acidic solution, the hydrolysis involves an

initial equilibrium between the ester S and hydrogen ion followed by a rate-determining reaction with water, R:

$$S + H^+ \underset{k}{\rightleftharpoons} SH^+ \quad (4)$$

$$SH^+ + R \rightarrow P \quad (5)$$

This general reaction scheme assumes that the product of the hydrolysis reaction does not recombine to form the ester.

For the generalized reaction, the rate of product formation is given by

$$\frac{dP}{dt} = k\,[SH^+]\,[R] \quad (6)$$

The concentration of the conjugated acid SH^+ can be expressed in terms of measurable quantities, because the pre-equilibrium requires that

$$K = \frac{[SH^+]}{[S][H^+]} \quad (7)$$

Thus,

$$[SH^+] = K[S][H^+] \quad (8)$$

and it follows that

$$\frac{dP}{dt} = kK[S][H^+][R] \quad (9)$$

Since water, R, is present in great excess, equation (9) reduce to the apparent rate law

$$\frac{dP}{dt} = k_H[S][H^+] \qquad (10)$$

in which

$$k_H = kK[R] \qquad (11)$$

The hydrogen ion concentration term in equation (10) indicates that the process is a specific hydrogen ion catalyzed reaction.

A rate-pH profile for the reaction can be obtained by studying the acid catalyzed hydrolysis of the ester at various concentration of hydrogen ion that is by hydrolyzing the ester in buffer solutions of different pH's. At a given pH, an apparent first-order reaction is observed :

$$\frac{dP}{dt} = k_{obs}[S] \qquad (12)$$

in which $$k_{obs} = k_H[H^+] \qquad (13)$$

taking the logarithm of equation (13)

$$\log k_{obs} = \log[H^+] + \log k_H \qquad (14)$$

or, equivalently, $$\log k_{obs} = -(-\log[H^+]) + \log k_H \qquad (15)$$

or $$\log k_{obs} = - pH + \log k_H \quad (16)$$

Thus, a plot of log k_{obs} against the pH of the solution in which the reaction is run gives a line of slope equal to −1.

The general reaction of specific hydroxide ion catalyzed decomposition of an ester, S, can be written as

$$S + OH^- \longrightarrow P \quad (17)$$

and the rate of product [P] formation is therefore given by

$$\frac{dP}{dt} = k_{OH}[S][OH^-] \quad (18)$$

Under buffer conditions, an apparent first-order reaction is again observed:

$$\frac{dP}{dt} = k_{obs}[S] \quad (19)$$

in which now $$k_{obs} = k_{OH}[OH^-] \quad (20)$$

$$K_W = [H^+][OH^-] \quad (21)$$

$$k_{obs} = \frac{k_{OH}K_W}{[H^+]} \quad (22)$$

taking the logarithm of equation (22)

$$\log k_{obs} = -\log[H^+] + \log k_{OH}K_W \quad (23)$$

or

$$\log k_{obs} = pH + \log k_{OH}K_W \quad (24)$$

In this case, a plot of log k_{obs} against pH should be linear with a slope equal to +1.

Frequently, a minimum rate is observed that cannot be attributed to either hydrogen ion or hydroxide ion participation in the reaction. This minimum is indicative of a solvent catalytic effect; that is, unionized water may be considered as the catalytic species. Because of the pH independence of this reaction, the rate law in given by

$$\frac{dP}{dt} = k_0[S] \quad (25)$$

where

$$k_{obs} = k_o \quad (26)$$

Sometimes a minimum plateau extends over a limited pH range indicating that solvent catalysis is the primary mode of reaction in this region.

The solvent catalysis may occur simultaneously with specific hydrogen ion or specific hydroxide ion catalysis, especially at pH values that are between the pH regions in which definitive specific ion and solvent catalytic effects are observed.

