CHAPTER IV

RESULTS AND DISCUSSION

A purpose of this research is to describe the chemical kinetics of ranitidine HCl solution which is always of great importance in a stability program. Since there are only a few publications relating to the chemical stability of ranitidine HCl, this study would be very useful for a development of ranitidine HCl solution. An ingredient in a formulation leading to a required property may enhance or retard the degradation rate of drug. The effects of pH, phosphate buffers, solvent polarity and solvent ionic strength on ranitidine HCl stability are included in this study.

The assay of ranitidine HCl by the HPLC method was modified from the method of Gupta (1988). The chromatograms are shown in Appendix VII.

Kinetics of Ranitidine HCl Degradation.

If a plot of concentration of drug remaining in a degradation process versus time is linear, the reaction kinetics is said to be zero-order. If the reaction kinetics is first-order, a plot of log (concentration of drug remaining) versus time is linear. A simple case of second-order kinetics is observed when a plot of 1/concentration versus time is linear. This occurs when rate = $k_2 [A]^2$ or when rate = $k_2 [A][B]$; where k_2 is the second-order rate constant, and [A] and [B] are concentrations of reactants A and B, respectively. The former is the case when only one kind of reactant involves in the degradation reaction. The latter is observed when "a" moles of A react with "b" moles of B and $b[A]_0 = a[B]_0$; where $[A]_0$ and $[B]_0$ are initial concentrations of A and B, respectively.

In this study, the regression equations of the zero-order, first-order, and second-order kinetics were calculated and shown in the Appendices. Coefficient of determinations (r^2) of all regression lines are concluded in tables 4-7.

Since the plots of ranitidine HCl degradation in pH 1 and 2 phosphate buffers (Figures 8-13) show inflection points around fifteen hours, the regression equations of their first portions were calculated and reported.

Almost all coefficient of determinations of the second-order plots of specific acid-base catalysis (Table 4), general acid-base catalysis (Table 5), ionic strength effect (Table 6), and solvent polarity effect (Table 7) have the highest values. Only the first-order plots of pH 7 and 10 in Table 4 have the highest r^2 values, the apparent second-order kinetics of ranitidine HCl degradation is therefore concluded.

Specific Acid-Base Catalysis.

As it was mentioned earlier that the inflection points occur in the reciprocal of concentration versus time plots of ranitidine HCl degradation in pH 1 and 2 phosphate buffers (Figure 12 and 13). This suggests some changes affecting the slopes of the plots, i.e., the second-order rate constants.

Teraoka, Otsuka and Matsuda (1993) investigated the percentage of ranitidine HCl degradation at seventy-two hours in pH 4, 5 and 6 acetate buffers. They found that the pH values of pH 4.01 and 5.01 solutions were increased to 4.47 and 5.32, respectively. They suggested that some degradation products affected the solution pH. But no change in the pH value was observed in the pH 6.18 solution.

Table 4: Coefficient of determinations (r^2) of zero-order, first-order, and second-order plots of ranitidine HCl degradation in pH 1-12 phosphate buffers.

pH	Coefficient of determination (r^2)		
	zero-order	first-order	second-order
1	0.7264	0.7298	0.7330
2	0.6208	0.6379	0.6567
3	0.8525	0.9297	0.9730
4	0.7800	0.9415	0.9956
5	0.7969	0.9291	0.9954
6	0.7743	0.9142	0.9864
7	0.8914	0.9874	0.9675
8	0.9638	0.9693	0.9662
9	0.9500	0.9755	0.9836
10	0.9790	0.9940	0.9588
11	0.9634	0.9918	0.9952
12	0.7990	0.9308	0.9944

Table 5: Coefficient of determinations (r^2) of zero-order, first-order, and second-order plots of ranitidine HCl degradation in pH 4, 5, and 6 phosphate buffers with various buffer concentrations.

pH	Total buffer concentration (M)	Coefficient of determination (r^2)		
		zero-order	first-order	second-order
4	0.1	0.7542	0.8654	0.9476
4	0.2	0.7843	0.9262	0.9672
4	0.4	0.7800	0.9415	0.9956
5	0.1	0.8185	0.9071	0.9710
5	0.2	0.6723	0.8624	0.9745
5	0.4	0.7969	0.9291	0.9954
6	0.1	0.8387	0.9306	0.9679
6	0.2	0.8471	0.9524	0.9847
6	0.3	0.7742	0.9141	0.9880

Table 6: Coefficient of determinations (r^2) of zero-order, first-order, and second-order plots of ranitidine HCl degradation in pH 5 and 12 phosphate buffers with various ionic strength values.

pH	Ionic strength	Coefficient of determination (r^2)		
		zero-order	first-order	second-order
5	0.2	0.7968	0.9090	0.9515
5	0.5	0.6729	0.8629	0.9742
5	0.8	0.7098	0.8647	0.9696
5	1.0	0.8680	0.9588	0.9806
5	1.2	0.7274	0.8383	0.9256
12	0.2	0.8010	0.9035	0.9634
12	0.5	0.9061	0.9728	0.9895
12	0.8	0.8629	0.9439	0.9860
12	1.0	0.8306	0.9312	0.9858
12	1.2	0.8138	0.9054	0.9641

Table 7: Coefficient of determinations (r^2) of zero-order, first-order, and second-order plots of ranitidine HCl degradation in various methanol-water mixtures.

Methanol (%w/w)	Dielectric Constant	Coefficient of determination (r^2)		
		zero-order	first-order	second-order
20	70.52	0.7211	0.8246	0.9127
40	61.04	0.6856	0.7758	0.8564
60	51.56	0.8007	0.9003	0.9683
80	42.08	0.7466	0.8276	0.8991
100	32.6	0.8272	0.9066	0.9571

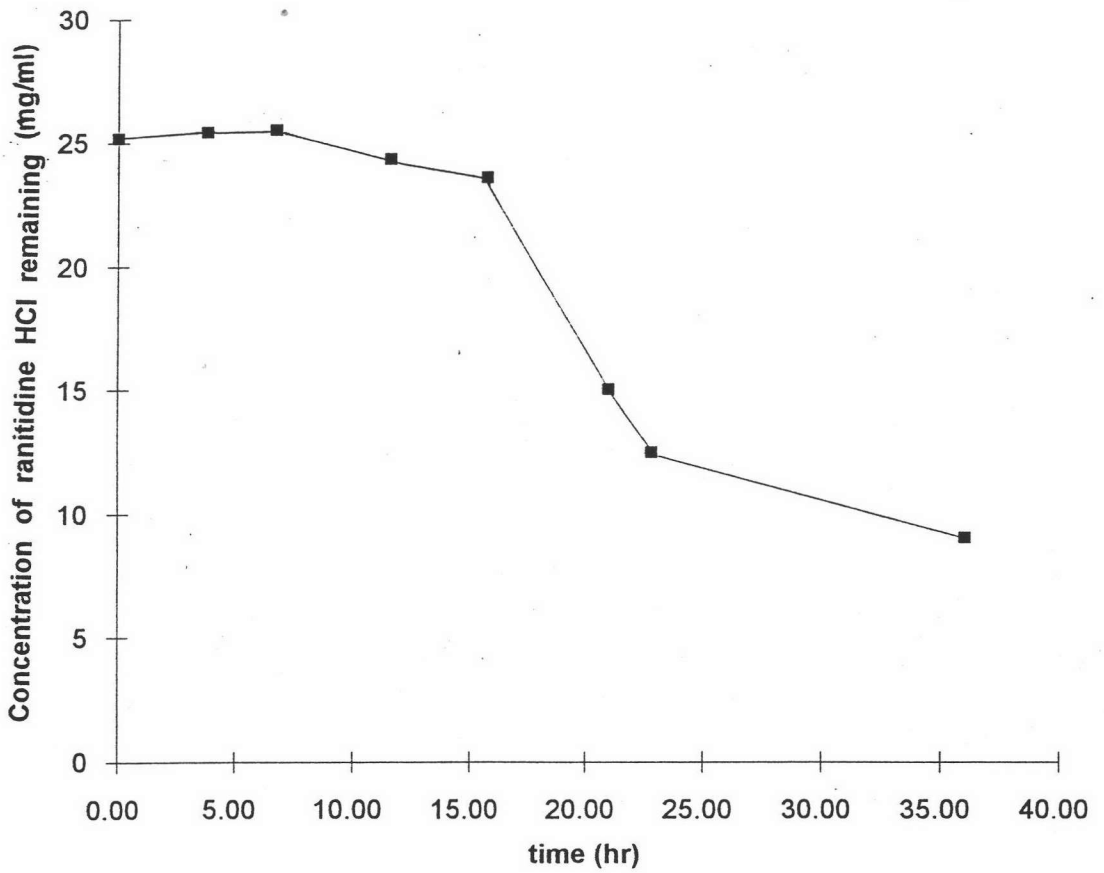

Figure 8: A zero-order plot of ranitidine HCl degradation in pH 1 phosphate buffer.

