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APPENDICES

APPENDIX I

Details of Ranitidine HCl

Details of Ranitidine HCl

(Mcevoy, 1988)

Chemistry

Ranitidine hydrochloride has solubilities of 660 mg/ml in water and 190 mg/ml in alcohol. The drug has pK_a's of 8.2 and 2.7. Ranitidine HCl occurs as white to pale yellow granular substance having slightly bitter taste and sulfur-like odor.

Ranitidine hydrochloride (N-(2-(((5(dimethylamino) methyl)-2-furfuryl)-thiol)-4-ethyl)-N-methyl-2-nitro-1,1-ethenediamine hydrochloride)

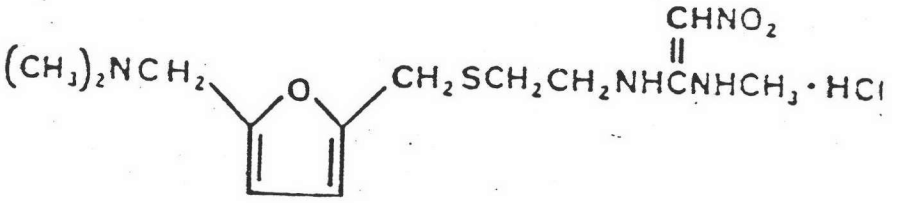


Figure 24: Chemical structure of ranitidine HCl.

Pharmacology

Ranitidine competitively inhibits the action of histamine on the H_2 receptors of parietal cells reducing gastric acid secretion under daytime and

nocturnal basal condition and also when stimulated by food, insulin, amino acid, histamine, or pentagastrin.

Pharmacokinetics

Ranitidine is rapidly absorbed from GI tract following an oral administration and from parenteral sites following IM injection. Following the oral administration, the drug undergoes extensive first-pass metabolism. The absolute bioavailabilities of orally administered ranitidine has been reported to be about 50%. Following the IM administration, the absolute bioavailalbility of ranitidine is 90-100%.

Ranitidine is widely distributed throughout the body and is 10-19% protein bound. The apparent volume of distribution of ranitidine is reported to be 1.2-1.9 l/kg.

The elimination half-life of ranitidine in adult is 1.7-3.2 hours and may be positively correlated with age. The elimination half-life prolongs in patients with renal impairment. Ranitidine is metabolized in the liver to ranitidine N-oxide, desmethyl and ranitidine-S-oxide. And it is excreted principally in urine via glomerular filtration and tubular secretion.

Adverse Effects

Adverse effects of ranitidine are generally infrequent and minor.

Headache (sometimes severe) occurs in approximately 3% of patients receiving the drug. Malaise, dizziness, somnolence, insomnia, and vertigo have been reported less frequently. Reversible mental confusion, agitation, mental

depression, and hallucinations have occurred, mainly in debilitated geriatric patients.

Constipation, nausia, vomiting and abdonimal discomfort or pain have occurred in patients receiving ranitidine.

Rash, which may be urticaria, maculopapular, and/or puritic, has been reported during ranitidine therapy.

Analysis of Ranitidine HCl

The ultraviolet spectrum of ranitidine HCl in an aqueous solution was recorded and shown in figure 23. The spectrum shows two absorption maxima at 228 and at 313 nm. The measurement at 313 nm is very convenient for quantitative determination of ranitidine HCl (Hohnjec et al., 1988).

Several HPLC analysis were reported such as the method of Beaulieu et al. (1988), the method of Gupta (1988) and the method of Teraoka, Otasuka and Matsuda (1993). The HPLC conditions of Gupta as follow: the apparatus used was ALC 202, Water Associates, with a multiple wavelength detector (Spectroflow monitor SF 770) and a recorder (Omiscribe 5213-12). A column used was microbondapak C_{18} (theoretical plates of 3000) with 30 cm.long and 9 mm i.d. The mobile phase was 10% V/V of methanol 7% V/V acetonitrile and 0.01 M phosphate buffer in water having pH of 5.8 ± 0.05. The flow rate was 2.0 ml/min and the sensitivity was set at 0.04 AUFS. The wavelength was set at 262 nm. The chart speed was 30.5 cm/hr and the temperature was ambient. The internal standard was caffeine

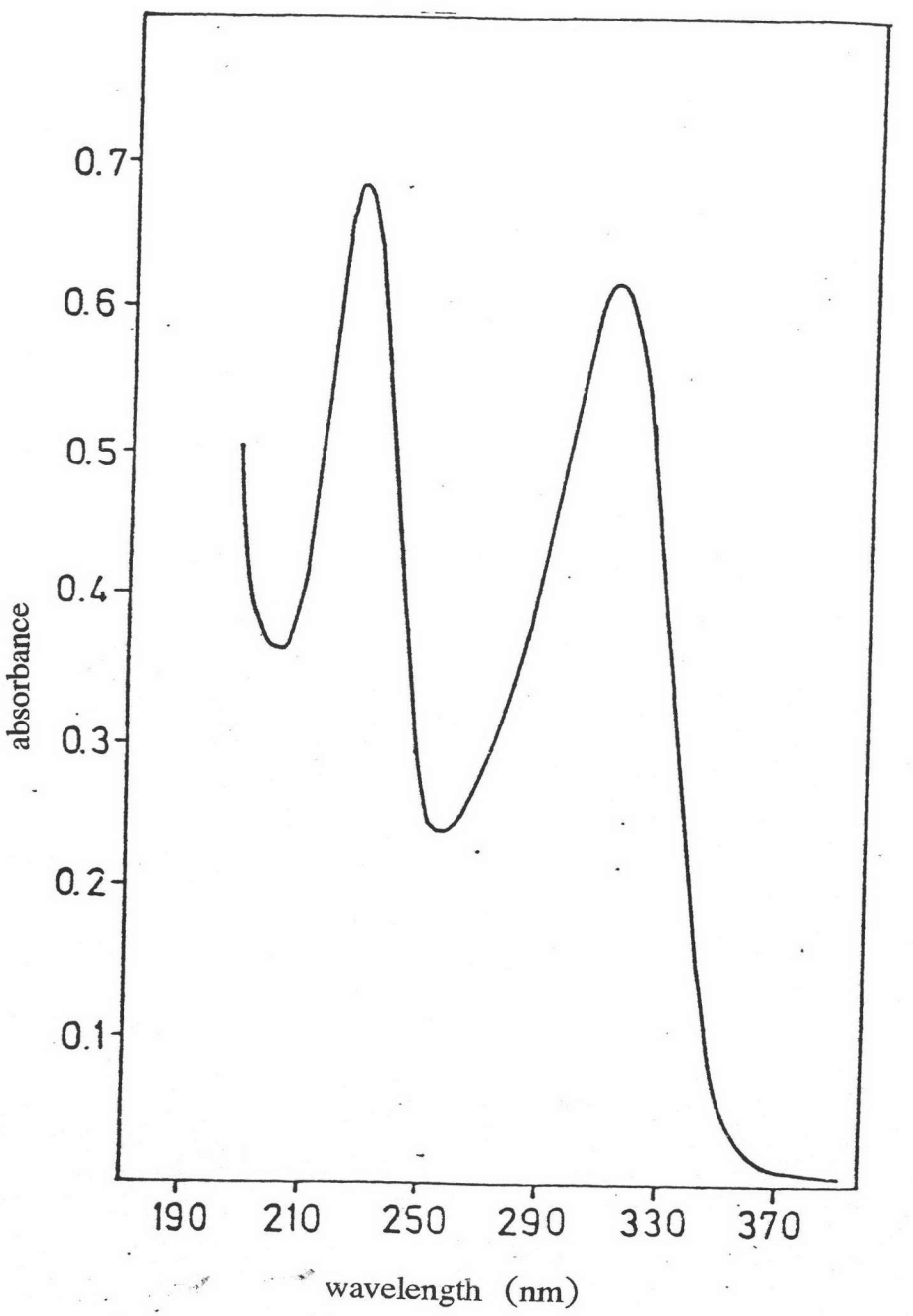
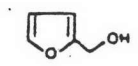


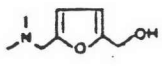
Figure 23: Ultraviolet spectrum of ranitidine hydrochloride in an aqueous solution. Instrument : Pye-Unicam SP8-100.

Degradation products and organate during synthesis were reported in Figure 24. The main impurities observed from eight samples of ranitidine HCl raw material from three manufacturers were 10, 4, 5, 6, 11, 12 and 13 (Beaulieu, 1988).



1

Furfuryl alcohol

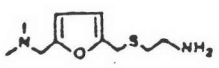


2

(5-Dimethylaminomethyl) furfuryl alcohol

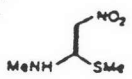
3

Fumaric acid



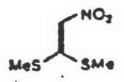
4

2-(2-Aminoethylthio)methyl
-5-(dimethylaminomethyl) furane



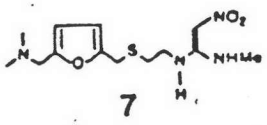
5

N-Methyl-1-methylthio
-2-nitro-1-etheneamine



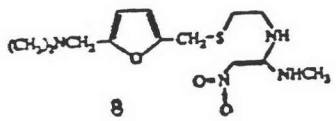
6

1,1-Bis-(methylthio)-2-nitroethene



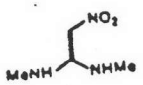
7

Ranitidine (*N*-[2-[[5- [(dimethylamino)methyl]
furfuryl]thio]ethyl]-*N'*-methyl-2-
nitro-1,1-ethenediamine)



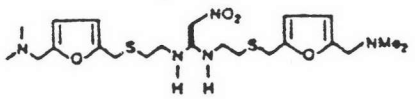
8

Ranitidine



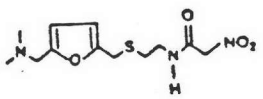
9

N,N'-Dimethyl-2-nitro-1,1-ethenediamine



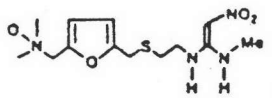
10

Bis-2,2-[[[5-[(dimethylamino)methyl]-2-
furanyl]methyl]thio]ethylamino-1-nitroethene



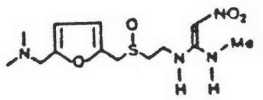
11

N-[2-[5-(Dimethylaminomethyl)-2-furanylmethyl]-
thioethyl]nitroacetamide



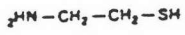
12

Ranitidine-*N*-oxide



13

Ranitidine-*S*-oxide



14

2-Aminoethanethiol

[a] Compounds **11**, **12**, and **13** are degradation products; **4** is an intermediate and a degradation product; all other compounds are synthetic intermediates.

Figure 24: Ranitidine HCl and its related compounds (Beaulieu, 1988).

APPENDIX II

Calibration Curve Data of Ranitidine HCl

Calibration Curve "a"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.716
8.00	7.768
16.00	16.06
24.00	25.44
32.00	32.02
40.00	39.17

PAR = −0.1060 + 0.9963conc $r^2 = 0.9970$

Calibration Curve "b"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.117
8.00	8.285
16.00	16.81
24.00	23.32
32.00	35.30
40.00	41.50

PAR = −0.2748 + 1.056conc $r^2 = 0.9940$

Calibration Curve "c"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.179
8.00	9.281
16.00	18.19
24.00	26.04
32.00	38.14
40.00	46.16

PAR = -0.5274+ 1.171conc $r^2 = 0.9970$

Calibration Curve "d"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.587
8.00	7.071
16.00	15.79
24.00	23.50
32.00	33.12
40.00	37.64

PAR = -0.2308 + 0.9846conc $r^2 = 0.9936$

Calibration Curve "e"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	2.901
8.00	5.976
16.00	14.90
24.00	20.01
32.00	30.80
40.00	38.77

PAR = −1.740+ 0.9984conc $r^2 = 0.9933$

Calibration Curve "f"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	2.827
8.00	5.145
16.00	12.66
24.00	20.24
32.00	27.05
40.00	35.63

PAR = −1.667 + 0.9159conc $r^2 = 0.9977$

Calibration Curve "g"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.766
8.00	7.463
16.00	17.59
24.00	27.71
32.00	37.64
40.00	47.66

PAR = -1.862+ 1.234conc r^2 = 0.9994

Calibration Curve "h"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.144
8.00	9.356
16.00	16.60
24.00	26.33
32.00	37.44
40.00	43.88

PAR = -0.3156 + 1.126conc r^2 = 0.9956

Calibration Curve "i"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.066
8.00	9.062
16.00	15.76
24.00	24.34
32.00	35.06
40.00	40.95

PAR = -0.5440+ 1.060conc $r^2 = 0.9944$

Calibration Curve "j"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.364
8.00	8.071
16.00	16.36
24.00	23.74
32.00	31.49
40.00	38.75

PAR = 0.6312 + 0.9597conc $r^2 = 0.9997$

Calibration Curve "k"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.011
8.00	7.953
16.00	17.15
24.00	29.44
32.00	35.54
40.00	47.36

PAR = -1.244+ 1.201conc r^2 = 0.9946

Calibration Curve "l"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.635
8.00	5.771
16.00	12.56
24.00	20.83
32.00	28.46
40.00	37.80

PAR = -1.581 + 0.9560conc r^2 = 0.9941

Calibration Curve "m"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	2.818
8.00	7.286
16.00	14.73
24.00	23.74
32.00	31.35
40.00	37.32

PAR = -0.5872+ 0.9739conc $r^2 = 0.9968$

Calibration Curve "n"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.591
8.00	6.805
16.00	14.31
24.00	23.47
32.00	32.11
40.00	41.27

PAR = -1.551 + 1.055conc $r^2 = 0.9978$

Calibration Curve "o"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.925
8.00	8.174
16.00	17.15
24.00	24.89
32.00	34.70
40.00	42.28

PAR = -0.3280 + 1.073conc $r^2 = 0.9991$

Calibration Curve "p"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.178
8.00	6.694
16.00	13.85
24.00	25.33
32.00	32.74
40.00	39.86