The pH dependency of specific acid-base-catalyzed reaction can be summarized in terms of the general rate law:

$$\frac{dP}{dt} = [k_0 + k_H[H^+] + k_{0H}[OH^-]][S] \quad (27)$$

for which

$$k_{obs} = k_0 + k_H[H^+] + k_{0H}[OH^-] \quad (28)$$

At low pH where $k_{0H}[OH^-] << k_H[H^+]$, the catalytic effect of OH^- ions can be neglected. Conversely at high pH where $k_H[H^+] << k_{0H}[OH^-]$, the catalytic effect of H^+ ions can be neglected. When the concentrations of both H^+ and OH^- are low or if the $k_H[H^+]$ and $k_{0H}[OH^-]$ are small in value, only k_0 is important and the reaction is said to be solvent catalyzed.

4.2 General Acid-Base Catalysis.

In most systems of pharmaceutical interest, buffers are used to maintain the solution at a particular pH. Often, in addition to the effect of pH on the reaction rate, there may be catalysis by one or more species of buffer components (Martin, Swarbrick and Cammarata, 1983).

A general acid catalysis is a catalysis by a proton acid other than the hydronium ion. The general acid catalyst is hence a Bronsted acid. A general base catalysis is a catalysis by a Bronsted base other than the hydroxide ion, acting as a proton acceptor. That is by sharing an electron pair with a proton (Connors, Amidon and Kennon, 1979).

The rate-pH profile of a reaction that is susceptible to general acid-base catalysis exhibits deviations from the behavior expected on the basis of equation (16) and (24). For example, in the hydrolysis of an antibiotic,

streptozotocin, rates in phosphate buffers exceed the rate expected for specific base catalysis. This effect is due to a general base catalysis by phosphate anion. Thus, the alkaline branch of the rate-pH profile is far from 1 (Figure 2) (Garrett, 1960).

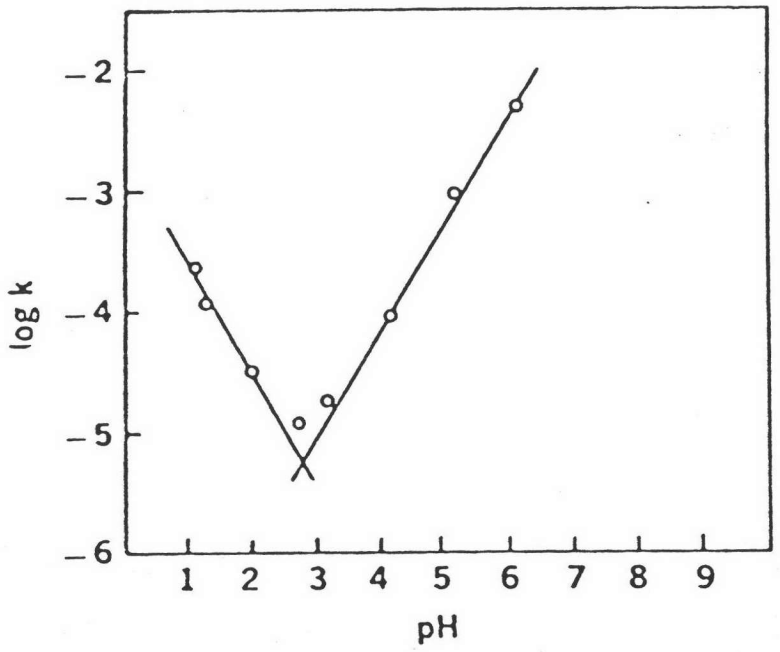

Figure 2: Rate-pH profile of a reaction susceptible to general base catalysis.

Verification of a general acid or general base catalysis may be made by determining the rates of degradation of a drug in a series of buffers that are all at the same pH (i.e., the ratio of salt to acid is constant) but they are prepared with an increasing concentration of buffer species. Windheuser and Higuchi (1962) found that the degradation of thiamine was unaffected at pH 3.90, where the buffer was principally acetic acid. At higher pH values, however, the rate increased in direct proportion to the concentration of acetate ion. In this case, acetate ion was the general base catalyst. Hence the rate of reaction may be written as:

$$\frac{d[P]}{dt} = [S]\{k_o + k_H[H^+] + k_{OH}[OH^-] + k_{HQ}[HQ] + k_Q[Q^-]\} \quad (29)$$

for which

$$k_{obs} = k_o + k_H[H^+] + k_{OH}[OH^-] + k_{HQ}[HQ] + k_Q[Q^-] \quad (30)$$

where k_o, k_H, k_{OH}, k_{HQ} and k_Q are the rate constants for solvent, hydronium ion, hydroxide ion, general acid and general base catalyzed reaction, respectively. HQ and Q^- are general acid (acetic acid) and general base (acetate ion), respectively