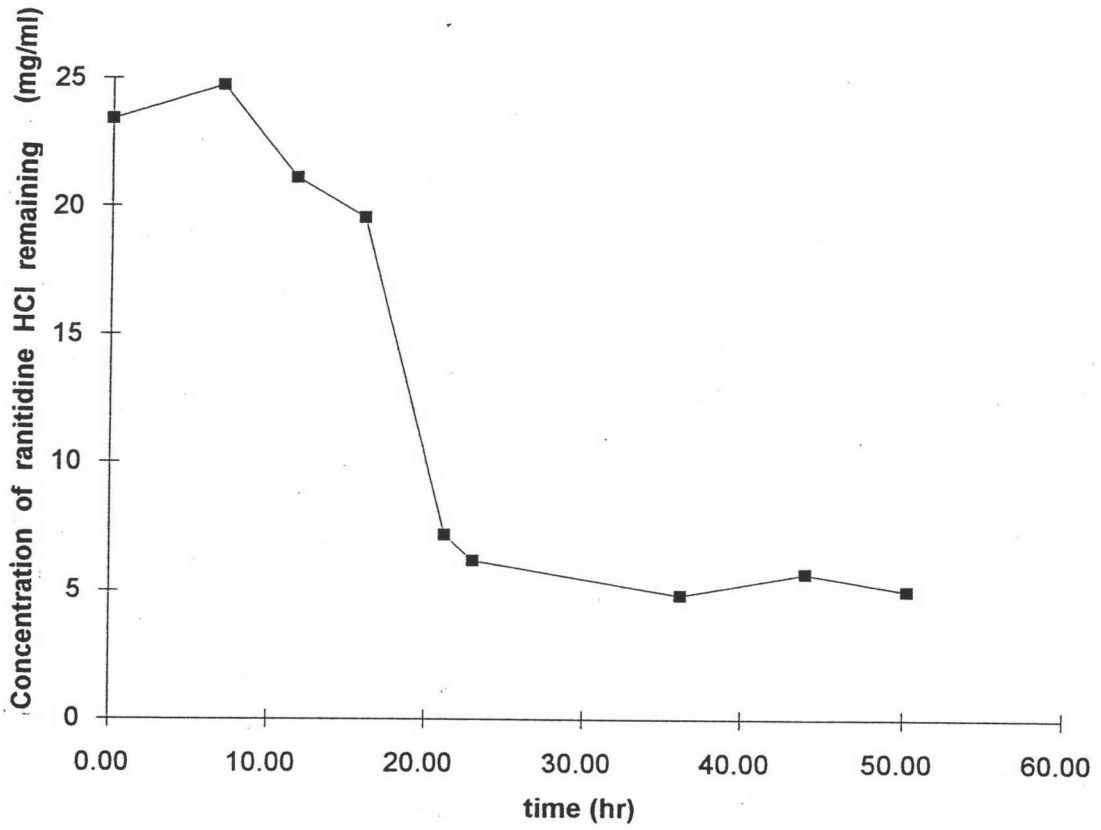

Figure 9: A zero-order plot of ranitidine HCl degradation in pH 2 phosphate buffer.

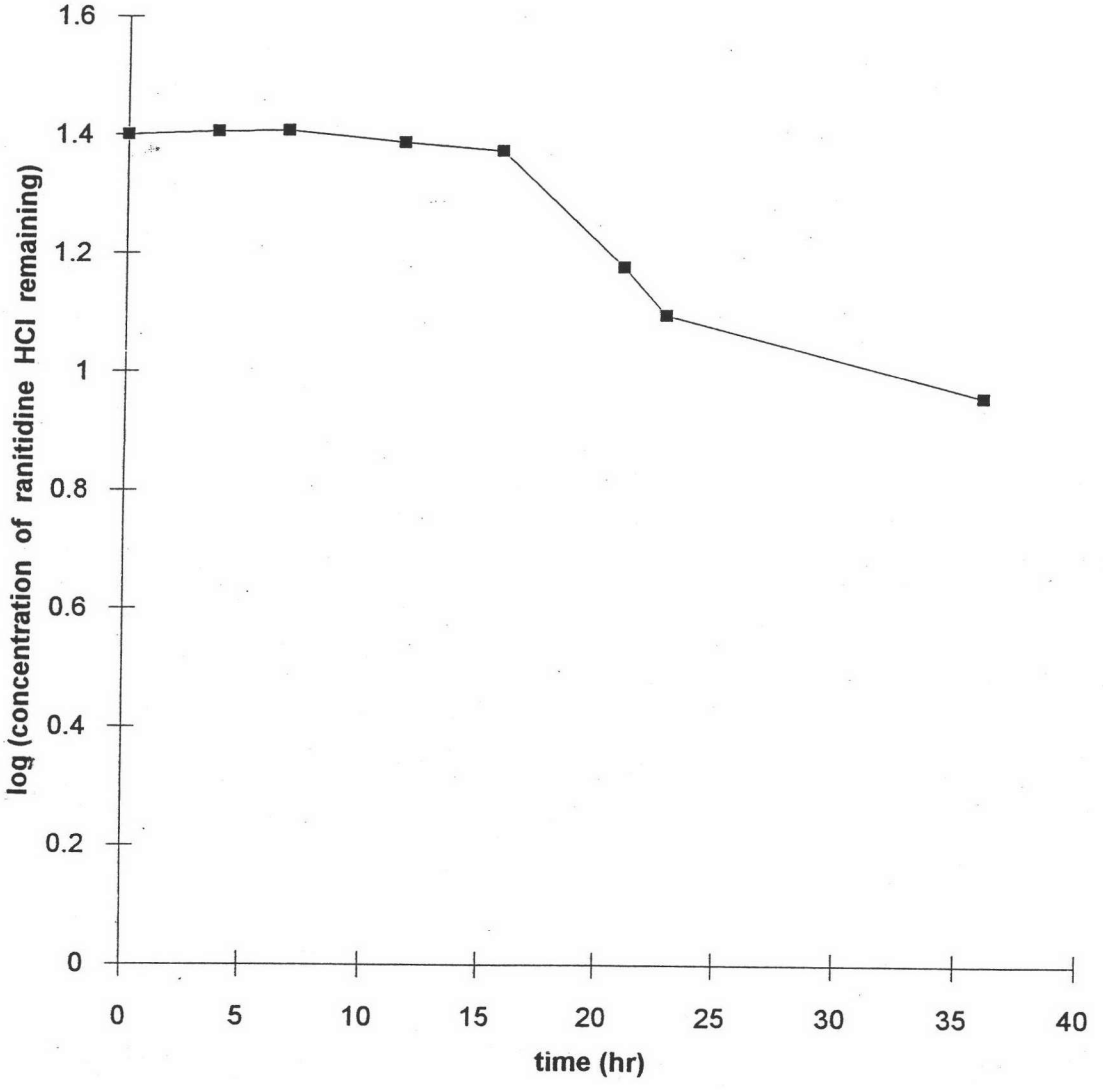

Figure 10: A first-order plot of ranitidine HCl degradation in pH 1 phosphate buffer.