PAR = -1.461 + 1.052conc $r^2 = 0.9946$

Calibration Curve "q"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.063
8.00	6.625
16.00	16.35
24.00	25.06
32.00	34.77
40.00	40.16

PAR = -0.6154 + 1.054conc $r^2 = 0.9941$

Calibration Curve "r"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.268
8.00	7.167
16.00	16.38
24.00	23.11
32.00	30.50
40.00	42.52

PAR = -0.7112 + 1.034conc $r^2 = 0.9941$

Calibration Curve "s"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.882
8.00	7.883
16.00	15.45
24.00	22.20
32.00	32.36
40.00	42.13

PAR = −0.4566+ 1.029conc r^2 = 0.9923

Calibration Curve "t"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.507
8.00	6.266
16.00	14.76
24.00	22.18
32.00	29.01
40.00	37.44

PAR = −0.6706 + 0.9450conc r^2 = 0.9988

Calibration Curve "u"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.201
8.00	7.401
16.00	15.03
24.00	22.76
32.00	33.02
40.00	40.19

PAR = -1.104 + 1.036conc $r^2 = 0.9980$

Calibration Curve: "v"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	3.083
8.00	8.089
16.00	16.21
24.00	23.42
32.00	32.55
40.00	39.69

PAR = -0.3926 + 0.9887conc $r^2 = 0.9986$

Calibration Curve "w"

concentration (mcg/ml)	peak area ratio (PAR)
4.00	4.141
8.00	7.106
16.00	14.80
24.00	23.91
32.00	32.79
40.00	42.02

PAR = -1.194 + 1.064conc $r^2 = 0.9970$

APPENDIX III

Stability Data of Ranitidine HCl

in pH 1-12 Phosphate Buffers

In pH 1 Phosphate Buffer

Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(c)	26.10	25.98	24.28	24.38	25.19 ±0.99
3.83	(c)	25.30	25.25	26.31	24.92	25.44 ± 0.60
6.75	(c)	26.29	25.55	24.90	25.38	25.53 ± 0.58
11.58	(c)	24.10	23.83	25.19	24.21	24.33 ± 0.59
15.75	(c)	22.66	23.72	24.53	23.43	23.58 ± 0.77
21.00	(c)	15.21	14.83	14.45	15.58	15.02 ± 0.49
22.83	(c)	12.92	10.87	14.44	11.62	12.46 ± 1.57
36.00	(c)	9.929	11.95	7.719	6.622	9.055 ± 2.37
38.75	No peak was detected .					-

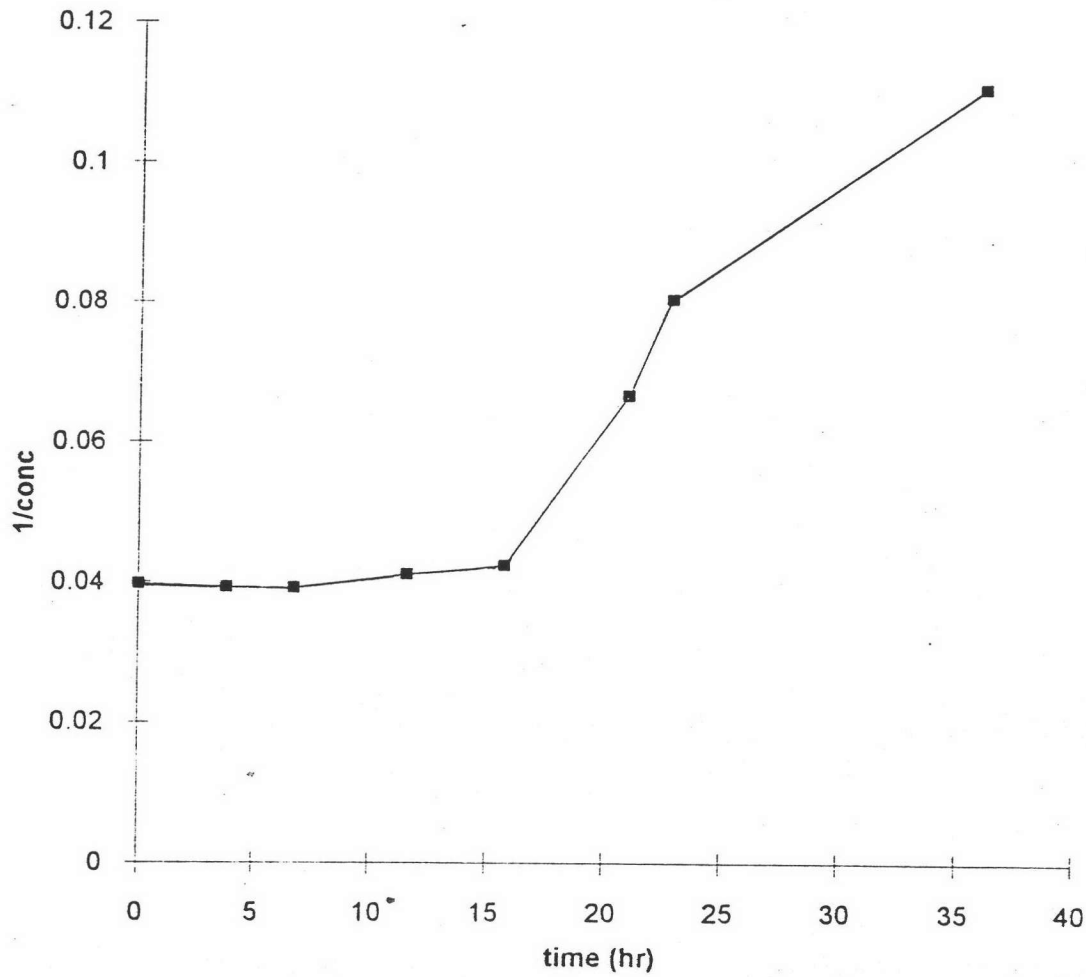
*calibration curves used are in parenthesis.

Zero-order : conc = 25.68 - 0.1142time $r^2 = 0.7264$.

First-order : $\log conc = 1.410 - 2.202 \times 10^{-3} time$ $r^2 = 0.7298$.

Second-order : $1/conc = 0.0389 + 1.901 \times 10^{-4} time$ $r^2 = 0.7330$.

(The regression lines were calculated in the the period of 0 - 15.75 hr.)



Second-order plot of ranitidine HCl degradation in pH 1 phosphate buffer (ionic strength = 0.5).

In pH 2 Phosphate Buffer

Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(c)	22.73	23.44	23.74	23.96	23.47 ± 0.54
7.00	(c)	25.00	25.16	23.99	24.72	24.72 ± 0.52
11.67	(c)	21.97	20.01	20.11	22.35	21.11 ± 1.22
16.00	(c)	21.23	19.40	20.26	17.27	19.54 ± 1.69
21.25	(c)	6.988	8.068	6.462	7.227	7.186 ± 0.67
23.08	(c)	6.094	5.759	5.705	7.178	6.184 ± 0.68
36.25	(c)	5.406	5.487	3.638	4.779	4.828 ± 0.85
44.00	(c)	6.147	4.993	5.759	5.833	5.683 ± 0.49
50.25	(c)	4.790	5.902	4.262	4.986	4.985 ± 0.68

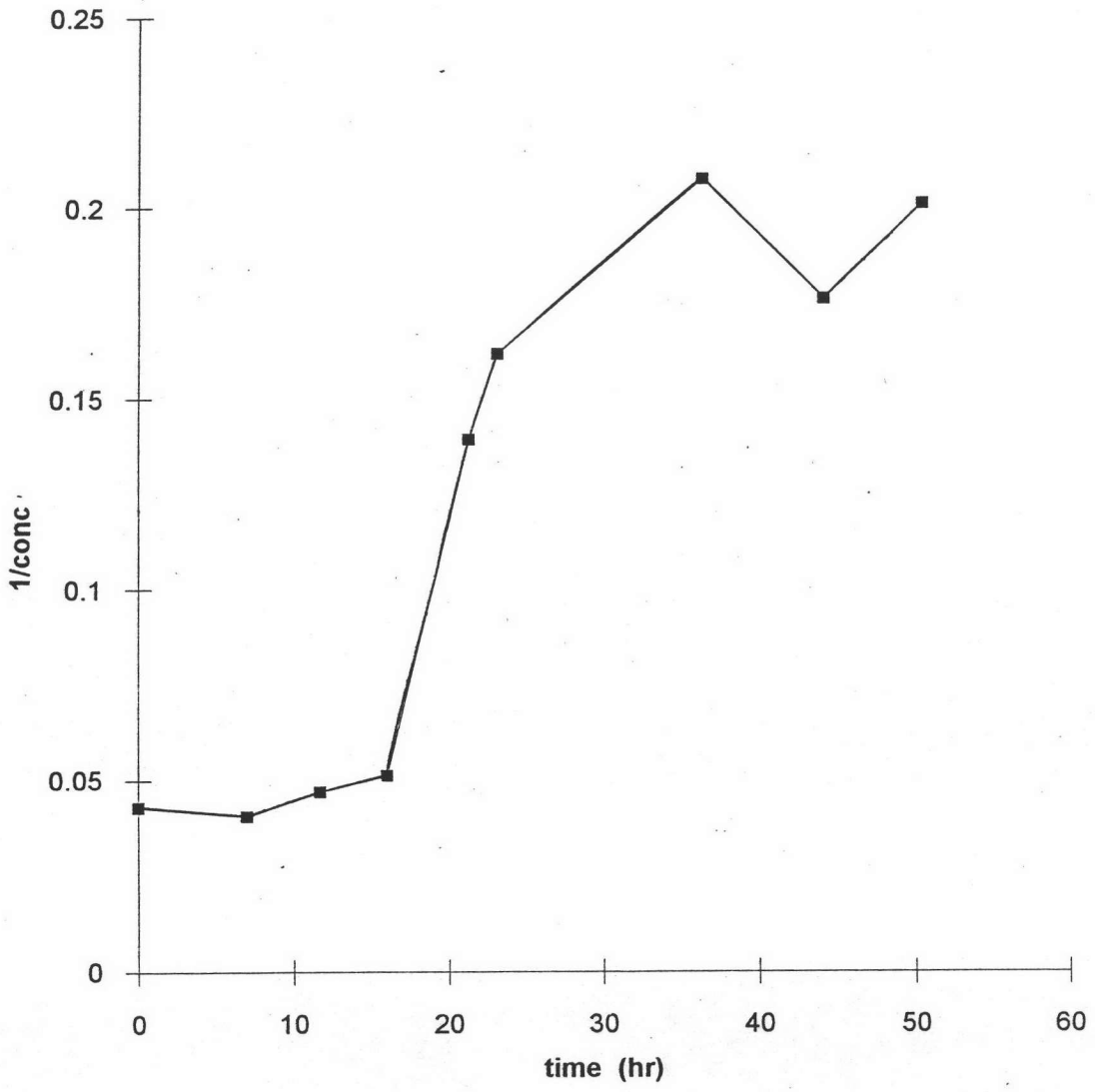
*calibration curves used are in parenthesis.

Zero-order : $conc = 24.50 - 0.2665 time$ $r^2 = 0.6208.$

First-order : $\log conc = 1.391 - 5.333 \times 10^{-3} time$ $r^2 = 0.6397.$

Second-order : $1/conc = 0.0405 + 5.676 \times 10^{-4} time$ $r^2 = 0.6208.$

The regression lines were calculated in the the period of 0 - 16.00 hr.



Second-order plot of ranitidine HCl degradation in pH 2 phosphate buffer (ionic strength = 0.5).

In pH 3 Phosphate Buffer

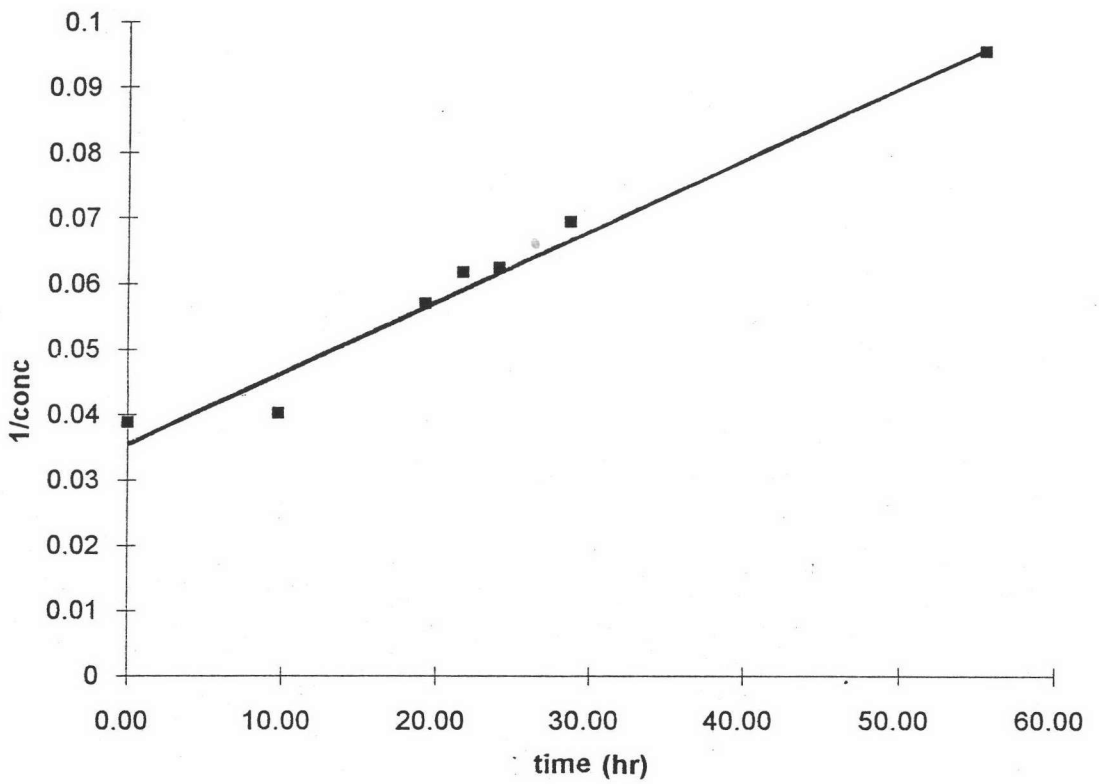
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)	Average Conc ± SD
0.00	(e) 25.45 25.56 26.06 26.05	25.78 ± 0.32
9.75	(e) 24.24 26.27 24.84 24.26	24.90 ± 0.95
19.25	(e) 18.00 18.94 16.47 16.79	17.42 ± 0.93
21.67	(e) 16.74 16.23 15.42 16.52	16.23 ± 0.58
24.08	(e) 16.04 17.06 15.52 15.52	16.04 ± 0.73
28.67	(e) 14.36 13.91 14.69 14.75	14.43 ± 0.39
55.25	(f) 10.90 10.99 9.646 10.51	10.51 ± 0.61
70.08	An insignificant peak was reported	-

*calibration curves used are in parenthesis.