Weble et al. (1958) demonstrated the general catalytic actions of acetic acid, sodium acetate, formic acid and sodium formate in decomposition of glucose. The equation for the overall rate of decomposition of glucose in water in the presence of acetic acid (HAc) and its conjugated base (Ac^-) can be written as:

$$\frac{-dG}{dt} = k_o[G] + k_H[H^+][G] + k_A[HAc][G] + k_{OH}[OH^-][G] + k_B[Ac^-][G] \quad (31)$$

in which [G] is the concentration of glucose, k_o is the specific reaction rate in water alone, and the other k values, which are known as catalytic coefficients, represent the specific rates associated with the various catalytic species. The overall first-order rate constant k, which involves all effects, is written as follows:

$$k = \frac{-d[G]/dt}{[G]} = k_O + k_H[H^+] + k_A[HAc] + k_{OH}[OH^-] + k_B[Ac^-] \quad (32)$$

5. Effect of Ionic Strength (Carstensen, 1990; Martin, Swarbrick and Cammarata, 1983).

Ionic strength may also lead to apparent deviations in the rate of reaction.To investigate the effect of ionic strength, an experiment is carried out in solutions of different concentrations of inert electrolyte. The definition of ionic strength is

$$\mu = \frac{1}{2} \sum M_i z_i^2 \qquad (33)$$

where M_i is the molarity of the i^{th} species and z_i is its charge.

In a reaction between ions, the reactants A and B have charges z_A and z_B and the activated complex $(A....B)^{\neq}$ has charge of (z_A+z_B). A reaction involving ions may be represented as:

$$A^{Z_A} + B^{Z_B} \qquad [A.....B]^{\neq(Z_A+Z_B)} \longrightarrow \text{Products} \qquad (34)$$

In a solution having concentration below 0.01 M, the rate constant k will depend on the ionic strength (μ) by the relationship:

$$\log k = \log k_o + 2Qz_Az_B\mu^{1/2} \qquad (35)$$

$$Q = (1.825 \times 10^6) \frac{[D]^{1/2}}{(T\epsilon)^3} \qquad (36)$$

where T is absolute temperature, ϵ is dielectric constant of the solution, and D is its density. At 25 °C in aqueous solutions, 2Q=1.02, k_o is the rate constant in an

infinitely dilute solution in which $\mu = 0$. Equation (35) informs that a plot of log k against $\mu^{1/2}$ should give a straight line with a slope of $1.02\ z_A\ z_B$. If one of the reactants is a neutral molecule, $z_A\ z_B = 0$ and the rate constant as seen from equation (35) should then be independent of the ionic strength in dilute solutions.

At high concentration of solute up to the ionic strength of 0.1, the rate constant is related to the ionic strength by:

$$\log k = \log k_o + \frac{2Q\ z_A\ z_B\ \mu^{1/2}}{1+ \beta\ \mu^{1/2}} \qquad (37)$$

where β is a constant related to the ionic diameters of the solutes.

At even higher ionic strength, the relationship becomes

$$\log k = \log k_o + b\mu \qquad (38)$$

in which b is a constant obtained from experimental data.

An Example is the degradation rate of penicillin G at pH's of 4.50, 6.80, and 8.75 (Figure 3) (Finholt, Jurgensen and Kristiansen, 1965). A positive slope at pH 6.80 and 8.75 indicated that the dominating process at these pH values are reactions between two species with the same charge, positive or negative. At pH 6.80 where 0.1 M phosphate buffer was used, the dominating process was a reaction between the negatively charged penicillin ion [P^-] and monohydrogen phosphate ion [HPO_4^{2-}]. At pH 8.75, 0.1 M borate buffer was used and the dominating processes were presumably

$$P^- + OH^- \rightarrow \text{Products} \qquad (39)$$

$$\text{or} \quad P^- + H_2BO_3^- \rightarrow \text{Products} \qquad (40)$$

Both reactions gave positive salt effect.