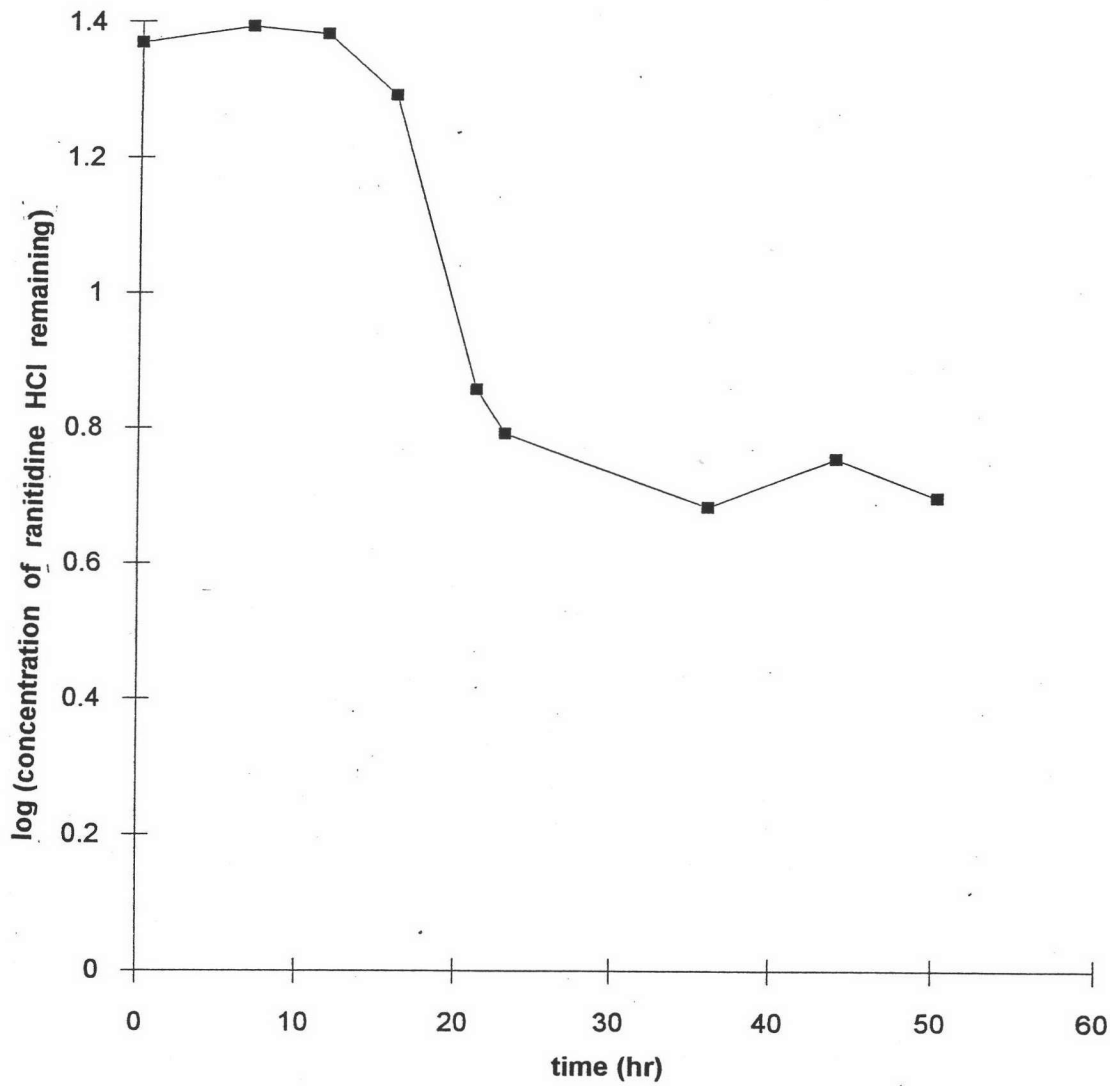

Figure 11: A first-order plot of ranitidine HCl degradation in pH 2 phosphate buffer.

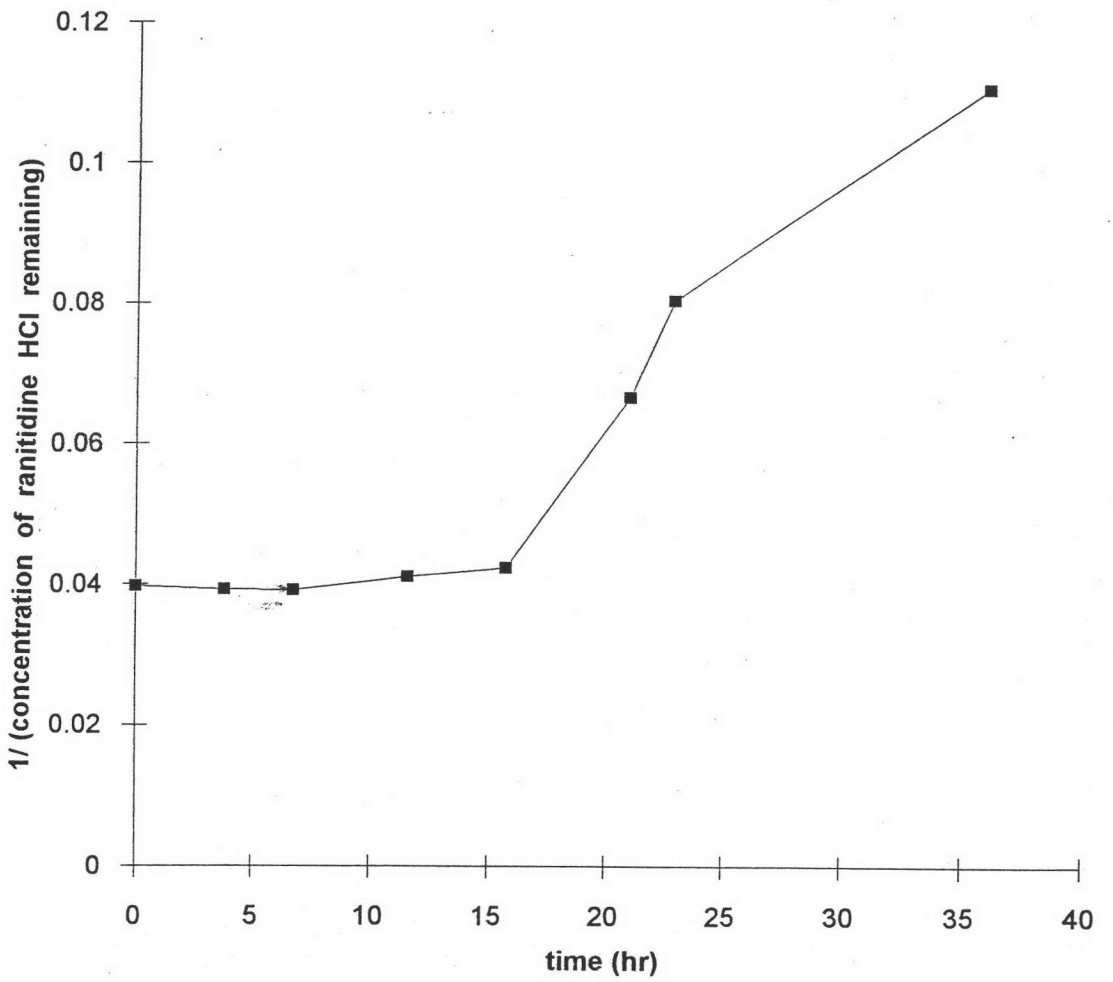

Figure 12: A second-order plot of ranitidine HCl degradation in pH 1 phosphate buffer.