Zero-order : conc = 24.63 - 0.2958time $r^2 = 0.8525$.

First-order : $\log conc = 1.407 - 7.549 \times 10^{-3} time$ $r^2 = 0.9297$.

Second-order : $1/conc = 0.0360 + 1.088 \times 10^{-3} time$ $r^2 = 0.9730$.



Second-order plot of ranitidine HCl degradation in pH 3 phosphate buffer (ionic strength = 0.5).

In pH 4 Phosphate Buffer

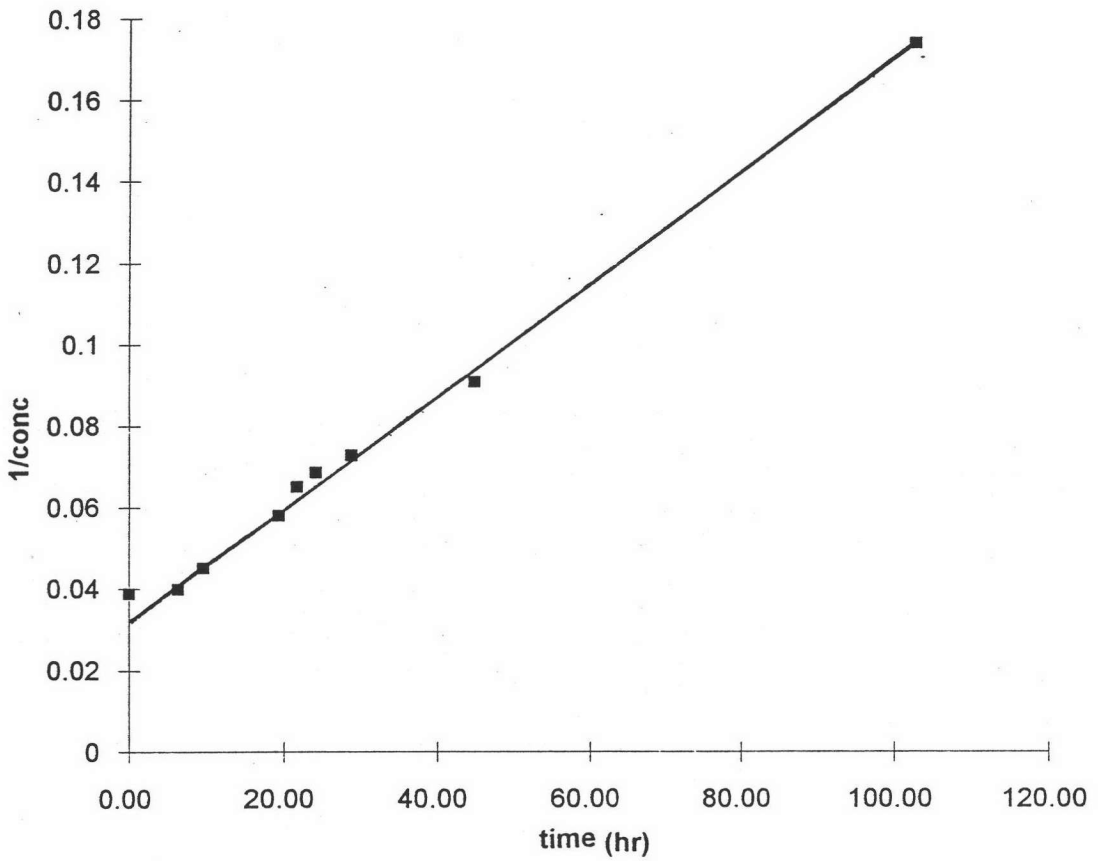
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD.
0.00	(e)	25.85	26.00	25.55	26.01	25.85 ± 0.21
6.42	(e)	24.54	24.74	24.95	26.19	25.10 ± 0.74
9.75	(e)	22.12	21.27	22.68	22.75	22.20 ± 0.68
19.25	(e)	17.24	18.21	16.02	17.51	17.24 ± 0.91
21.67	(e)	15.12	13.04	16.58	16.78	15.38 ± 1.73
24.08	(e)	15.42	13.58	15.00	14.44	14.61 ± 0.80
28.67	(e)	14.64	14.64	12.54	13.14	13.74 ± 1.07
44.75	(f)	11.47	12.35	10.76	9.523	11.02 ± 1.19
102.58	(g)	5.277	6.300	5.731	5.744	5.763 ± 0.42

*calibration curves used are in parenthesis.

Zero-order : $conc = 22.21 - 0.1905 time$ $r^2 = 0.7800.$

First-order : $\log conc = 1.370 - 6.407 \times 10^{-3} time$ $r^2 = 0.9415.$

Second-order : $1/conc = 0.0339 + 1.348 \times 10^{-3} time$ $r^2 = 0.9956.$



Second-order plot of ranitidine HCl degradation in pH 4 phosphate buffer (ionic strength = 0.5).

In pH 5 Phosphate Buffer

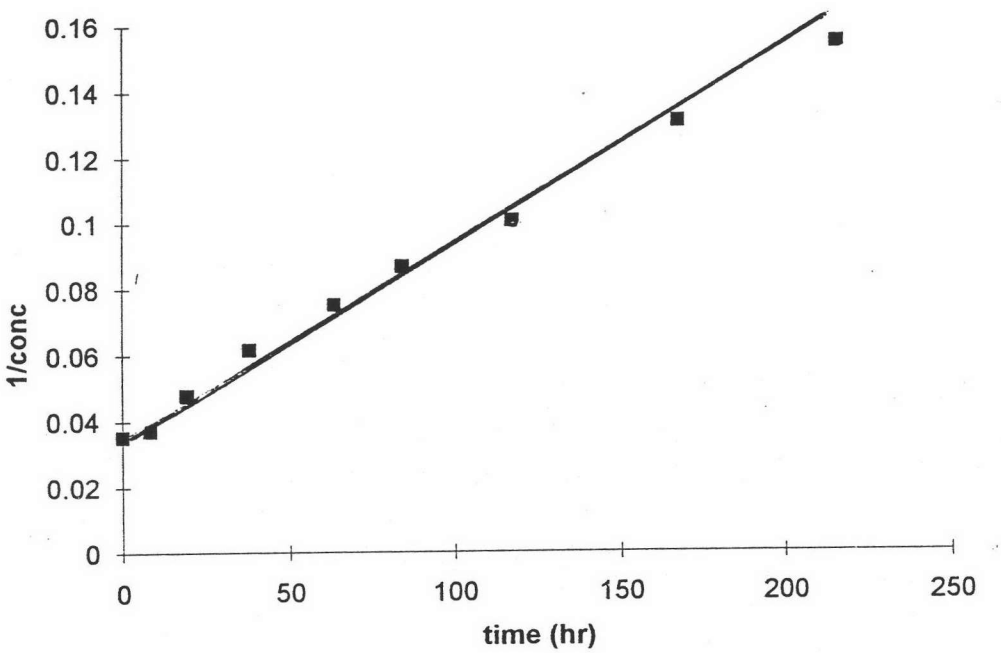
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	26.51	30.12	28.48	28.38	28.31 ±1.48
8.17	(o)	28.17	23.13	27.14	29.69	27.03 ± 2.80
19.16	(p)	20.56	21.04	21.56	21.05	21.05 ± 0.41
37.92	(p)	16.52	16.73	15.25	16.47	16.24 ± 0.67
63.58	(p)	13.22	13.21	13.40	13.29	13.28 ± 0.09
84.25	(p)	12.07	11.64	11.84	10.64	11.55 ± 0.63
117.25	(p)	10.11	10.75	10.16	8.776	9.949 ± 0.83
167.17	(q)	8.052	7.203	7.742	7.668	7.666 ± 0.35
215.50	(q)	6.975	6.005	5.999	6.981	6.490 ± 0.56

*calibration curves used are in parenthesis.

Zero-order : $conc = 23.39 - 0.0966 time$ $r^2 = 0.7969.$

First-order : $\log conc = 1.379 - 2.958 \times 10^{-3} time$ $r^2 = 0.9291.$

Second-order : $1/conc = 0.0370 + 5.538 \times 10^{-4} time$ $r^2 = 0.9955.$



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 0.5).

In pH 6 Phosphate Buffer

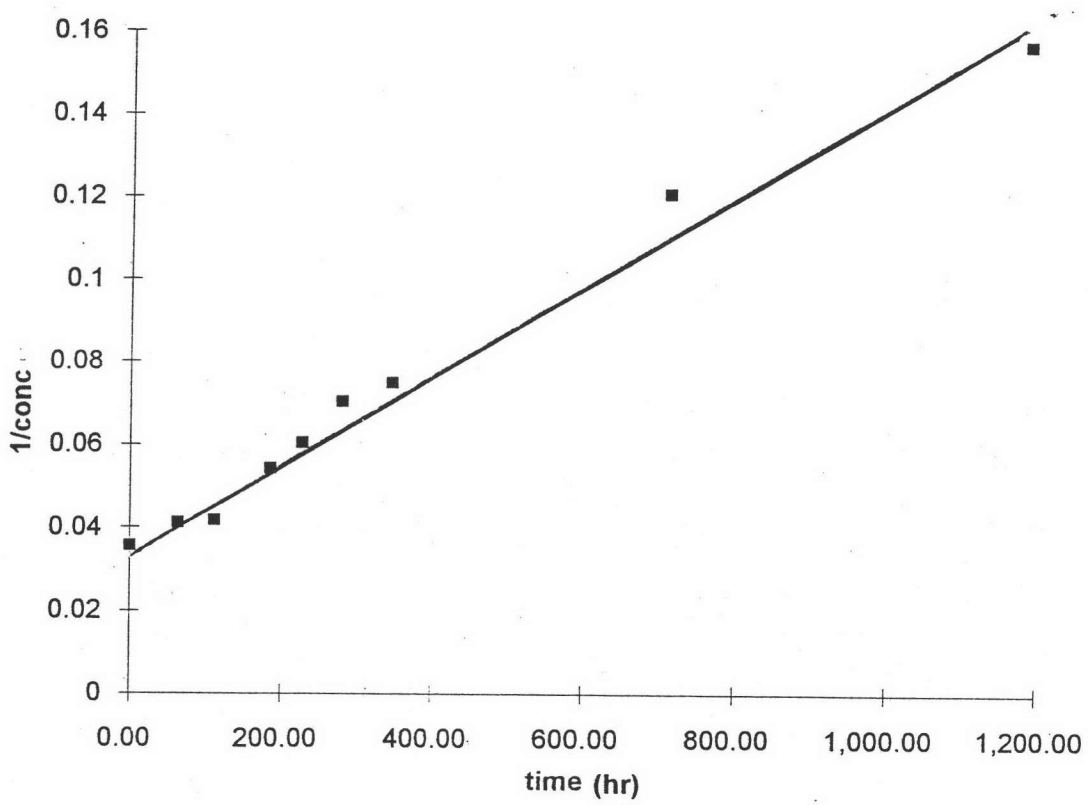
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)				Average Conc ± SD
0.00	(o) 29.69	27.36	27.15	28.08	28.07 ± 1.15
64.42	(p) 22.58	24.73	25.68	24.34	24.33 ± 1.30
111.42	(p) 23.63	24.34	22.88	24.94	23.95 ± 0.89
184.92	(q) 18.98	17.09	18.88	18.72	18.42 ± 0.89
227.33	(q) 16.56	15.34	17.14	17.08	16.53 ± 0.83
280.58	(q) 14.61	14.44	13.87	13.86	14.20 ± 0.39
346.42	(r) 12.58	13.87	13.49	13.45	13.34 ± 0.55
713.08	(t) 8.831	7.662	8.104	8.620	8.304 ± 0.52
1,188.00	(u) 6.020	6.375	6.483	6.723	6.400 ± 0.29

*calibration curves used are in parenthesis.

Zero-order : conc = 23.01 -0.0172time $r^2 = 0.7743$.

First-order : $\log conc = 1.378 - 5.469 \times 10^{-4} time$ $r^2 = 0.9142$.

Second-order : $1/conc = 0.0360 + 1.063 \times 10^{-3} time$ $r^2 = 0.9864$.



Second-order plot of ranitidine HCl degradation in pH 6 phosphate buffer (ionic strength = 0.5).