At pH 4.50, there was no salt effect. The buffer used, 0.1 M acetate buffer, had no catalytic effect. Since the rate decreased with increasing pH between pH 4 and 5, the rate-determining process at pH 4.50 must be a water attack on unionized penicillinic acid [HP].

$$HP + H_2O \rightarrow \text{Products} \qquad (41)$$

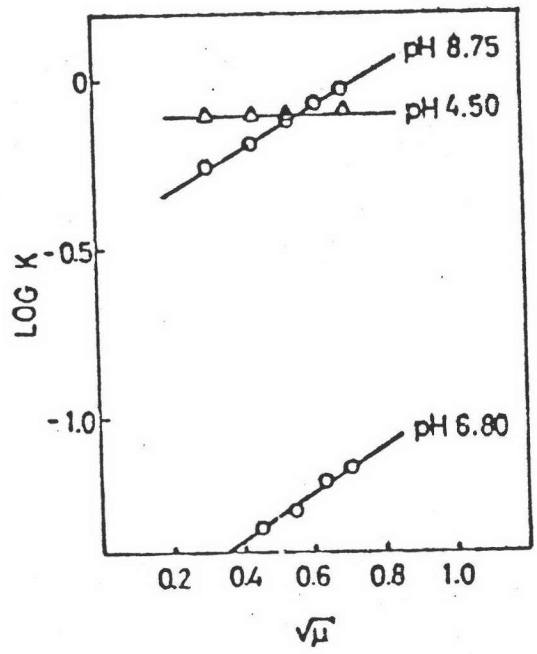

Figure 3: Effect of the ionic strength (μ) on the pseudo first-order rate constant (k) of the degradation of penicillin G at different pH values at 60 °C.

6. Effect of Dielectric Constant (Martin, Swarbrick and Cammarata, 1983).

The effect of dielectric constant on the rate constant (k) of an ionic reaction extrapolating to infinite dilution where the ionic strength effect is zero is determined by equation (42):

$$\ln k = \ln k_{\epsilon=\alpha} - \frac{N z_A z_B e^2}{RTr^{\neq}} \frac{1}{\epsilon} \qquad (42)$$

In which $k_{\epsilon=\alpha}$ is the rate constant in a medium of infinite dielectric constant, N is Avogadro's number, z_A and z_B are the charges on the two ions, e is the unit of electric charge, T is the absolute temperature, R is the gas constant, 1.987 calories/deg mole, $r^{\neq}$ is the distance between ions in the activated complex, and ϵ is dielectric constant of the solution. The dielectric constant of a dilute solution equals approximately to that of the solvent. The term $\ln k_{\epsilon=\alpha}$ is obtained by plotting ln k against $1/\epsilon$ and extrapolating to $1/\epsilon = 0$. The ln k versus $1/\epsilon$ plot should give a straight line with a positive slope for reactant ions of opposite charges and a negative slope for reactants of same charges. For a reaction between ions of opposite charge, an increase in dielectric constant of the solvent results in a decrease in the rate constant. For ions of like charge, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.

When a reaction occurs between a dipole molecule and an ion A, the equation can be written as:

$$\ln k = \ln k_{\epsilon=\alpha} + \frac{N z_A^2 e^2}{2RT} \left\{\frac{1}{r_A} - \frac{1}{r^{\neq}}\right\} \frac{1}{\epsilon} \qquad (43)$$

in which Z_A is the charge on the ion A, r_A is the radius of the ion, and $r\neq$ is the radius of the activated complex. Equation (43) predicts that a straight line should be obtained when ln k is plotted against $1/\in$, the reciprocal of the dielectric constant. Since $r\neq$ is the radius of the combined ion and neutral molecule in the transition state, it is larger than r_A, the radius of the ion. Therefore, the second term on the right side of the equation will always be positive, that is the slope of the line will consequently be positive. Therefore, ln k will increase with increasing values of $1/\in$, that is, the rate of reaction between an ion and a neutral molecule will increase with decreasing dielectric constant of the medium. This relationship, however, does not hold if different solvents are used or if the solutions are not dilute in which ionic strength effects become significant.