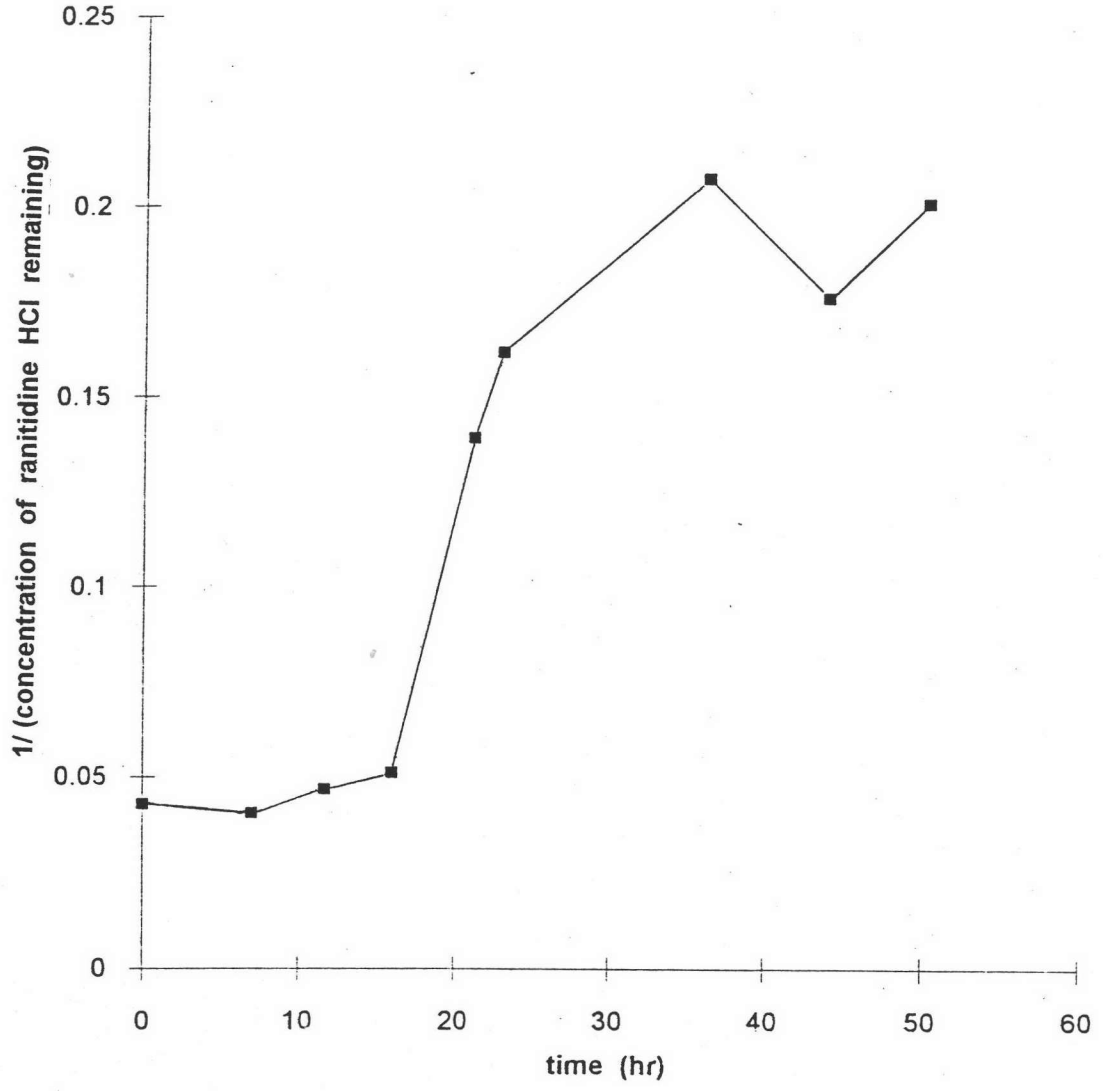

Figure 13: A second-order plot of ranitidine HCl degradation in pH 2 phosphate buffer.

In this study, the pH values of pH 1 and 2 phosphate buffers containing ranitidine HCl were also measured against time and are shown in Figure 14 and 15. As ranitidine HCl degraded, the pH values of the drug solutions increased. The inflection points of the reciprocal of concentration versus time plots (Figure 12 and 13) should be a result of the pH value increments. All inflection points should associate with the first ionization constant (pK_1) of ranitidine HCl (2.70) and phosphoric acid (2.21) since charges of ranitidine HCl and phosphoric acid which are different at the pH values of above and below their pK_1 values lead to different reaction rates. Higher pH values in this lower acidic region would lead to a faster rate of ranitidine HCl degradation. The second-order rate constants obtained from the first portion of the reciprocal of concentration versus time plots (the portion of plots prior to the inflection points) were used for construction of a pH-rate profile since the pH values in this region were closer to the required pH values.

Ranitidine HCl was reported to have only one pK_a at 2.19 by Hohnjec, et al. (1986). Teraoka, Otsuka Matsuda (1993) also reported only one pK_a but at 8.38. Two ionization constants of ranitidine HCl (pK_1=2.7 and pK_2=8.2) was also reported (Mecevoy, 1988) and it is assumed in this study.

A pH-rate profile of ranitidine HCl degradation is shown in Figure 16. The profile indicates an acid catalysis. Since phosphoric acid has three ionization constants (pK_1=2.21, pK_2=7.21 and pK_3=12.67), different fractions of buffer components are present at different pH values (Martin, Swarbrick and Cammarata, 1983). The two ionization constants (pK_1=2.7 and pK_2=8.2) of ranitidine HCl imply its charges at a pH below its pK_1, between its pK_1 and pK_2, and above its pK_2 to be RH^+, R and R^-, respectively. Therefore, dominant species in the range of pH studied are:

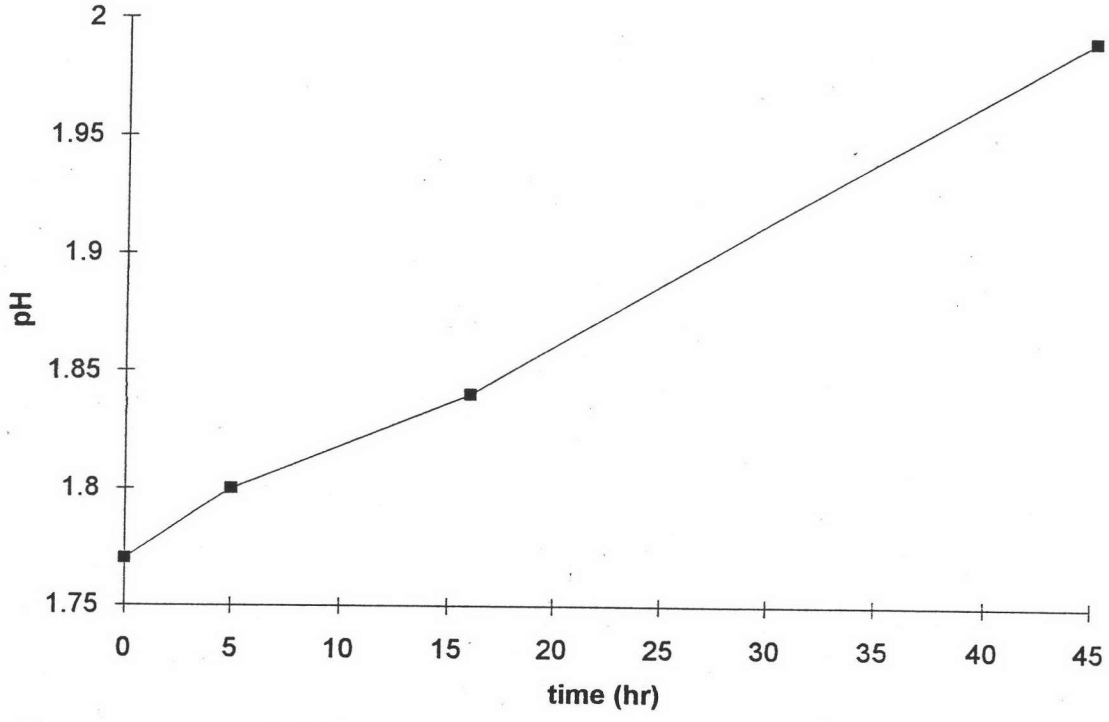

Figure 14: pH changes as a result of ranitidine HCl degradation in pH 1 phosphate buffer.

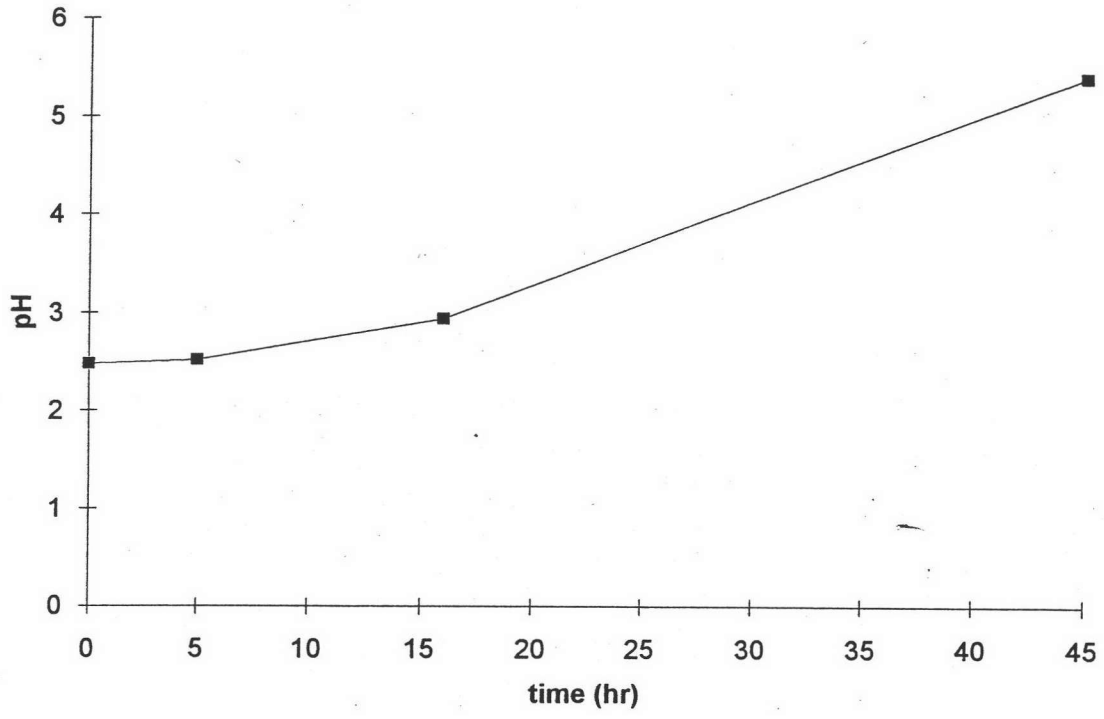

Figure 15: pH changes as a result of ranitidine HCl degradation in pH 2 phosphate buffer.