In pH 7 Phosphate Buffer

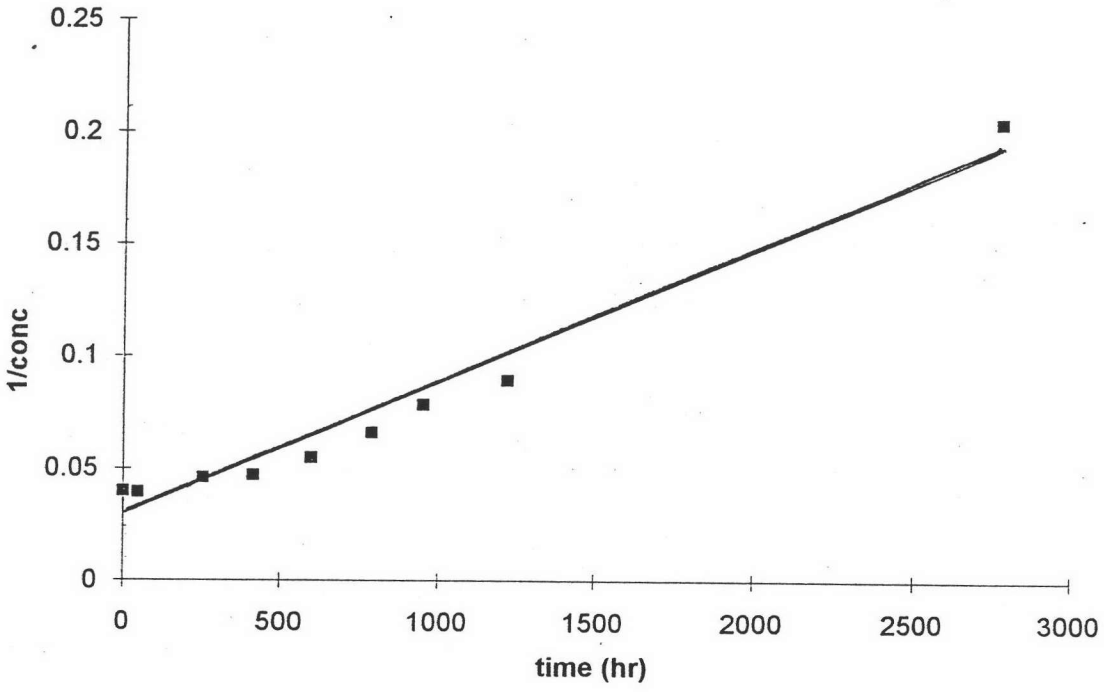
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(a)	24.68	25.96	24.45	25.27	25.09 ± 0.68
48.67	(b)	24.04	26.61	25.81	25.07	25.38 ± 1.09
258.42	(c)	21.88	21.34	22.21	21.81	21.81 ± 0.36
417.33	(d)	21.28	20.77	22.18	20.85	21.27 ± 0.65
595.50	(e)	17.79	18.44	17.03	19.85	18.28 ± 1.20
787.67	(g)	14.61	16.11	15.12	14.96	15.20 ± 0.64
952.75	(h)	13.48	11.22	13.22	13.30	12.80 ± 1.06
1,218.75	(j)	12.04	11.41	10.24	11.23	11.23 ± 0.74
2,771.92	(s)	5.187	4.637	5.010	4.808	4.910 ± 0.24

*calibration curves used are in parenthesis.

Zero-order : $conc = 23.32 - 7.641 \times 10^{-3} time$ $r^2 = 0.8914$.

First-order : $\log conc = 1.404 - 2.652 \times 10^{-4} time$ $r^2 = 0.9874$.

Second-order : $1/conc = 0.0268 + 5.987 \times 10^{-5} time$ $r^2 = 0.9675$.



Second-order plot of ranitidine HCl degradation in pH 7 phosphate buffer (ionic strength = 0.5).

In pH 8 Phosphate Buffer

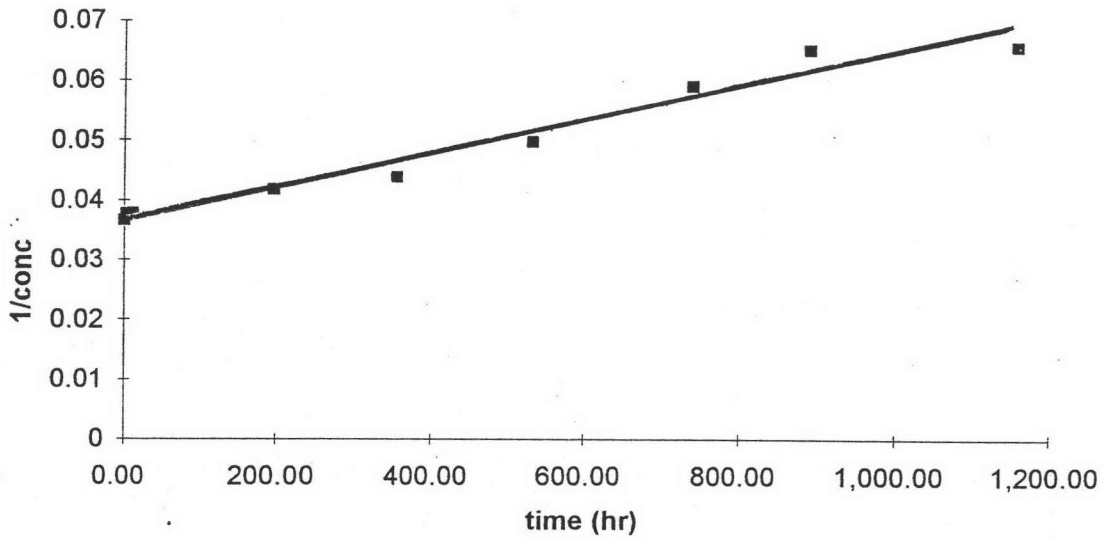
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)				Average Conc ± SD
0.00	(b) 26.58	27.11	27.54	28.06	27.32 ± 0.63
3.33	(b) 27.68	26.05	25.33	27.10	26.58 ± 1.05
11.50	(b) 28.13	26.53	24.69	26.23	26.40 ± 1.41
195.08	(c) 23.64	23.63	24.98	23.72	24.00 ± 0.66
354.00	(d) 21.00	23.50	23.04	23.72	22.82 ± 1.24
532.17	(e) 21.88	19.58	19.13	19.82	20.10 ± 1.22
738.33	(g) 17.23	15.21	16.54	18.86	16.96 ± 1.52
889.42	(h) 15.38	14.19	15.73	16.21	15.38 ± 0.86
1156.58	(j) 15.26	14.77	15.68	15.20	15.23 ± 0.37

*calibration curves used are in parenthesis.

Zero-order : $conc = 26.48 - 0.0112 time$ $r^2 = 0.9638$.

First-order : $\log conc = 1.427 - 2.237 \times 10^{-4} time$ $r^2 = 0.9693$.

Second-order : $1/conc = 0.0368 + 2.730 \times 10^{-5} time$ $r^2 = 0.9662$.



Second-order plot of ranitidine HCl degradation in pH 8 phosphate buffer (ionic strength = 0.5).

In pH 9 Phosphate Buffer

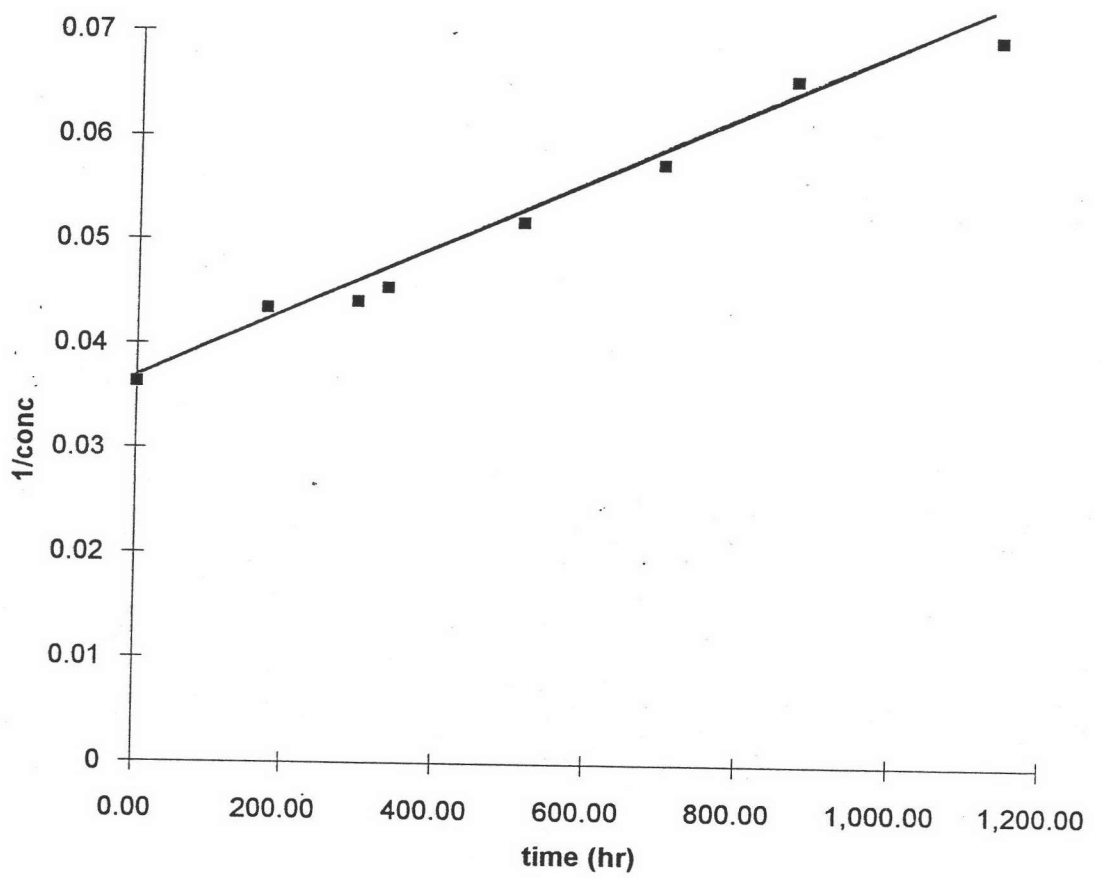
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(b)	25.46	28.78	27.43	28.33	27.50 ± 1.17
174.25	(c)	23.05	22.77	23.56	22.70	23.02 ± 0.39
293.50	(c)	22.70	22.01	23.41	22.66	22.70 ± 0.57
333.50	(d)	20.54	24.05	21.48	22.02	22.02 ± 1.48
510.83	(e)	18.99	19.98	18.14	20.22	19.33 ± 0.96
695.25	(e)	18.52	17.00	18.08	16.20	17.45 ± 1.05
868.25	(h)	15.05	16.08	14.71	15.27	15.28 ± 0.58
1,135.33	(j)	13.91	14.58	14.73	14.42	14.41 ± 0.36

*calibration curves used are in parenthesis.

Zero-order : conc = 25.92 - 0.0114time r^2 = 0.9500.

First-order : $\log conc = 1.422 - 2.515 \times 10^{-4} time$ r^2 = 0.9755.

Second-order : $1/conc = 0.0365 + 3.026 \times 10^{-5} time$ r^2 = 0.9836.



Second-order plot of ranitidine HCl degradation in pH 9 phosphate buffer (ionic strength = 0.5).

In pH 10 Phosphate Buffer

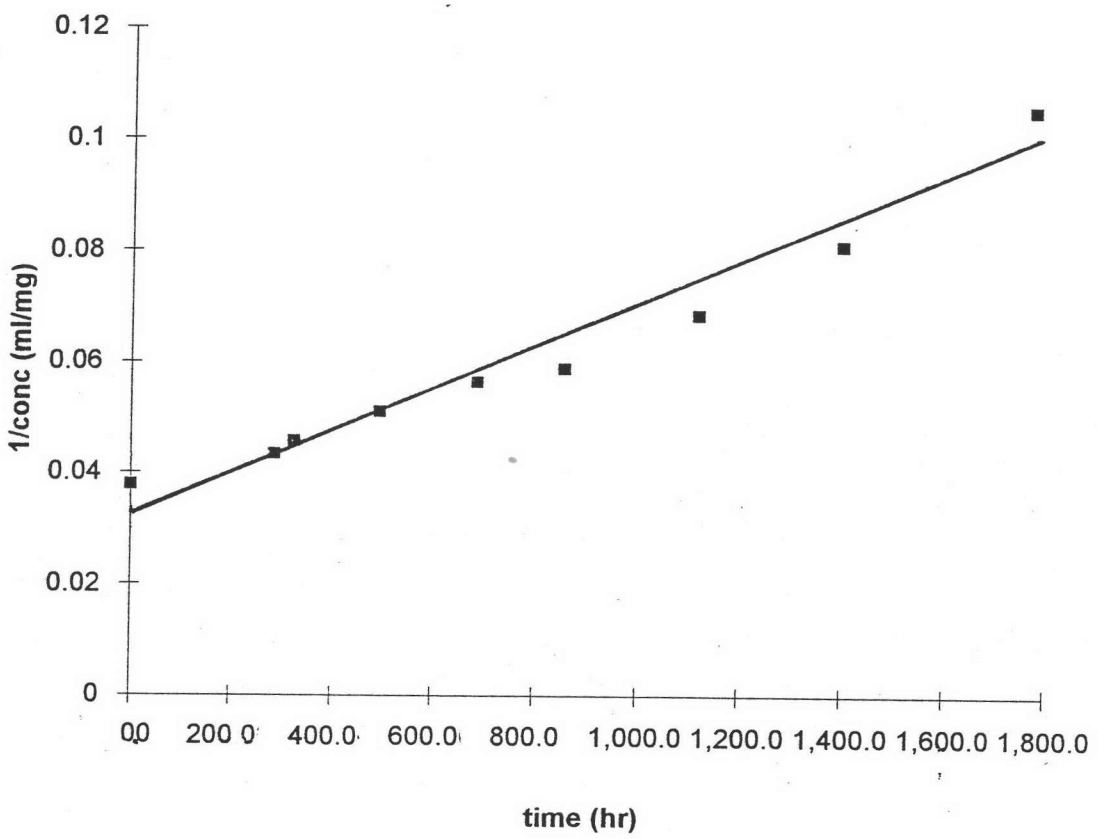
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(b)	27.96	25.08	25.15	27.78	26.49 ± 1.59
283.75	(c)	22.56	22.80	21.98	25.11	23.11 ± 1.38
323.75	(d)	21.11	21.75	22.51	22.41	21.95 ± 0.65
494.67	(e)	20.55	19.02	18.90	20.22	19.67 ± 0.84
685.25	(g)	18.21	17.45	16.51	18.87	17.76 ± 1.02
856.92	(h)	17.22	16.50	17.41	17.02	17.04 ± 0.39
1,118.33	(j)	15.64	14.41	14.14	14.40	14.65 ± 0.67
1,396.92	(k)	13.58	12.40	12.06	11.60	12.41 ± 0.85
1,773.00	(m)	9.506	10.28	8.845	9.543	9.544 ± 0.59

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 25.20 - 9.287 \times 10^{-3}\text{time}$ $r^2 = 0.9790$.