To determine the effect of dielectric constant on the rate of glucose decomposition in an acidic solution, Heimlich and Martin (1960) carried out tests in dioxane-water mixtures. The result is shown in Figure 4. A straight line of positive slope was evidenced for a reaction between a positive ion and a dipole molecule as predicted by equation (43). The dielectric constant of medium should be an important consideration in the stabilization of glucose solutions since replacing water with a lower dielectric constant solvent markedly increased the rate of breakdown of glucose.

Chemical Stability of Ranitidine HCl.

The stability of ranitidine HCl has been the subject of many investigations. Most of these studies are in the field of IV admixture but little is known about the kinetics of the reaction. Sarkar et al. (1991) studied the stability of 350 mg/ml ranitidine HCl in 5% dextrose injection solution in a polyolefin container. This preparation was stable for 30 and 10 days after freezing and refrigeration, respectively. A concentration of ranitidine HCl injection solution

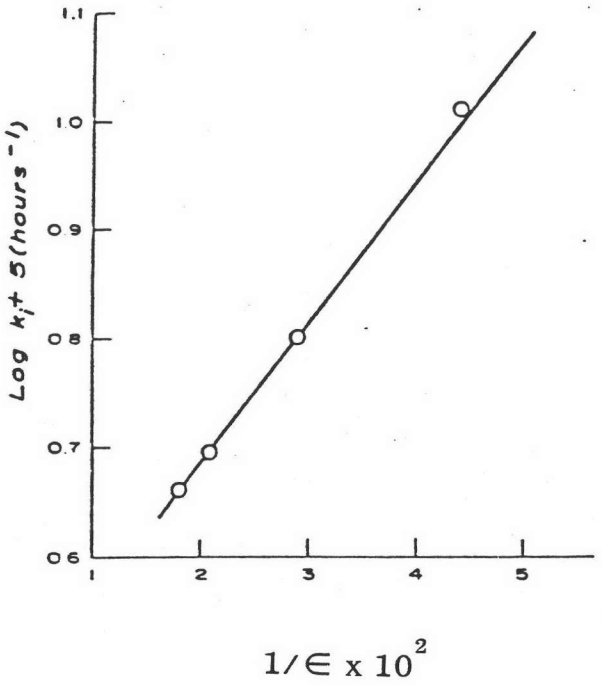

Figure 4: Variation of the logarithm of the rate constant (k) for glucose degradation with the reciprocal of the dielectric constant.

(25 mg/ml) declined by less than 10% of the initial concentration when 100, 200 and 300 mg doses were mixed with 1200 ml of a TPN solution and allowed to stand at room temperature (23 °C) for seven days (Walker, and Bayliff, 1985). Bullock et al. (1985) ranitidine HCl reported that in concentrations of 50 and 100 mcg/ml in parenteral nutrient solutions containing 4.25% and 2.125% crystalline amino acids was stable for 24 hours at room temperature. The concentration of the amino acids contained in the PN solution was not affected by the addition of ranitidine HCl in the concentration of 100 mcg/ml. PN solutions that contained ranitidine HCl should be used whithin 24 hours. Stewart et al. (1990) studied the stability of ranitidine in concentrations of 0.5, 1.0 and 2.0 mg/ml in admixture vehicles which were 0.9% sodium chloride, 5% dextrose, 10% dextrose, 5% dextrose and 0.45% sodium chloride, and 5% dextrose with lactated Ringer's (DLR) injections in polyvinyl chloride bags. Three bags were prepared for each test solution and stored under each of the following conditions: seven days at room temperature (23 ± 1 °C) in normal laboratory lighting, thirty days at 4 °C and sixty days at −20 °C following by either seven days at room temperature (in light) or fourteen days at 4 °C. Ranitidine concentrations remained >90% of initial concentrations under all storage conditions except in the frozen DLR admixtures. Drug loss in the DLR admixtures was greater at the lower ranitidine concentrations. The only visual changes were yellow colour in the thaw DLR admixtures and those containing 2.0 mg/ml ranitidine in 5% dextrose and 0.45% sodium chloride. Slight increases in the pH of some admixtures were noted. Ranitidine of all concentrations was stable for seven days at room temperature and thirty days at 4 °C in all vehicles studied. At the studied concentrations, the drug was stable in the frozen admixtures for sixty days and the refrigerated admixture for fourteen days, except in DLR admixtures that should not store frozen.