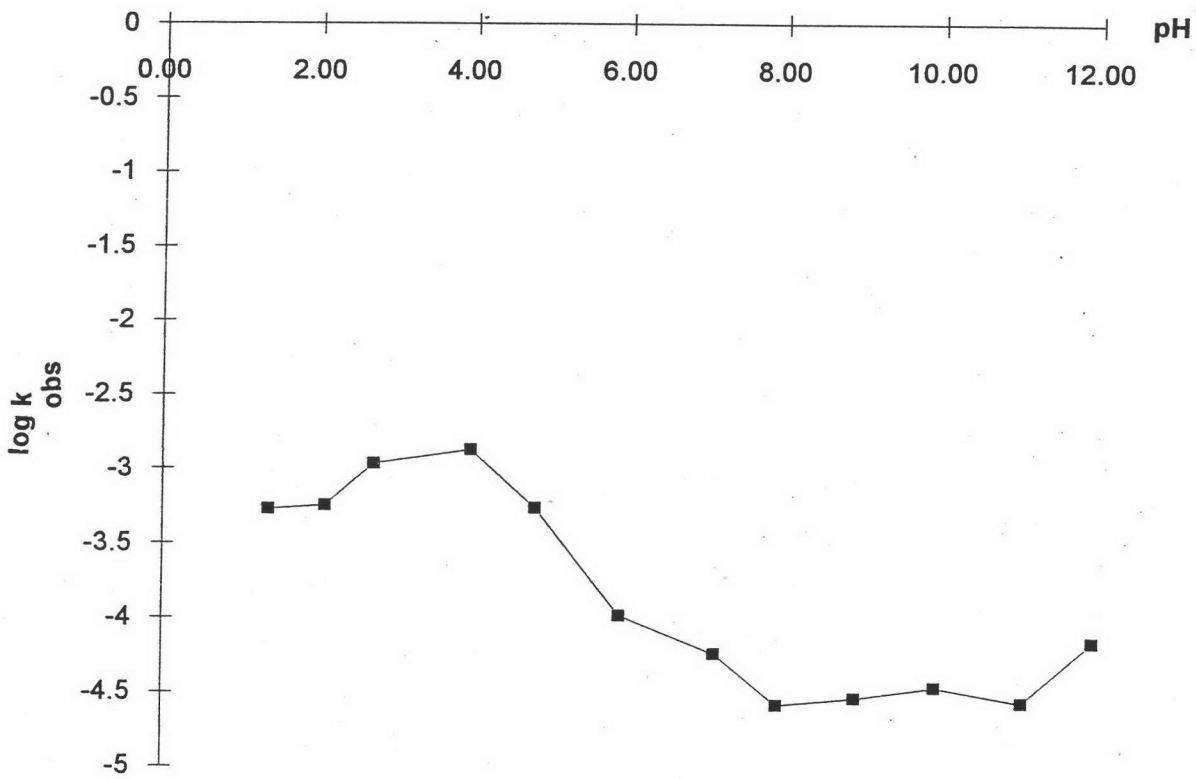

Figure 16: A pH–rate profile of ranitidine HCl degradation in phosphate buffers (ionic strength = 0.5).

pH 1, 2: RH^+, H_3PO_4

pH 3, 4: RH^+, R and $H_2PO_4^-$

pH 4-8: R, $H_2PO_4^-$

pH 8-11: R^-, R and HPO_4^{2-}

pH 12: R^-, HPO_4^{2-} and PO_4^{3-}

From the pH-rate profile, the degradation rates in pH 1 and 2 buffer solutions are less than those in pH 3 and 4 solutions. This can be assumed that the reaction rate catalysis by H_3PO_4 is less than that by $H_2PO_4^-$. An increase in pH value from one to four would result in an increase in dihydrogen phosphate ion fraction which might be responsible for the degradation rate increment. In a contrary, an increase in pH value from four to eight results in a drop of degradation rate. This may be because of a decrease in dihydrogen phosphate ion fraction. Furthermore, the slope of the pH-rate profile in the pH range of 4-7 which is 0.49 indicates the general acid catalysis. The specific acid catalysis (or the catalysis by hydrogen ion) cannot be concluded since the slope is not equal to -1 and the degradation rate is lowered at a very low pH region.

The slope of the pH-rate profile in the pH range of 8-11 is 0.01. The slope value of nearly zero indicates solvent catalysis. Therefore, there are no specific and general base catalysis. In the other words, hydroxide ion and monohydrogen phosphate ion do not catalyze the degradation rate of ranitidine HCl.

In pH 12 solution, the degradation rate increases. Both HPO_4^{2-} and PO_4^{3-} are dominant species at this pH but HPO_4^{2-} is not a catalytic species. Therefore, phosphate ion may act as a general base in this very high pH region. Gupta (1988) also reported a high degradation rate of ranitidine HCl in a strong basic solution.

It is interesting that the pH values of drug solutions at the end of experiments had changed (Table 8). The final pH values of pH 1-8 drug solutions are greater than their original pH values of buffer solutions. While the final pH values of pH 9-12 drug solutions are less than their original buffer pH values. Therefore, it can be concluded that the degradation process of ranitidine HCl must produce a degradation product capable of changing the solution pH although the solution is buffered. An explanation is that the kinetics of ranitidine HCl degradation may be an equilibrium reaction having a base as a degradation product. In an acidic solution, a forward reaction is favored and thus the pH value is increased. In a basic solution, a reverse reaction is favored and this leads to a decrease in pH value. A further study must be performed to conclude a specific kinetics and mechanism. Since the values of coefficient of determination of the second-order kinetics in this study are high, the pseudo second-order kinetic can be assumed here.

General Acid-Base Catalysis.

Since the kinetics of ranitidine HCl degradation in the buffer solutions were apparently second-order, a rate equation can simply be written as:

$$\frac{-d[R]}{dt} = k_{obs}[R]^2 \qquad (44)$$

where [R] is the concentration of ranitidine HCl remaining at time t and k_{obs} is the observed second-order rate constant.

Since the pH-rate profile indicates the general acid catalysis, the catalytic effect of the buffer components on the degradation process has to be taken into account. To evaluate the contribution of the buffer species, the k_{obs} value can be expressed as:

Table 8: Data of a pH-rate profile of ranitidine HCl degradation in phosphate buffers (ionic strength = 0.5).

pH of buffer solution	Buffer capacity (β)*	$k_{obs} \times 10^4$ (ml/mg x hr)	log k_{obs}	Final pH of drug solution
1.36	0.012	1.901	-3.271	1.99
2.08	0.027	5.676	-3.246	5.45
2.70	0.027	10.88	-2.963	-[a]
3.96	0.104	13.48	-2.870	5.74
4.80	0.006	5.538	-3.257	5.78
5.89	0.036	1.067	-3.972	6.40
7.12	0.115	0.5987	-4.223	7.56
7.93	0.044	0.2730	-4.564	8.80
8.93	0.005	0.3026	-4.519	8.16
9.94	0.008	0.3604	-4.443	8.20
11.06	0.007	0.3515	-4.545	8.56
11.95	0.0300	0.7256	-4.139	9.65

[a] did not measure.

* Calculated by $$\beta = \frac{2.3CK_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

$$k_{obs} = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{buffer}[buffer] \quad (45)$$

where k_0, k_{H+}, and k_{OH-} are the rate constants of solvent, hydronium ion, and hydroxide ion catalyzed degradation, respectively, and k_{buffer} is the sum of the rate constants for the degradation catalyzed by each of the buffer components. From this equation, a plot of k_{obs} versus total buffer concentration would give a slope and an intercept that are k_{buffer} and $k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-]$, respectively (Table 9, Figure 17).

The slopes of the k_{obs} versus [buffer] plot, which is k_{buffer}, in pH 4, 5 and 6 solutions are 4.052×10^{-3}, 1.193×10^{-3}, and -7.5×10^{-6}, respectively. It means that the catalysis by buffer components at different pH values are different. Since fractions of buffer components in different pH values are not constant, each buffer component does not have the same catalytic effect on ranitidine HCl degradation.