First-order : $\log \text{conc} = 1.425 - 2.430 \times 10^{-4}\text{time}$ $r^2 = 0.9940$.

Second-order : $1/\text{conc} = 0.0329 + 3.604 \times 10^{-5}\text{time}$ $r^2 = 0.9588$.



Second-order plot of ranitidine HCl degradation in pH 10 phosphate buffer (ionic strength = 0.5).

In pH 11 Phosphate Buffer

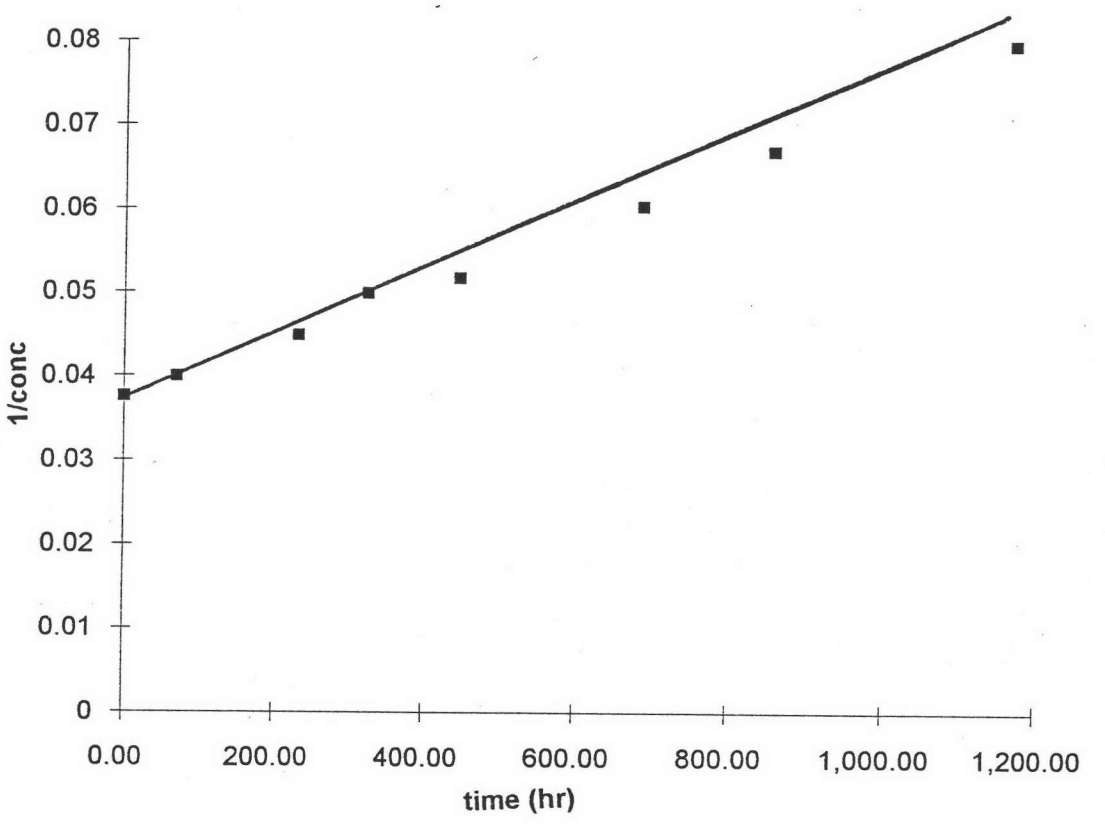
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(b)	26.60	26.42	26.85	26.62	26.62 ± 0.18
69.75	(c)	25.02	25.48	23.15	26.45	25.03 ± 1.38
231.75	(c)	22.27	21.98	21.64	23.28	22.29 ± 0.71
323.75	(d)	20.60	19.00	18.86	21.80	20.07 ± 1.41
446.83	(e)	18.63	20.38	18.59	19.85	19.36 ± 0.90
687.00	(g)	14.00	16.90	17.90	17.68	16.62 ± 1.80
857.92	(i)	14.85	15.33	14.79	14.97	14.98 ± 0.24
1,167.92	(j)	13.25	11.50	13.02	12.58	12.59 ± 0.78

*calibration curves used are in parenthesis.

Zero-order : conc = 25.28 - 0.1180time $r^2 = 0.9634$.

First-order : $\log conc = 1.412 - 2.747 \times 10^{-4} time$ $r^2 = 0.9918$.

Second-order : $1/conc = 0.0372 + 3.515 \times 10^{-5} time$ $r^2 = 0.9952$.



Second-order plot of ranitidine HCl degradation in pH 11 phosphate buffer (ionic strength = 0.5).

In pH 12 Phosphate Buffer

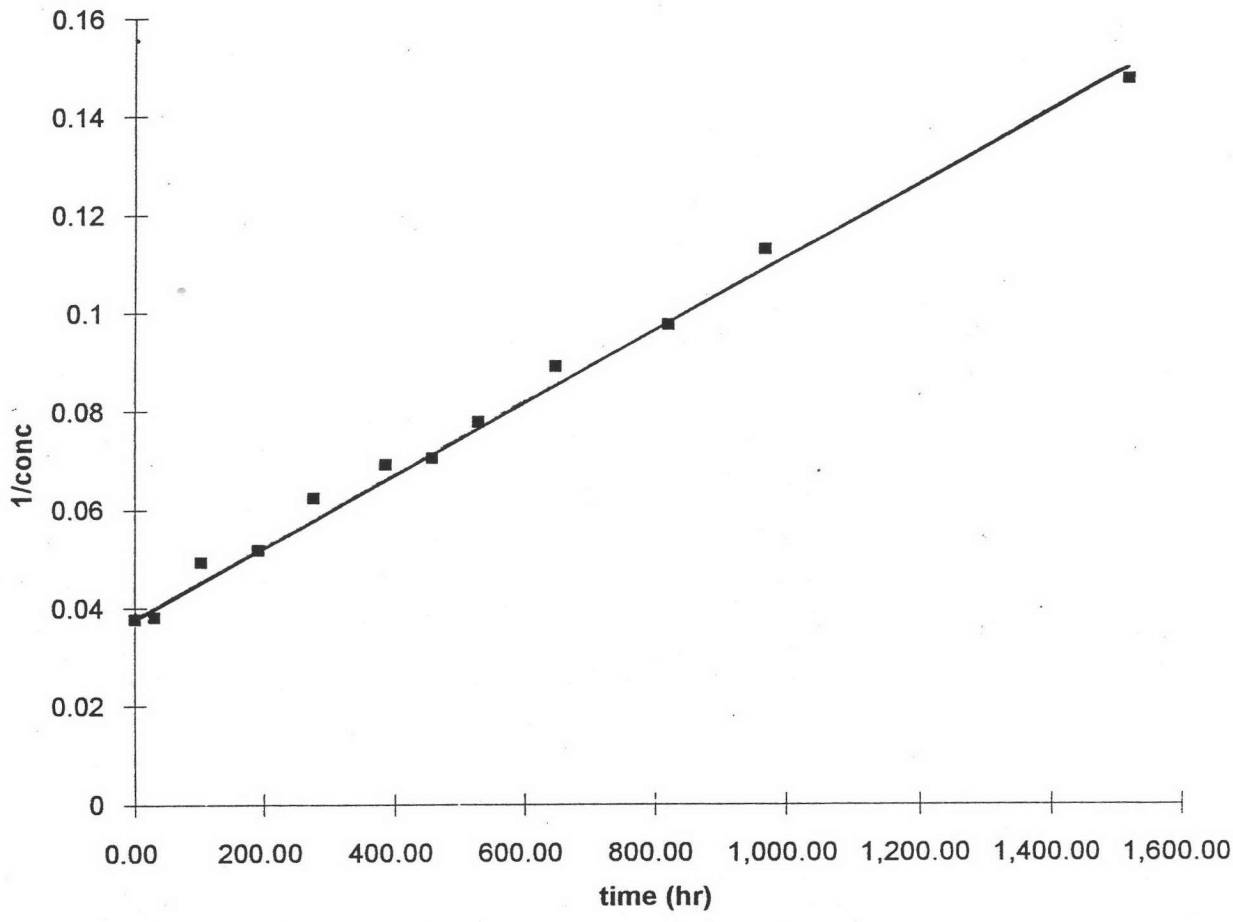
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(e)	27.33	27.04	25.17	26.50	26.51 ± 0.96
29.08	(e)	25.07	25.74	26.95	27.17	26.23 ± 1.00
102.33	(g)	22.59	20.53	18.52	19.48	20.28 ± 1.75
190.67	(g)	19.01	18.31	21.12	18.88	19.33 ± 1.23
274.00	(h)	15.61	16.45	16.10	16.02	16.04 ± 0.35
384.67	(i)	13.22	15.48	15.12	14.02	14.46 ± 1.03
454.92	(i)	14.48	14.02	13.82	14.48	14.20 ± 0.33
526.67	(j)	12.38	11.86	12.69	14.50	12.86 ± 1.15
645.67	(j)	11.32	11.23	11.69	10.75	11.25 ± 0.39
818.17	(k)	10.92	9.716	10.20	10.29	10.28 ± 0.49
965.50	(k)	6.972	9.221	10.04	9.321	8.888 ± 1.33
1,516.00	(n)	5.144	5.392	6.366	10.31	6.803 ± 2.40

*calibration curves used are in parenthesis.

Zero-order : $conc = 21.93 - 0.0129 time$ $r^2 = 0.7990.$

First-order : $\log conc = 1.354 - 3.958 \times 10^{-4} time$ $r^2 = 0.9308.$

Second-order : $1/conc = 0.0395 + 7.256 \times 10^{-5} time$ $r^2 = 0.9944.$



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 0.5).

APPENDIX IV

Catalytic Effect of Phosphate Buffer

on Ranitidine HCl Degradation

pH 4 0.1 M Phosphate Buffer

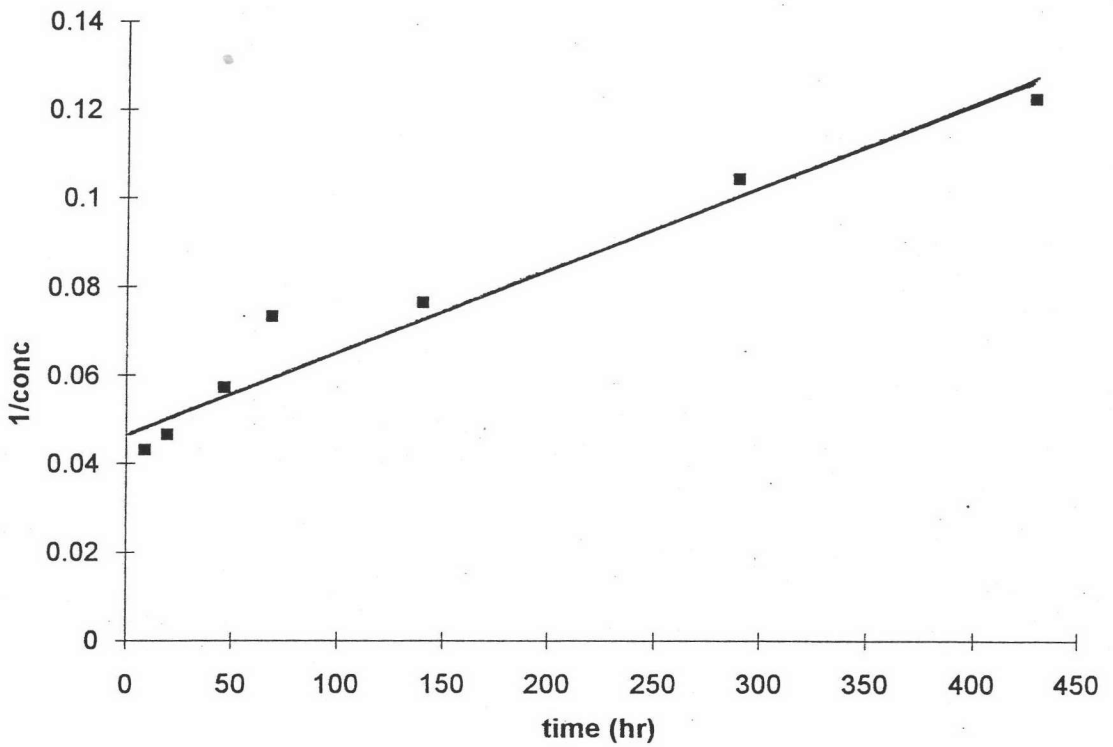
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(n)	26.59	23.38	26.83	25.06	25.46 ± 1.60
8.83	(n)	23.91	24.71	23.96	20.27	23.21 ± 2.00
19.58	(n)	19.28	24.06	20.23	22.26	21.46 ± 2.13
46.42	(n)	17.26	17.82	17.42	17.51	17.50 ± 0.24
68.58	(n)	13.24	13.53	13.77	14.13	13.67 ± 0.38
139.92	(o)	13.93	12.17	13.07	13.30	13.12 ± 0.73
289.33	(p)	10.28	10.19	8.900	9.120	9.622 ± 0.71
428.50	(q)	7.704	9.031	7.839	8.192	8.192 ± 0.60

*calibration curves are used in parenthesis.