Ranitidine stability in dextrose solution appeared to be concentration dependent; greater percentages of drug remaining over time as the intial concentration increased from 0.05 to 2 mg/ml (Galante et al., 1990). A TPN containing lipids and glucose was prepared aseptically in three ethylene-vinyl acetate bags. Ranitidine HCl in concentrations of 100 mg and 200 mg were added to the first two bags to yield concentrations of 50 and 100 mcg/ml, respectively. The third bag served as a control. No appreciable changes in pH occurred over 72 hours and no visual changes were observed. At concentrations of 50 and 100 mcg/ml, approximately 80% of ranitidine HCl activity declined during the study period. Approximately 10% of the initial concentration was lost in 12 hours. In both cases, there was no variation in particle-size distribution compared with that in the control bag at time zero. Ranitidine HCl appeared to be stable for up 12 hours at room temperature in the admixtures studied and the lipid emulsion apparently was not altered during this period (Cano et al., 1988).

At least 86% of the original concentration of ranitidine was retained at 48 hours in the dextrose-amino acid TPN solution containing 3.7% lipid emulsion, 0.9% sodium chloride injection, and 10% lipid emulsion. Additionally, ranitidine did not appear to have an adverse effect on the stability of lipid emulsion or the amino acid in the admixture (Williams, Hak and Duckes, 1990).

The study of all chemical stability data of ranitidine HCl has been determined by HPLC. Gupta (1988) indicated the stability data of ranitidine in tablet and injection solution by reverse phase high performance liquid chromatography method. The mobile phase which resolved ranitidine, its degradation composition and internal standand (caffeine) was 10% V/V methanol, 7% V/V acetonitrile and 0.01 M phosphate buffer in water at pH 5.8 $\pm$ 0.05. The column was microbondapak. The wavelength of 262 nm was used

since ranitidine and caffeine had good absorption at this wavelength. Ranitidine appeared to be stable to heat on the acidic side and very susceptible to decomposition on the basic side. It lost 84.4% of potency after it had been boiled with sodium hydroxide for 20 minutes with a new peak in the chromatogram. It lost 37.8% of the potency if it had been treated with hydrogen peroxide solution for 20 minutes at room temperature.

Beaulieu et al. (1988) developed HPLC methods to determine ranitidine and related compounds in pure drug powder and tablets. The HPLC conditios were as follows: the apparatus used was Varian model 5060 fitted with a 5 μl loop, an autosampler (Spectra-Physics model SP8780 x R), a detector set at 228 nm (Varian model UV 100), a 3 μm Spherisorb cyanobonded phase column (150x4.6 nm, Chromatography Sciences Company). The conditions were set at ambient temperature with a mobile phase flow rate of 1.0 ml/min. The mobile phase was 70% V/V 0.025 M ammonium hydrogen phosphate and 30% V/V acetonitrile adjusted with 0.025 M ammonium hydroxide to obtain a final solution pH of 5 .

The chemical stability study of ranitidine HCl in solution and in the solid state at various temperatures was investigated by high performance liquid chromatography. Ranitidine HCl was unstable in lower pH buffer solutions (Figure 5) and the percent degradation after 72 hours increased as the pH of the buffer solution was reduced and shown in Figure 6. The percent degradation in the unbuffered solution in Figure 7 increased dose-dependently. The critical relative humidity (CRH) of the ranitidine HCl bulk powder was 67%. The amount of water adsorbed on to the sample above the CRH was proportional to the relative humidity (RH) level. The percent degradation of the powder below 50% RH was negligible. The percent degradation at 60-70% RH was higher