The catalytic effects of the buffer components on the degradation of ranitidine HCl were investigated at a constant pH, temperature and ionic strength but at different buffer concentrations. Since phosphate buffer solutions were used in this research, the buffer term can be written as:

$$k_{buffer}[buffer] = k_{H_3PO_4}[H_3PO_4] + k_{H_2PO_4^-}[H_2PO_4^-] + k_{HPO_4^{2-}}[HPO_4^{2-}]$$

$$+ k_{PO_4^{3-}}[PO_4^{3-}] \quad (46)$$

where $k_{H_3PO_4}$, $k_{H_2PO_4^-}$, $k_{HPO_4^{2-}}$ and $k_{PO_4^{3-}}$ are the rate constants of phosphoric acid, dihydrogen phosphate ion , monohydrogen phosphate ion and phosphate ion catalyzed degradation, respectively.

Table 9: Observed rate constants obtained from ranitidine HCl degradation in pH 4, 5, and 6 phosphate buffers with various buffer concentrations (ionic strength= 0.5).

pH	Total buffer conc (M)	$k_{obs} \times 10^{4}$ (ml/mg x hr)	k versus [buffer] plot
4.02	0.1	1.879	intercept = -3.282×10^{-4}
4.00	0.2	3.159	slope = 4.052×10^{-3}
3.96	0.4	13.48	$r^2 = 0.9468$
4.83	0.1	1.967	intercept = 7.58×10^{-5}
4.82	0.2	3.120	slope = 1.193×10^{-3}
4.80	0.4	5.538	$r^2 = 0.9999$
5.85	0.1	1.078	intercept = 1.109×10^{-4}
5.88	0.2	1.141	slope = -7.5×10^{-6}
5.89	0.3	1.063	$r^2 = 0.0328$

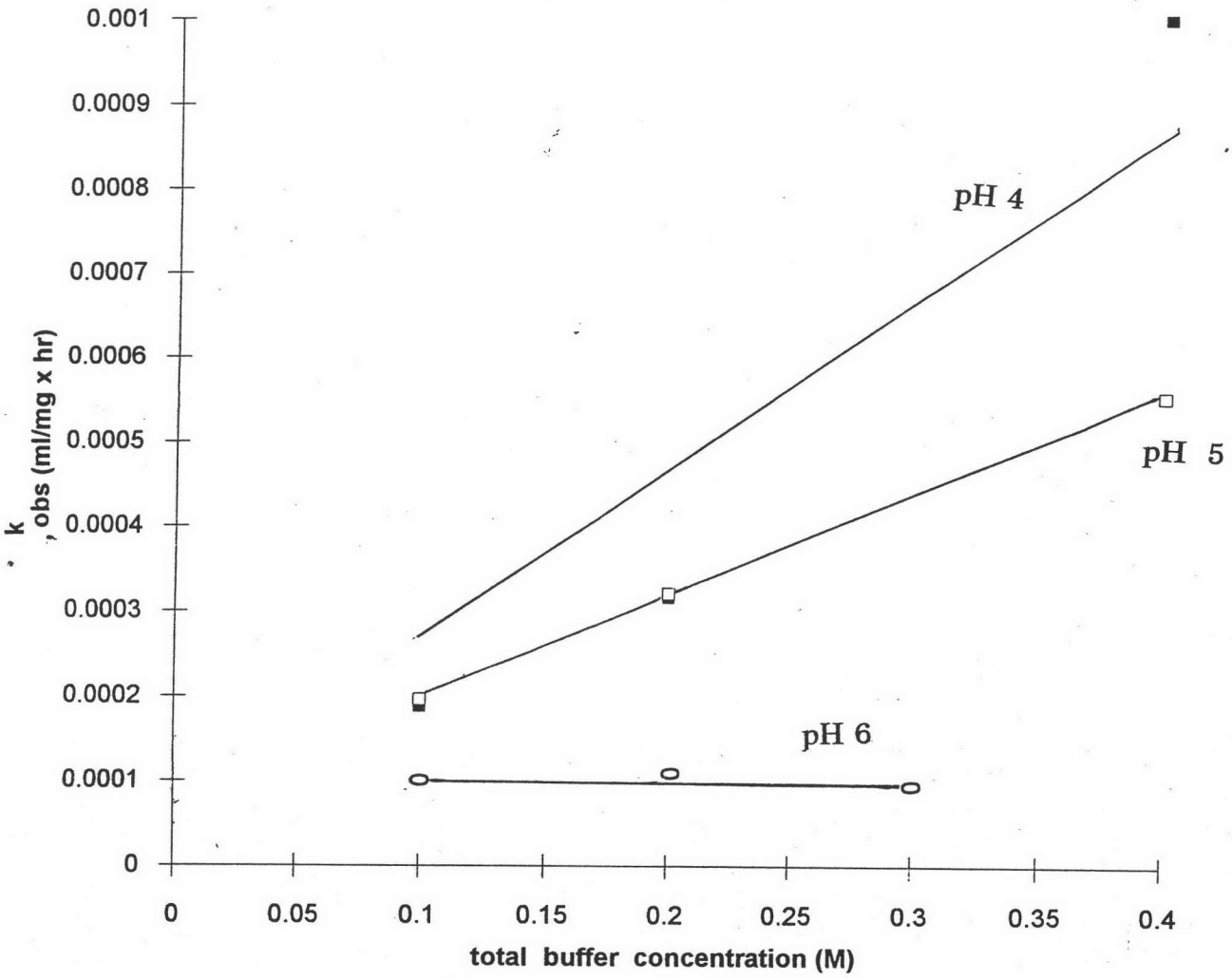

Figure 17: Effect of total phosphate buffer concentration on the degradation rate of ranitidine HCl.

pH 4: intercept = -3.282×10^{-4} ; slope = 4.052×10^{-3} ; r^2 = 0.9468.

pH 5: intercept = 7.580×10^{-5} ; slope = 1.193×10^{-3} ; r^2 = 0.9999.

pH 6: intercept = 1.109×10^{-4} ; slope = -7.500×10^{-6} ; r^2 = 0.0328.

In a solution of phosphate buffer having a pH of four, which is about the midpoint of its pK_1 (2.21) and pK_2 (7.21), $[H_2PO_4^-]$ is dominant (fraction of $H_2PO_4^-$ = 0.98) and $[H_3PO_4] \cong [HPO_4^{2-}]$. In pH 5 phosphate buffer, $[H_2PO_4^-]$ decreases (fraction of $H_2PO_4^-$ = 0.95) while $[HPO_4^{2-}]$ increase. And $[HPO_4^{2-}]$ should increase (fraction of HPO_4^{2-} = 0.42) in pH 6 phosphate buffer. Since pK_3 of phosphoric acid is 12.67, $[PO_4^{3-}]$ is negligible and can be ignored in pH 4, 5 and 6 solution. As a consequence, k_{buffer} is likely to be $k_{H_2PO_4^-}$ in pH 4 and 5 solutions since its values depend on $[H_2PO_4^-]$. In pH 6 solution, k_{buffer} ($\cong$ 0) is likely to be $k_{HPO_4^{2-}}$ because HPO_4^{2-} increases and it is not a catalytic species as it was stated previously.

It is obvious from the pH-rate profile that the hydroxide ion does not catalyze the degradation rate of ranitidine HCl. Therefore, the $k_{OH^-}[OH^-]$ in equation (45) can be dropped out. To assure whether the hydronium ion catalyses the degradation reaction, a plot of the intercept of the k_{obs} vs [buffer] plot versus $[H^+]$ should be drawn (Figure 18). Since the intercept of the k_{obs} versus [buffer] plot equals $k_0 + k_{H^+}[H^+]$, the intercept and slope of the plot of intercept of the k_{obs} versus [buffer] plot versus $[H^+]$ are k_0 (1.296×10^{-4} ml/mg.hr) and k_{H^+} (-4.488 (mg/ml)$^{-2}$ hr^{-1}) respectively. The negative value of k_{H^+} assures that the hydronium ion does not catalyze the degradation rate of ranitidine HCl.

Influence of Ionic Strength.