Zero-order : $conc = 21.01 - 4.597 \times 10^{-3 \times time}$ $r^2 = 0.7542$.

First-order : $\log conc = 1.322 - 1.080 \times 10^{-3 \times time}$ $r^2 = 0.8654$.

Second-order : $1/conc = 0.0467 + 1.879 \times 10^{-4 \times time}$ $r^2 = 0.9476$.



Second-order plot of ranitidine HCl degradation in pH 4 (0.1 M phosphate buffer).

pH 4 0.2 M Phosphate Buffer

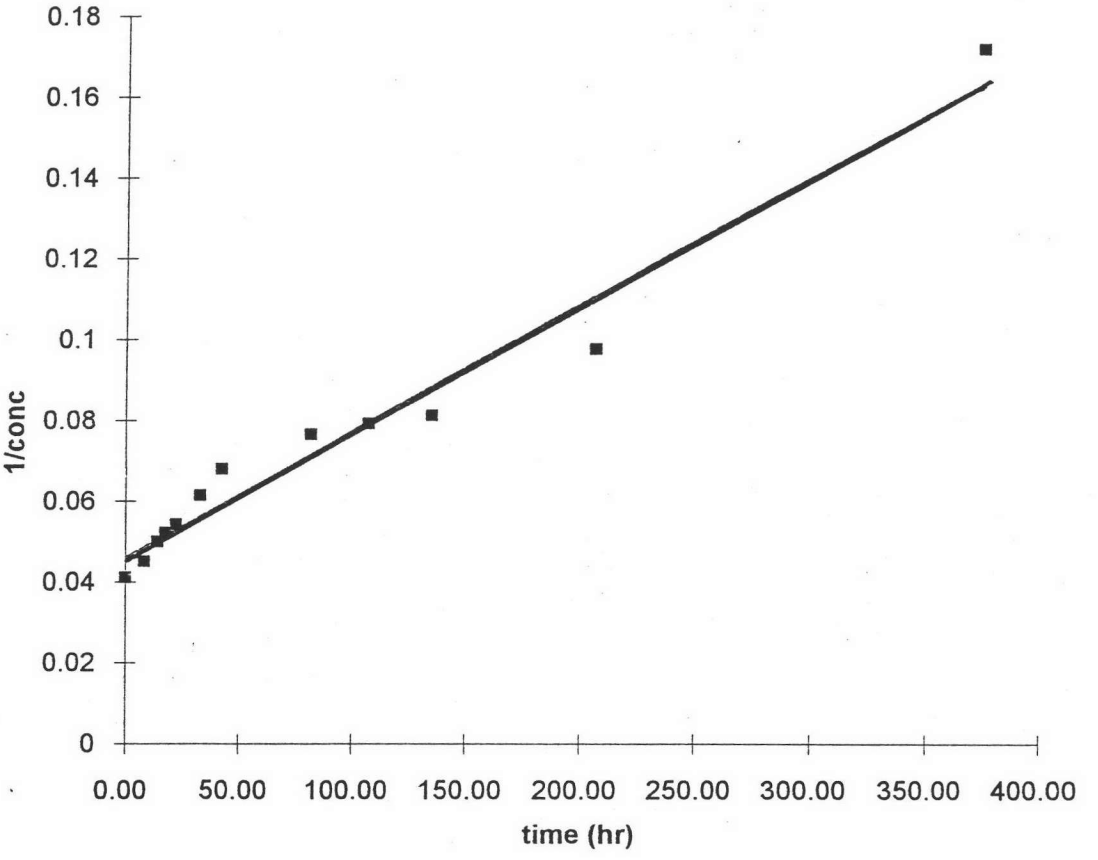
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	24.91	23.49	24.46	24.29	24.29 ± 0.59
8.08	(k)	22.40	21.41	22.07	22.84	22.18 ± 0.60
14.00	(k)	20.89	19.06	19.17	21.01	20.03 ± 1.06
17.42	(k)	20.01	19.91	18.91	17.80	19.16 ± 1.03
22.17	(k)	17.60	17.49	19.44	19.23	18.44 ± 1.04
33.00	(k)	16.06	16.54	14.59	18.03	16.31 ± 1.42
42.42	(k)	15.59	14.38	15.76	13.11	14.71 ± 1.23
81.75	(l)	13.15	13.09	12.05	14.08	13.09 ± 0.83
107.50	(l)	12.09	12.69	13.26	12.54	12.64 ± 0.48
135.00	(l)	12.34	13.12	12.41	11.37	12.31 ± 0.72
206.75	(l)	10.07	10.15	10.66	10.07	10.24 ± 0.28
374.50	(m)	6.369	5.790	5.738	5.421	5.830 ± 0.39

*calibration curves used are in parenthesis.

Zero-order : $conc = 19.49 - 0.0428 time$ $r^2 = 0.7843.$

First-order : $\log conc = 1.300 - 1.496 \times 10^{-3} time$ $r^2 = 0.9262.$

Second-order : $1/conc = 0.0457 + 3.159 \times 10^{-4} time$ $r^2 = 0.9672.$



Second-order plot of ranitidine HCl degradation in pH 4(0.2 M phosphate buffer).

pH 4 0.4 M Phosphate Buffer

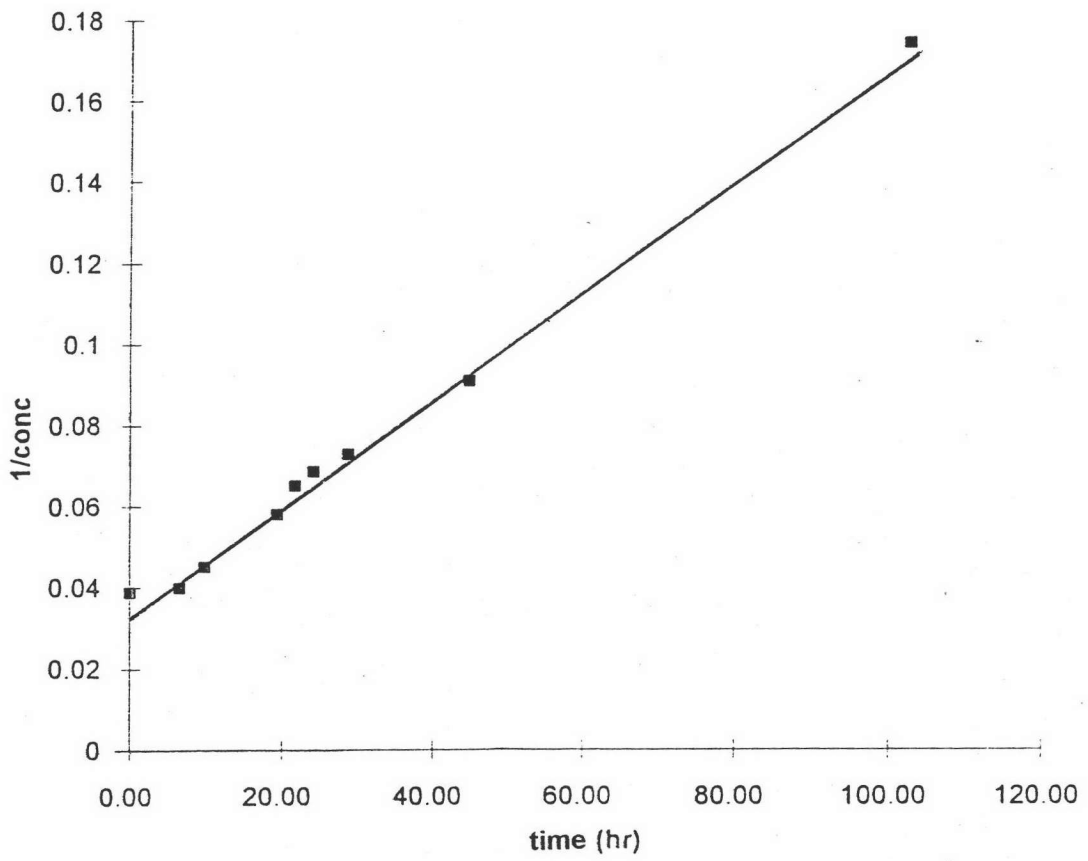
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(e)	25.85	26.00	25.55	26.01	25.85 ± 0.21
6.42	(e)	24.54	24.74	24.95	26.19	25.10 ± 0.74
9.75	(e)	22.12	21.27	22.68	22.75	22.20 ± 0.68
19.25	(e)	17.24	18.21	16.02	17.51	17.24 ± 0.91
21.67	(e)	15.12	13.04	16.58	16.78	15.38 ± 1.73
24.08	(e)	15.42	13.58	15.00	14.44	14.61 ± 0.80
28.67	(e)	14.64	14.64	12.54	13.14	13.74 ± 1.07
44.75	(f)	11.47	12.35	10.76	9.523	11.02 ± 1.19
102.58	(g)	5.277	6.300	5.731	5.744	5.763 ± 0.42

*calibration curves used are in parenthesis.

Zero-order : $conc = 22.21 - 0.1905 time$ $r^2 = 0.7800.$

First-order : $\log conc = 1.370 - 6.407 \times 10^{-3} time$ $r^2 = 0.9415.$

Second-order : $1/conc = 0.0339 + 1.348 \times 10^{-3} time$ $r^2 = 0.9956.$



Second-order plot of ranitidine HCl degradation in pH 4 (0.4 M phosphate buffer).

pH 5 0.1 M Phosphate Buffer

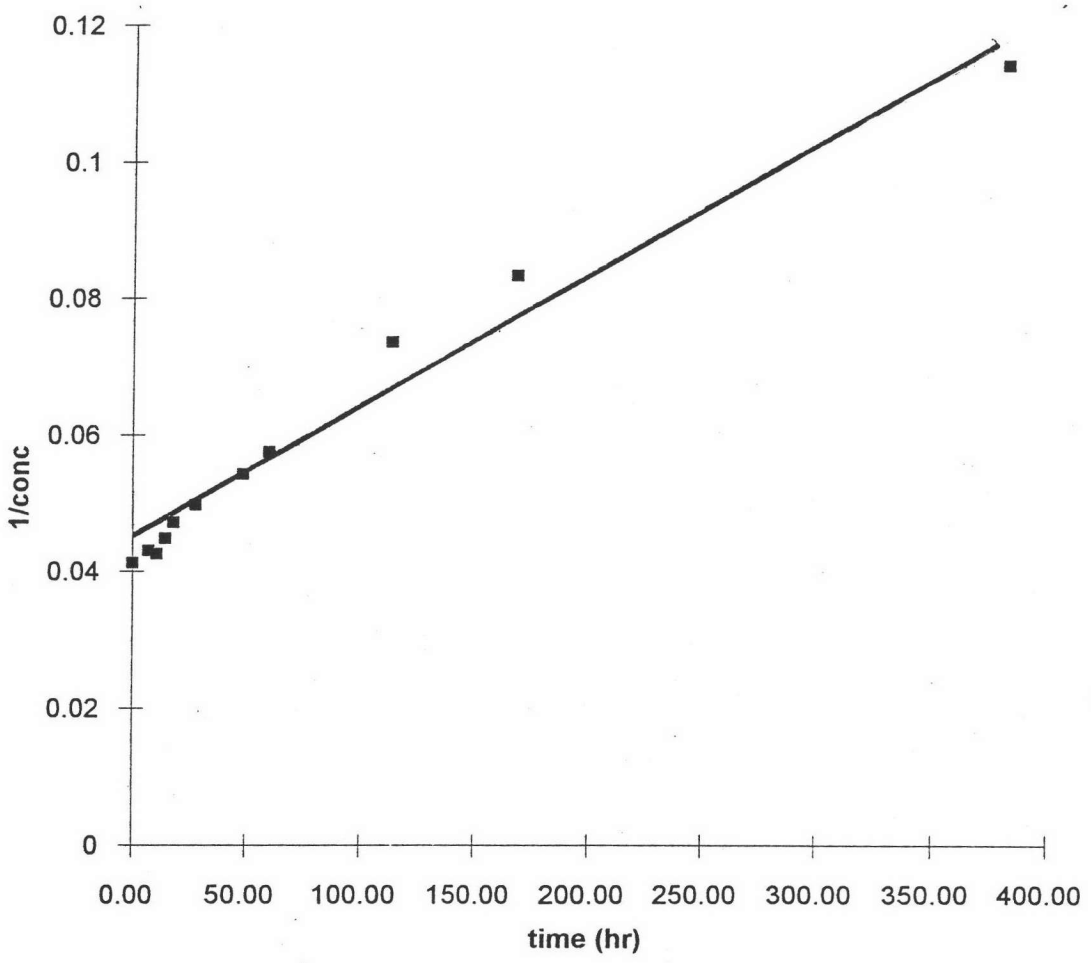
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	23.21	24.95	22.10	26.67	24.23 ± 2.00
7.17	(k)	23.13	22.52	21.71	25.68	23.26 ± 1.71
10.75	(k)	23.70	24.64	22.39	23.13	23.46 ± 0.45
14.50	(k)	23.03	19.75	23.07	23.44	22.32 ± 1.72
18.00	(k)	21.17	20.57	21.63	21.46	21.20 ± 0.47
28.08	(k)	19.38	19.51	20.06	21.46	20.10 ± 0.95
48.50	(k)	18.73	18.47	18.33	18.23	18.44 ± 0.22
60.00	(l)	17.91	17.42	17.15	17.13	17.40 ± 0.36
113.17	(l)	14.41	12.54	13.50	13.99	13.61 ± 0.80
168.33	(l)	12.58	11.17	12.28	12.00	12.00 ± 0.61
381.08	(m)	8.395	9.640	8.293	8.776	8.776 ± 0.61

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 21.80 - 0.0412\ \text{time}$ $r^2 = 0.8185.$