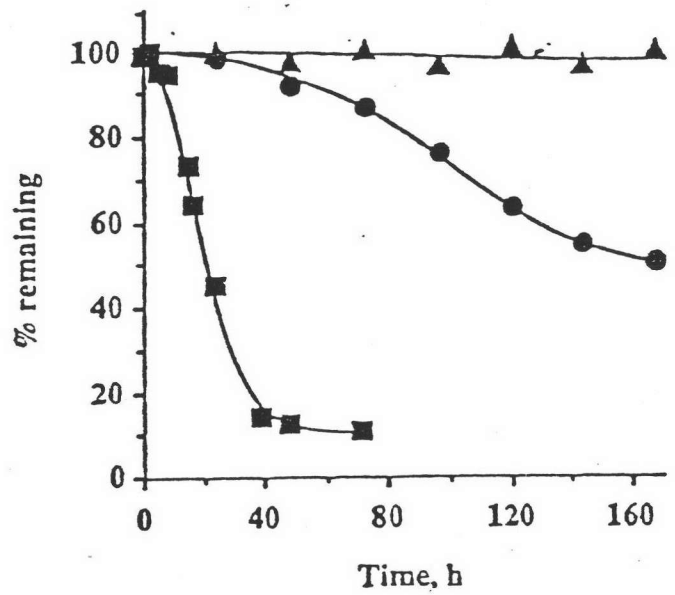

Figure 5: Degradation profiles of ranitidine HCl in 0.1 M acetate buffer solutions (ionic strength = 0.1) at 65 °C. Key: (■) pH 4.01: (●) pH 5.01: (▲) pH 6.18.

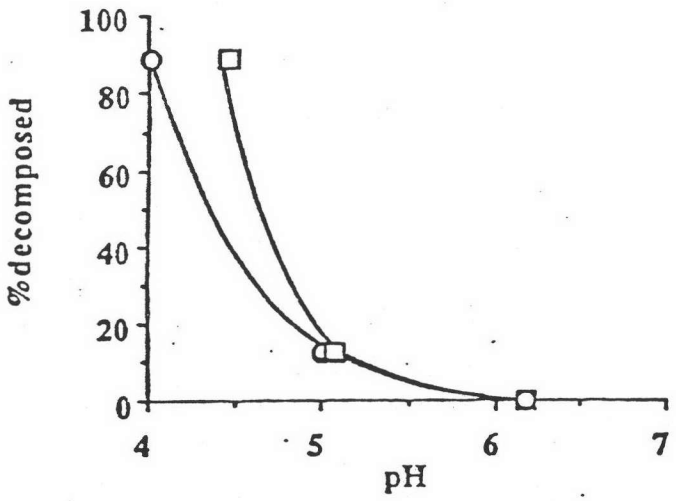

Figure 6: Relationship between percent degradation of ranitidine HCl after 72 h of storage and pH of buffer solutions at 65 °C. Key: (O) pH of the initial buffer: (□) pH after 72 h.

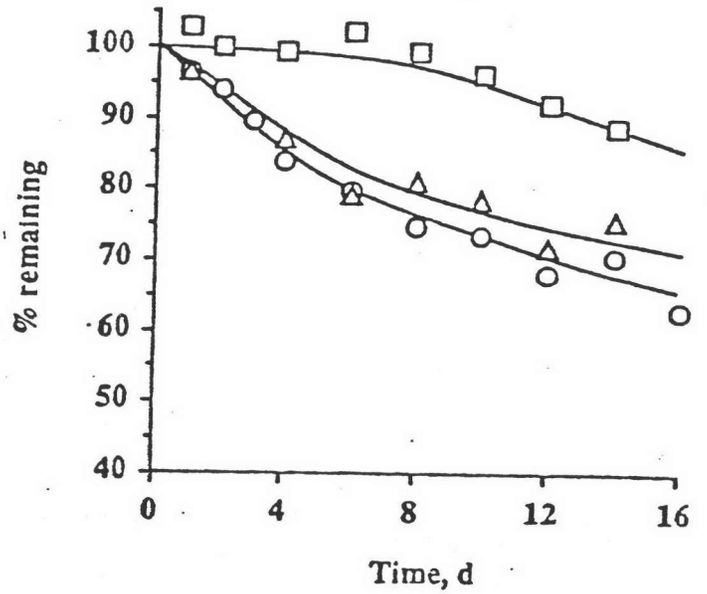

Figure 7: Degradation profiles of ranitidine HCl in distilled water at 65°C. Key: (O) 69.4 w/w %:(△) 13.0w/w%:(□) 1.3 w/w%.

than that above 70% RH. Ranitidine HCl was unstable around the CRH (Teraoka, Otsuka and Matsuda, 1993).