When one or more of the reactants are ions, real solutions may deviate from ideality. For a dilute solution of 1-1 electrolyte where μ is less than 0.01, the effect of ionic strength (μ) on the rate constant can be approximated as (Martin, Swarbrick and Commarata, 1983):

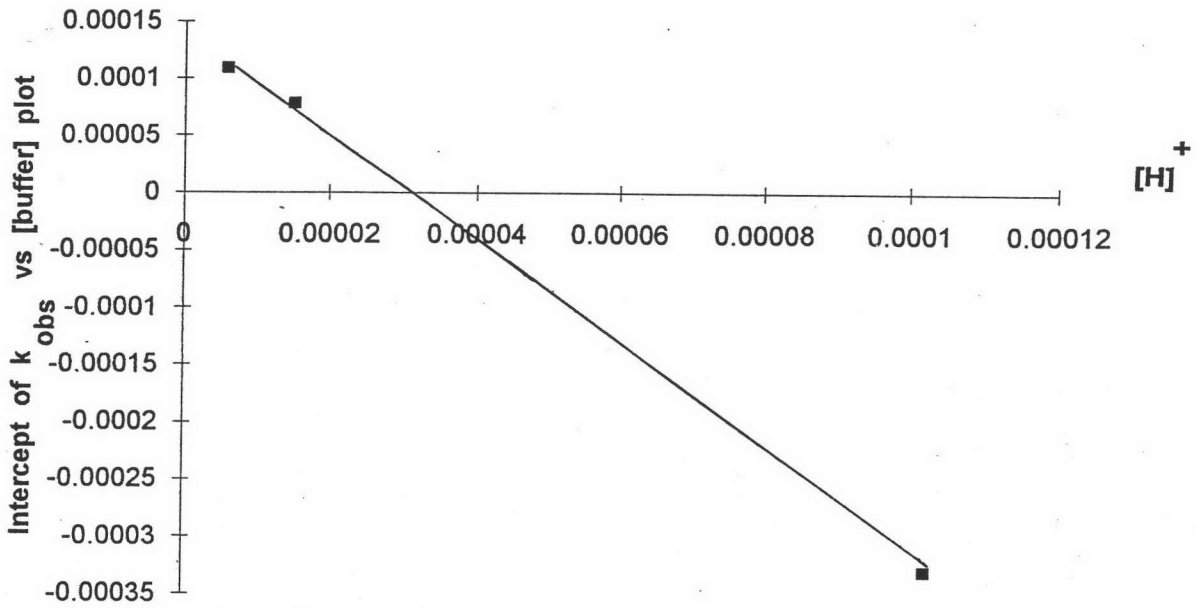

Figure 18: A plot of intercept of k_{obs} vs [buffer] plot against hydronium ion concentration (intercept = 1.296×10^{-4}, slope = -4.488, $r^2 = 0.9968$).

$$\log k = \log k_0 + 1.02\, Z_A\, Z_B\, \mu^{1/2} \qquad (47)$$

for an aqueous solution at 25°C. This equation may be valid for higher charged ions but with lower concentrations. However, this procedure has no theoretical justification. Furthermore, even at quite low concentrations there is often evidence for complex formation between an ion reactant and an added ion of opposite sign which renders equation (47) invalid.

At a high concentration of solute up to the ionic strength of 0.1 the rate is related to the ionic strength as described previously in equation (37). It predicts a linear relationship if log k is plotted against $\mu^{1/2}/(1 + \mu^{1/2})$ with a slope proportional to the product $Z_A Z_B$ for an aqueous solution at 25 °C .

Data of ionic strength effect on ranitidine HCl degradation in pH 5 and 12 phosphate buffer solutions are presented in table 10 and 11, respectively. Slopes of the plot of log k_{obs} versus $\mu^{1/2}/(1 + \mu^{1/2})$ (Figure 19) are 4.093 and -0.0268 for pH 5 and 12, respectively. This suggests the reaction between like charges in pH 5 phosphate buffer. The possible charges of the reactants are +4 and +1, or −4 and −1, or +2 and +2, or −2 and −2. In pH 12 phosphate buffer, at least one of the reactants is neutral since the slope is nearly zero.

In pH 5 phosphate buffer, the slope of the log k_{obs} versus $\mu^{1/2}$ (Figure 20) plot which is 1.378 indicates the possible charges of the reactants to be +1 and +1, or −1 and −1. The slope of −0.0144 in pH 12 phosphate buffer also informs that at least one reactant is neutral.

Although the ionic strength of the solutions studied are greater than 0.01, a plot of log k_{obs} against $\mu^{1/2}$ should be used since charges of possible reactants (RH^+, R, R^-, H_3PO_4, $H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}, H^+, OH^-, H_2O) are +1, 0, −1,

Table 10: Effect of ionic strength on ranitidine HCl degradation in pH 5 phosphate buffer.

Ionic strength (μ)	$\mu^{1/2}$	$\frac{\mu^{1/2}}{(1+\mu^{1/2})}$	$k_{obs} \times 10^4$ (ml/mg x hr)	log k_{obs}
0.20	0.4472	0.309	1.723	-3.764
0.50	0.7071	0.4142	3.120	-3.506
0.80	0.8944	0.4721	7.126	-3.147
1.00	1.000	0.5000	8.682	-3.061
1.20	1.095	0.5227	13.20	-2.879

Table 11: Effect of ionic strength on ranitidine HCl degradation in pH 12 phosphate buffer.

Ionic strength (μ)	$\mu^{1/2}$	$\frac{\mu^{1/2}}{(1+\mu^{1/2})}$	$k_{obs} \times 10^{5}$ (ml/mg x hr)	$\log k_{obs}$
0.20	0.4472	0.309	2.731	-4.564
0.50	0.7071	0.4142	2.715	-4.566
0.80	0.8944	0.4721	2.889	-4.539
1.00	1.000	0.5000	2.894	-4.539
1.20	1.095	0.5227	2.503	-4.602

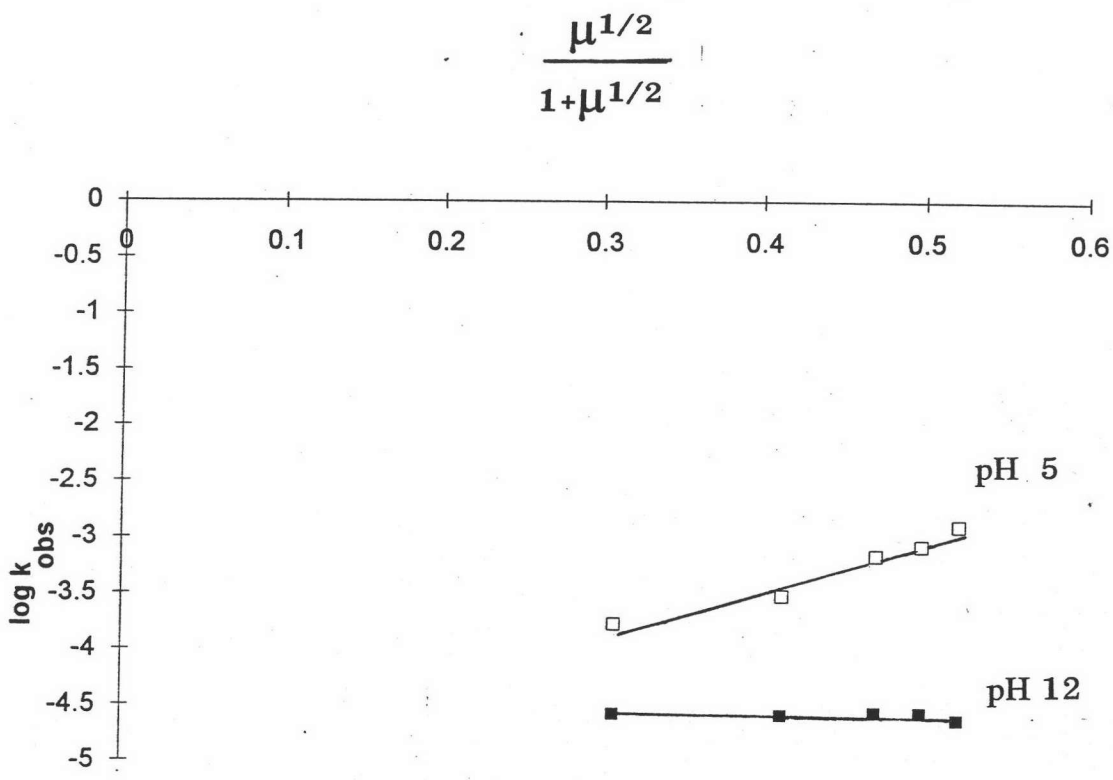

Figure 19: A plot of $\log k_{obs}$ versus $\frac{\mu^{1/2}}{1+\mu^{1/2}}$.

pH 5: intercept = −5.087 , slope = 4.093 , r^2 = 0.9577.

pH 12: intercept = −4.550 , slope = −0.0268 , r^2 = 7.990 x 10^{-3}.