First-order : $\log \text{conc} = 1.343 - 1.194 \times 10^{-3}\ \text{time}$ $r^2 = 0.9071.$

Second-order : $1/\text{conc} = 0.0440 + 1.967 \times 10^{-4}\ \text{time}$ $r^2 = 0.9710.$



Second-order plot of ranitidine HCl degradation in pH 5 (0.1 M phosphate buffer).

pH 5 0.2 M Phosphate Buffer

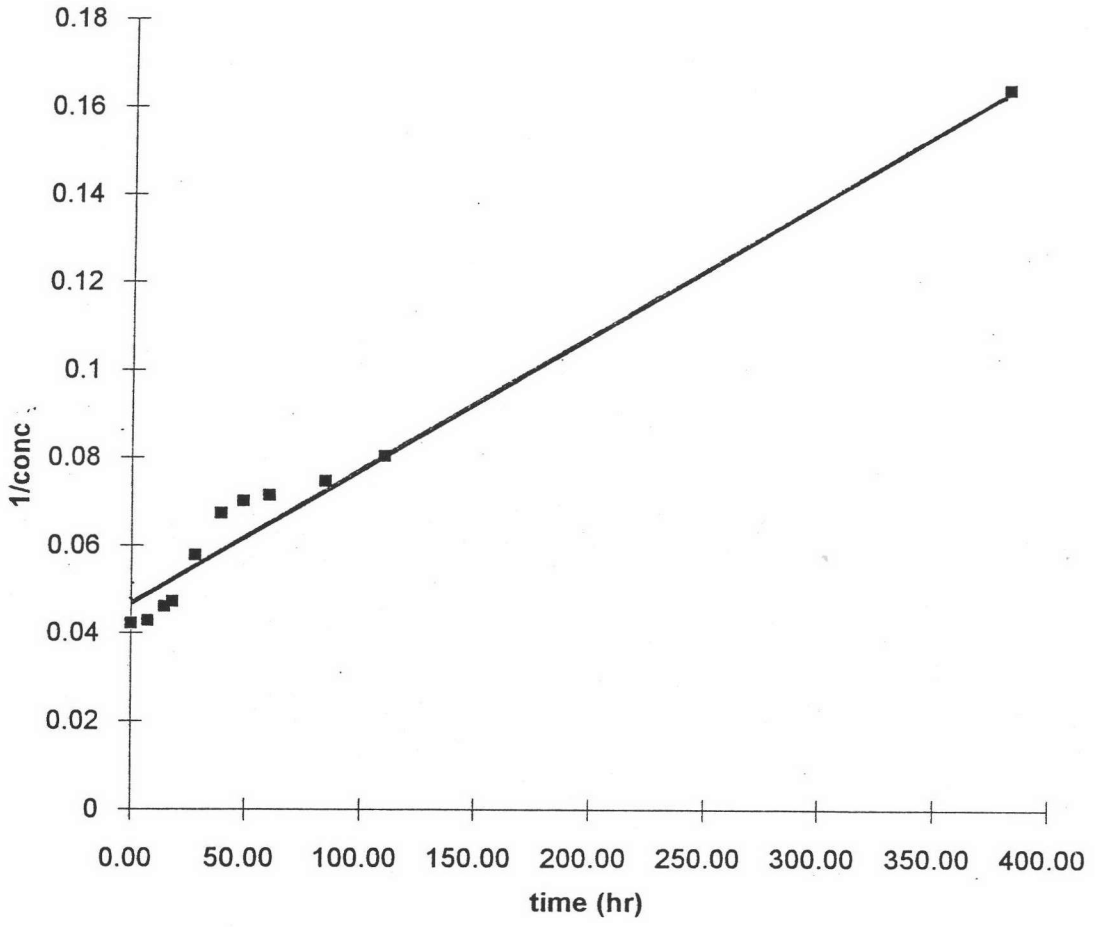
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	21.72	24.17	23.70	25.18	23.69 ± 1.45
7.17	(k)	23.70	22.17	23.22	24.56	23.41 ± 1.00
14.50	(k)	20.43	22.59	22.98	21.17	21.79 ± 1.20
18.00	(k)	22.90	20.78	21.27	19.91	21.22 ± 1.26
28.08	(k)	19.29	16.64	16.86	16.54	17.33 ± 1.31
39.00	(k)	15.28	13.68	15.73	14.82	14.88 ± 0.88
48.67	(k)	15.49	13.68	13.71	14.28	14.29 ± 0.85
60.00	(l)	14.96	13.48	14.10	13.56	14.02 ± 0.68
84.25	(l)	14.68	13.03	12.50	13.40	13.40 ± 0.93
110.17	(l)	10.62	11.89	14.80	12.54	12.46 ± 1.75
381.08	(m)	5.745	6.609	5.757	6.365	6.119 ± 0.44

*calibration curves used are in parenthesis.

Zero-order : $conc = 19.58 - 0.0414 time$ $r^2 = 0.6723.$

First-order : $\log conc = 1.299 - 1.460 \times 10^{-3} time$ $r^2 = 0.8624.$

Second-order : $1/conc = 0.0469 + 3.120 \times 10^{-4} time$ $r^2 = 0.9545.$



Second-order plot of ranitidine HCl degradation in pH 5 (0.2 M phosphate buffer).

pH 5 0.4 M Phosphate Buffer

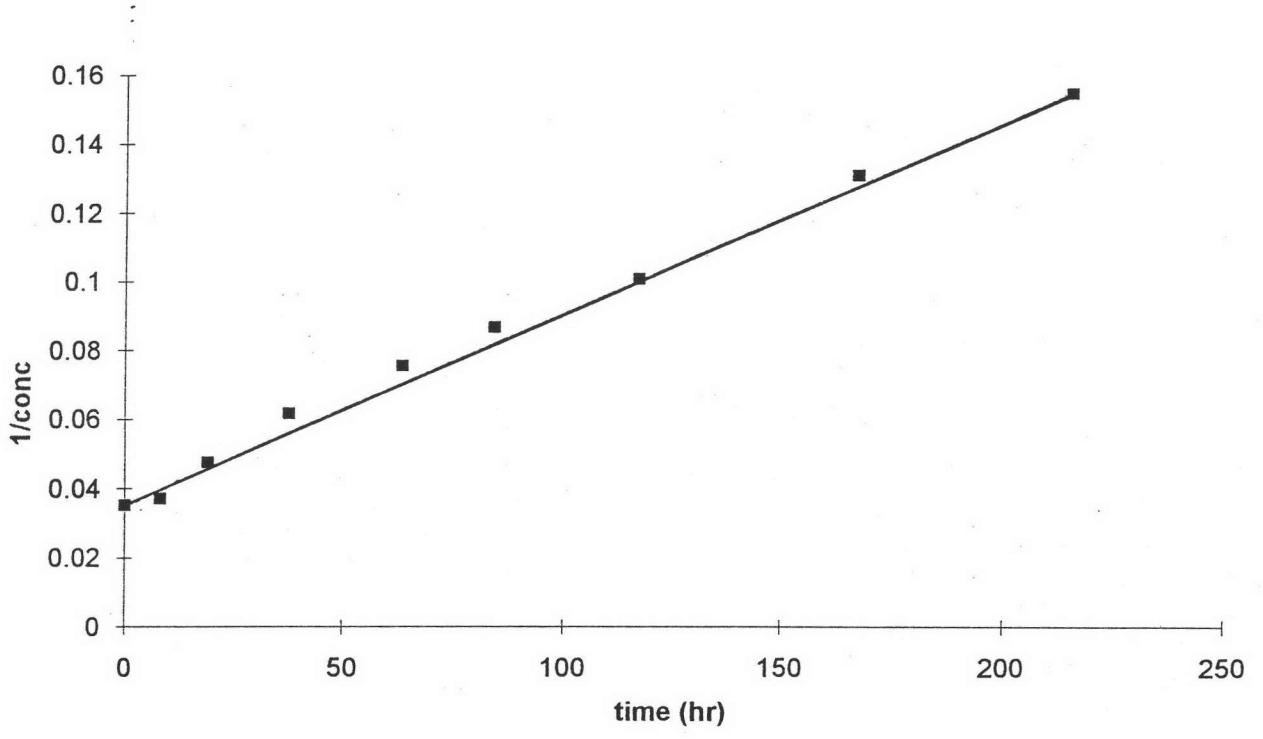
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	26.51	30.12	28.48	28.38	28.31 ±1.48
8.17	(o)	28.17	23.13	27.14	29.69	27.03 ± 2.80
19.16	(p)	20.56	21.04	21.56	21.05	21.05 ± 0.41
37.92	(p)	16.52	16.73	15.25	16.47	16.24 ± 0.67
63.58	(p)	13.22	13.21	13.40	13.29	13.28 ± 0.09
84.25	(p)	12.07	11.64	11.84	10.64	11.55 ± 0.63
117.25	(p)	10.11	10.75	10.16	8.776	9.949 ± 0.83
167.17	(q)	8.052	7.203	7.742	7.668	7.666 ± 0.35
215.50	(q)	6.975	6.005	5.999	6.981	6.490 ± 0.56

*calibration curves used are in parenthesis.

Zero-order : $conc = 23.39 - 0.0966 time$ $r^2 = 0.7969$.

First-order : $\log conc = 1.379 - 2.958 \times 10^{-3} time$ $r^2 = 0.9291$.

Second-order : $1/conc = 0.0370 + 5.538 \times 10^{-4} time$ $r^2 = 0.9955$.



Second-order plot of ranitidine HCl degradation in pH 5 (0.4 M phosphate buffer).

pH 6 0.1 M Phosphate Buffer

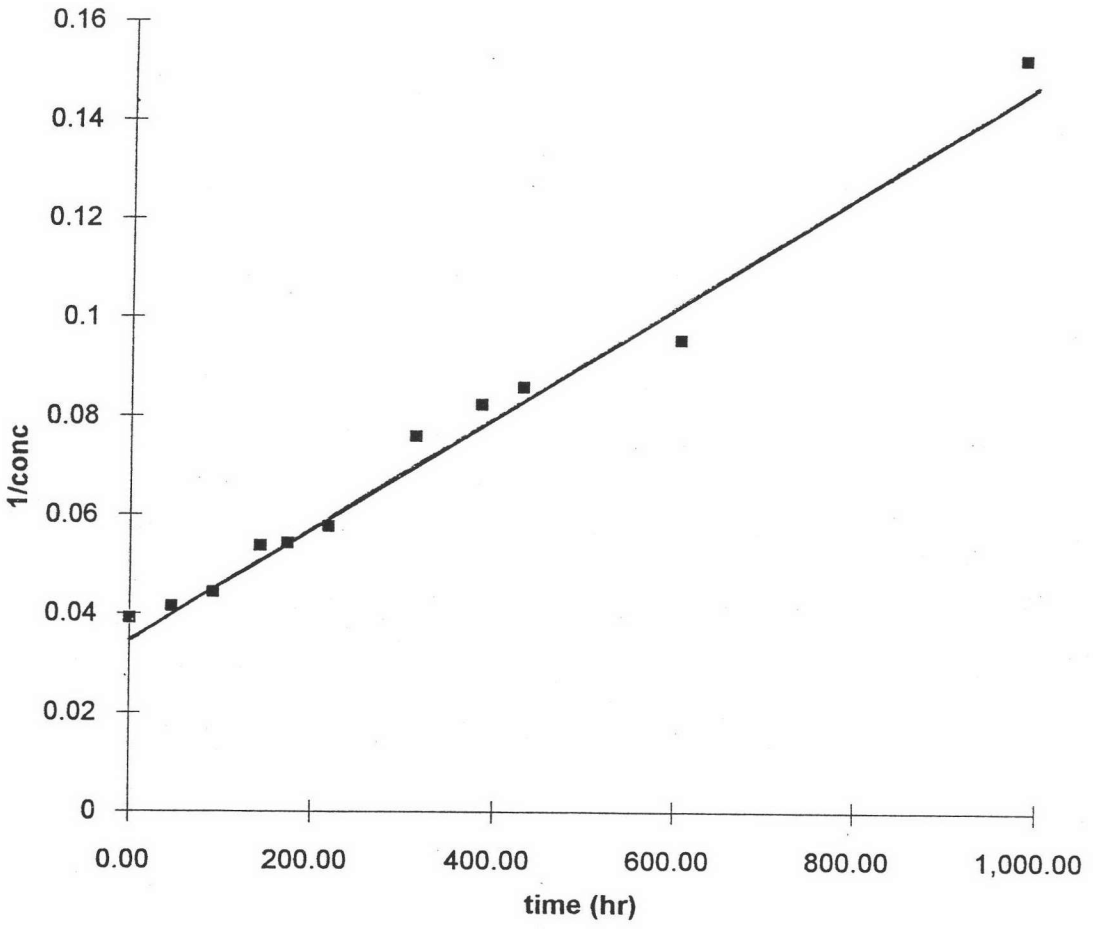
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	26.08	26.36	24.16	22.52	24.78 ± 1.80
47.00	(k)	25.36	23.37	23.22	24.27	24.06 ± 0.98
142.75	(l)	22.94	21.46	23.60	26.21	23.55 ± 1.98
172.50	(l)	21.60	19.03	16.86	19.16	19.16 ± 1.94
217.58	(l)	17.66	17.02	17.75	18.57	17.75 ± 0.64
312.50	(m)	12.23	13.10	13.90	16.37	13.90 ± 1.78
384.50	(m)	12.16	11.75	12.05	10.19	11.54 ± 0.91
478.00	(n)	9.869	11.75	12.05	11.19	11.21 ± 0.97
604.83	(n)	11.62	9.494	12.28	10.94	11.08 ± 1.19
980.92	(q)	7.291	7.099	6.761	6.630	6.945 ± 0.30

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 22.99 - 0.0197\text{time}$ $r^2 = 0.8387.$

First-order : $\log \text{conc} = 1.382 - 5.980 \times 10^{-4}\text{time}$ $r^2 = 0.9306.$