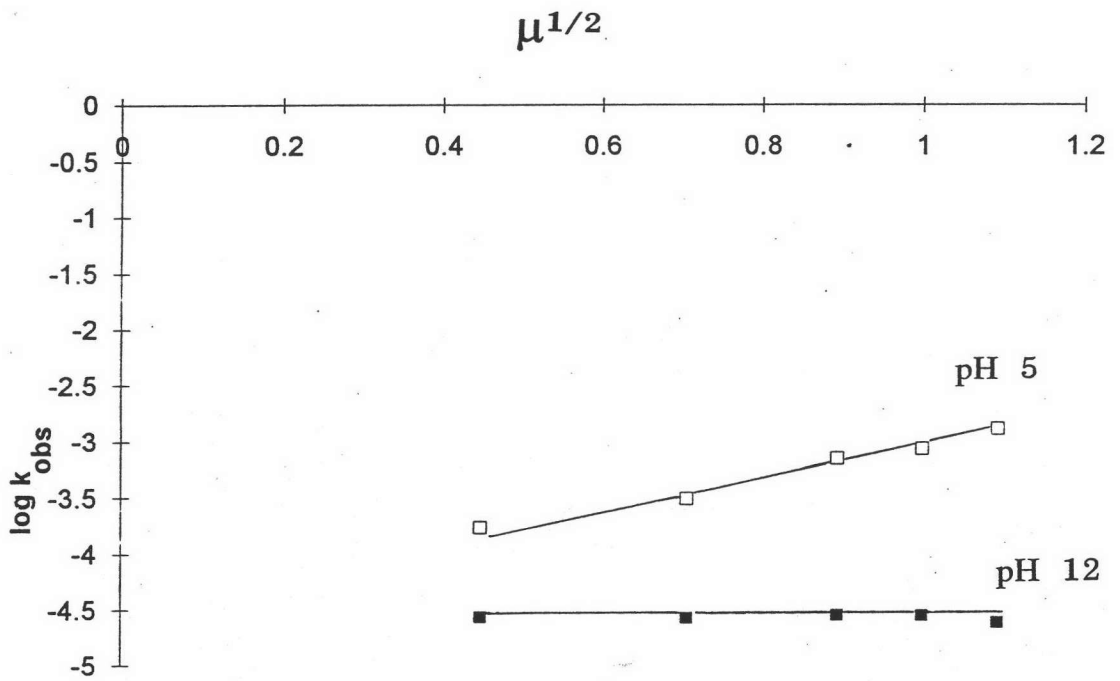

Figure 20: A plot of log k obs versus $\mu^{1/2}$.

pH 5: intercept = −4.414 , slope = 1.378 , r^2 = 0.9843.

pH 12: intercept = −4.550 , slope = −0.0144 , r^2 = 0.0209.

-2 and -3 and -2 is not the charge on ranitidine HCl. Thus, the slope of 4.093 of the log k_{obs} vs $\mu^{1/2} / (1 + \mu^{1/2})$ plot (in pH 5 solution) cannot be explained. The r^2 of the log k_{obs} versus $\mu^{1/2}$ plot is also greater.

Since the isoelectric point of ranitidine HCl is at (2.7+8.2)/2 = 5.45, about equal concentrations of RH^+ and R^- are present in pH 5 solution (although R is dominant at this pH). The possible reaction is therefore between RH^+ and RH^+; or between R^- and R^- from a kinetic point of view. Although $H_2PO_4^-$ is dominant at pH 5 and it is a catalytic species, it is not considered to involve in a slow step because the second-order kinetics is assumed in all pH range studied even at a pH where there is no general acid-base catalysis. $H_2PO_4^-$ should involve in the fast step of the reaction.

In pH 12 solution, the possible reaction is between R^- and H_2O; or between R and other species. As it was stated previously that PO_4^{3-} may act as a general base. The general base catalysis usually involves three molecules of the reactants, i.e., the drug molecule, water, and a general base. Therefore, the reaction in pH 12 solution is most likely to be between R^- and H_2O (catalyzed by PO_4^{3-}) in a slow step. In addition, R^- dominates at this pH.

The Influence of Solvent Polarity.

Table 12 presents data of solvent polarity effect on the degradation rate of ranitidine HCl. A plot of ln k_{obs} versus $1/\in$, where $\in$ is the dielectric constant of solvent, has a positive slope (Figure 21). There are two possibilities associated with this plot. Firstly, the reactants are ions of opposite charge. The classical electrostatic theory may be used to predict the dependence of the rate constant of reactions between ions on the dielectric constant of the solvent as shown in equation (42). The equation predicts a linear plot of ln k against $1/\in$

Table 12: Effect of dielectric constant on the degradation rate of ranitidine HCl.

Methanol (%w/w)	Dielectric constant	$k_{obs} \times 10^4$ (ml/mg x hr)	ln k_{obs}
100	32.60	8.325	-7.091
80	42.08	3.084	-8.084
60	51.56	1.656	-8.706
40	61.04	0.5873	-9.743
20	70.52	0.4240	-10.07

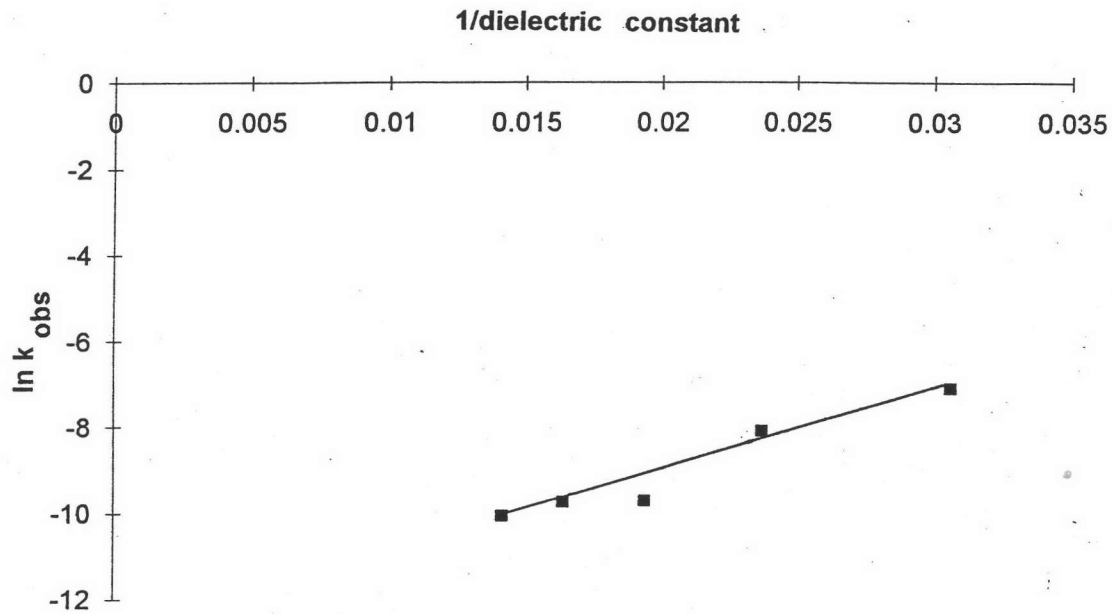

Figure 21: Effect of dielectric constant on the degradation rate of ranitidine HCl. (intercept = −12.56 , slope = 183.10 , and r^2 = 0.9707).

with a positive slope if the ions are of opposite charge and a negative slope if the reactants have the same sign.

Secondly, the positive slope of the ln k_{obs} versus $1/\in$ plot may indicate a reaction between an ion and a neutral molecule as it was previously described in equation (43). Since $r \neq$ is larger than r, the rate of the reaction should be somewhat greater in a medium of lower dielectric constant. This seems to be true in most cases, but this equation cannot be taken too seriously as a quantitative explanation.

All possible reactants in this system are RH^+, R, R^-, H^+, OH^-, H_2O, and methanol. In the first case where the reaction occurs between two ions of opposite sign, the possible reaction is between RH^+ and R^-; or between R^- and H^+; or between RH^+ and OH^- which are all unlikely since RH^+ is negligible in this neutral pH and H^+ and OH^- has not been reported to catalyze ranitidine HCl degradation at neutral pH. The second case is therefore considered. Possible reactions between an ion and a neutral molecule are R^- + H_2O and R^- + methanol. R is excluded since its reactions with H_2O or methanol would lead to a slope of zero. Since the rate constant increases with increasing the concentration of methanol, the reaction between R^- and methanol is assumed. If this is the case, then methanol also has a specific solvent effect.