Second-order : $1/\text{conc} = 0.0353 + 1.078 \times 10^{-4}\ \text{time}$ $r^2 = 0.9679.$



Second-order plot of ranitidine HCl degradation in pH 6 (0.1 M phosphate buffer).

pH 6 0.2 M Phosphate Buffer

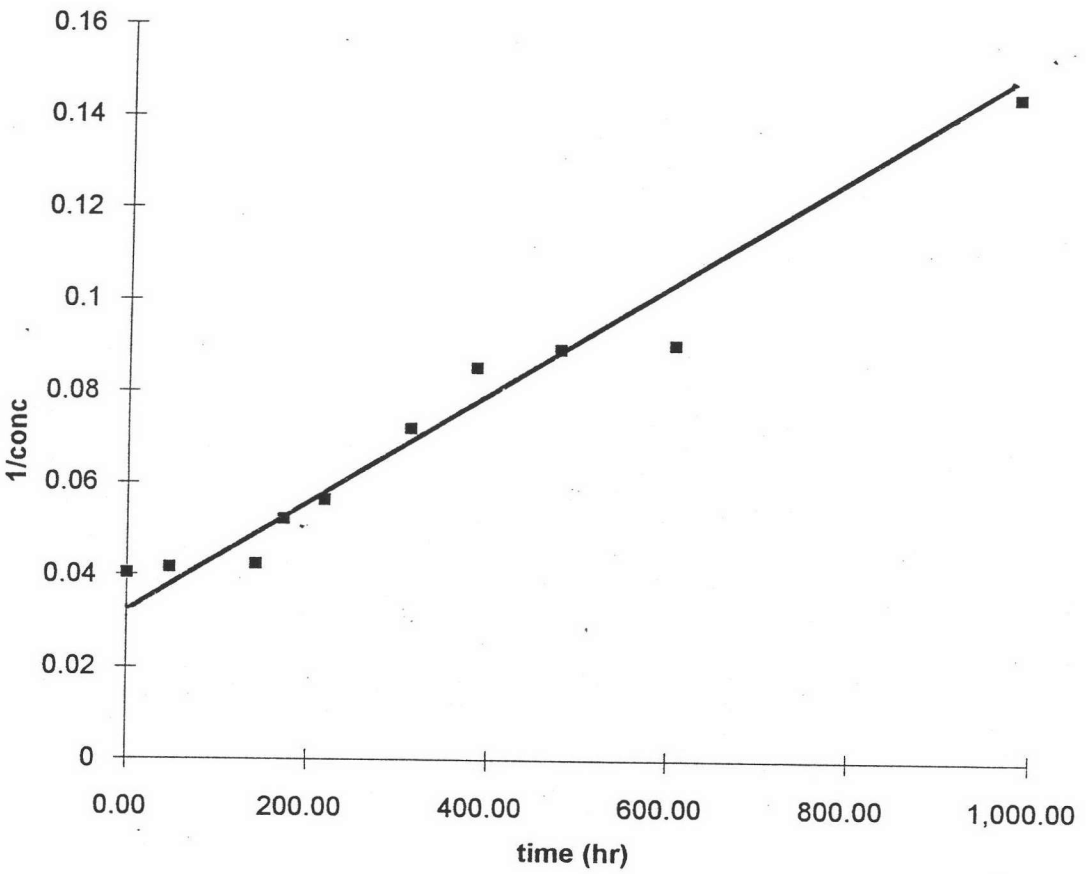
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	26.01	25.17	24.74	26.71	25.66 ± 0.88
47.00	(k)	24.06	24.66	23.23	24.63	24.14 ± 0.65
92.67	(l)	20.83	24.92	23.26	21.50	22.63 ± 1.84
142.75	(l)	18.61	19.16	17.87	18.77	18.60 ± 0.54
172.50	(l)	17.00	19.69	18.89	18.28	18.47 ± 1.13
217.58	(l)	17.75	18.56	16.00	17.21	17.38 ± 1.07
312.50	(m)	13.92	13.22	12.36	13.18	13.17 ± 0.64
384.42	(m)	12.56	12.91	11.78	11.39	12.16 ± 0.70
430.00	(m)	12.32	11.33	11.01	11.97	11.66 ± 0.60
604.83	(n)	10.31	9.601	11.22	10.87	10.50 ± 0.71
980.92	(q)	6.720	6.785	6.227	6.578	6.578 ± 0.25

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 22.50 - 0.0197\text{time}$ $r^2 = 0.8471.$

First-order : $\log \text{conc} = 1.373 - 6.124 \times 10^{-4}\text{time}$ $r^2 = 0.9524.$

Second-order : $1/\text{conc} = 0.0359 + 1.141 \times 10^{-4}\text{time}$ $r^2 = 0.9847.$



Second-order plot of ranitidine HCl degradation in pH 6 (0.2 M phosphate buffer).

pH 6 0.3 M Phosphate Buffer

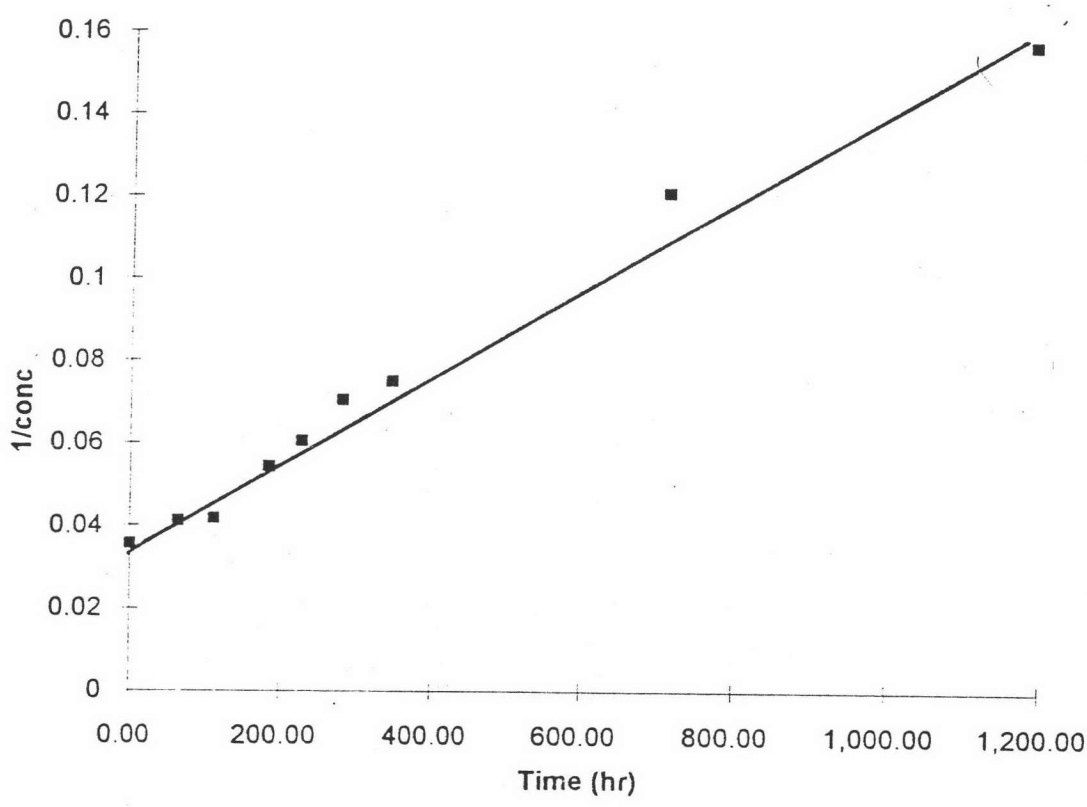
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	29.69	27.36	27.15	28.08	28.07 ± 1.15
64.42	(p)	22.58	24.73	25.68	24.34	24.33 ± 1.30
111.42	(p)	23.63	24.34	22.88	24.94	23.95 ± 0.89
184.92	(q)	18.98	17.09	18.88	18.72	18.42 ± 0.89
227.33	(q)	16.56	15.34	17.14	17.08	16.53 ± 0.83
280.58	(q)	14.61	14.44	13.87	13.86	14.20 ± 0.39
346.42	(r)	12.58	13.87	13.49	13.45	13.34 ± 0.55
713.08	(t)	8.831	7.662	8.104	8.620	8.304 ± 0.52
1,188.00	(u)	6.020	6.375	6.483	6.723	6.400 ± 0.29

*calibration curves used are in parenthesis.

Zero-order : conc = 23.01 - 0.0172time $r^2 = 0.7743$.

First-order : $\log conc = 1.378 - 5.469 \times 10^{-4} time$ $r^2 = 0.9142$.

Second-order : $1/conc = 0.0360 + 1.063 \times 10^{-4} time$ $r^2 = 0.9864$.



Second-order plot of ranitidine HCl degradation in pH 6 (0.3 M phosphate buffer).

APPENDIX V

Ionic Strength Effect on Ranitidine HCl

Degradation at pH 5 and 12

pH 5 Phosphate Buffer (Ionic Strength = 0.2 M)

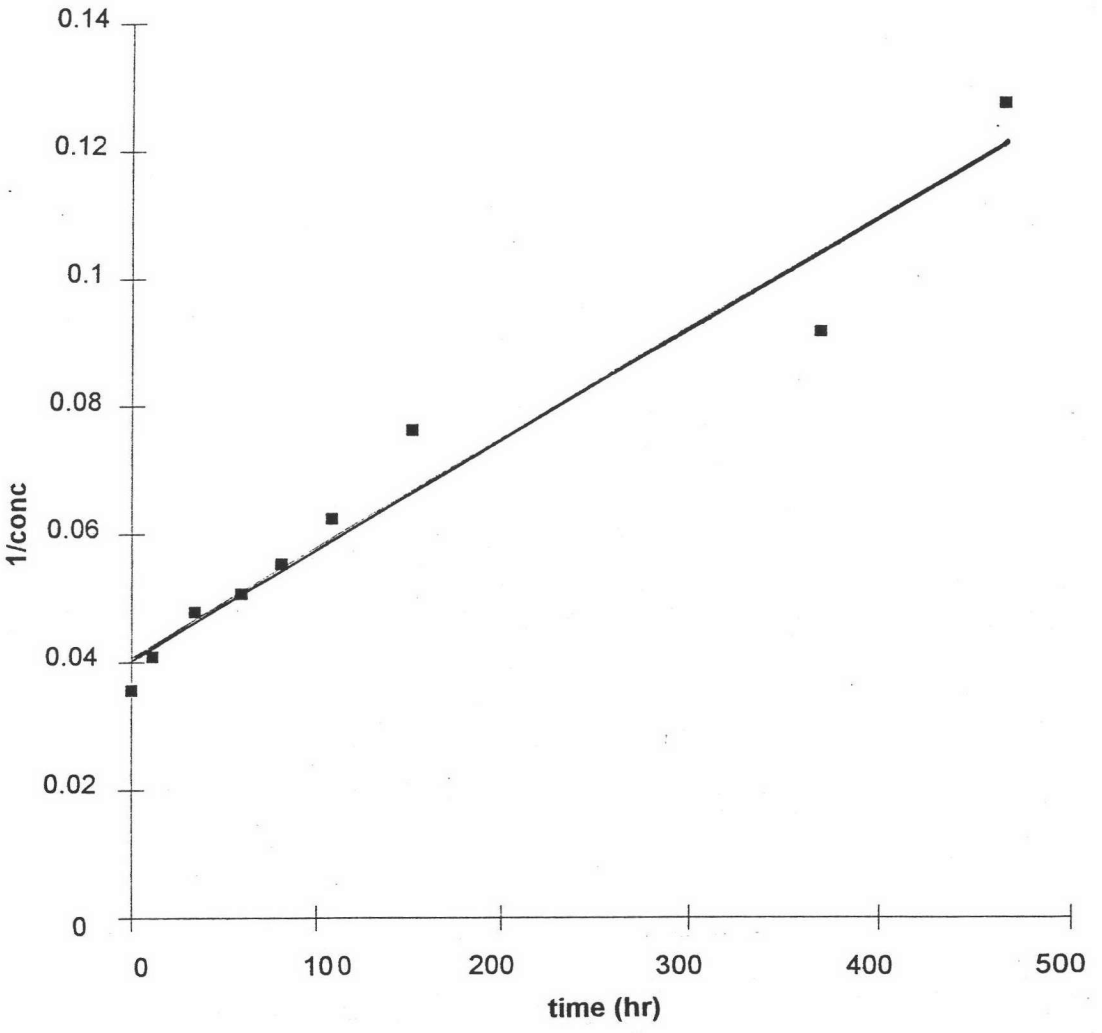
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	26.01	29.29	29.17	28.16	28.16 ± 1.52
11.50	(o)	24.52	26.07	25.11	22.36	24.52 ± 1.57
34.75	(r)	21.19	20.03	21.81	20.73	20.94 ± 0.75
60.42	(p)	20.28	18.48	20.53	19.82	19.78 ± 0.91
81.00	(p)	18.46	17.19	19.11	17.55	18.08 ± 0.87
108.50	(p)	17.02	16.81	14.88	15.45	16.04 ± 1.04
151.92	(q)	12.87	13.77	12.77	13.14	13.14 ± 0.45
368.75	(r)	10.32	10.65	11.73	11.01	10.93 ± 0.60
465.50	(s)	8.119	7.550	7.927	7.865	7.865 ± 0.24

*calibration curves used are in parenthesis.

Zero-order : $conc = 22.74 - 0.0352 time$ $r^2 = 0.7968.$

First-order : $\log conc = 1.364 - 1.020 \times 10^{-3} time$ $r^2 = 0.9090.$

Second-order : $1/conc = 0.0407 + 1.723 \times 10^{-4} time$ $r^2 = 0.9515.$



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 0.2 M).

pH 5 Phosphate Buffer (Ionic Strength = 0.5 M)

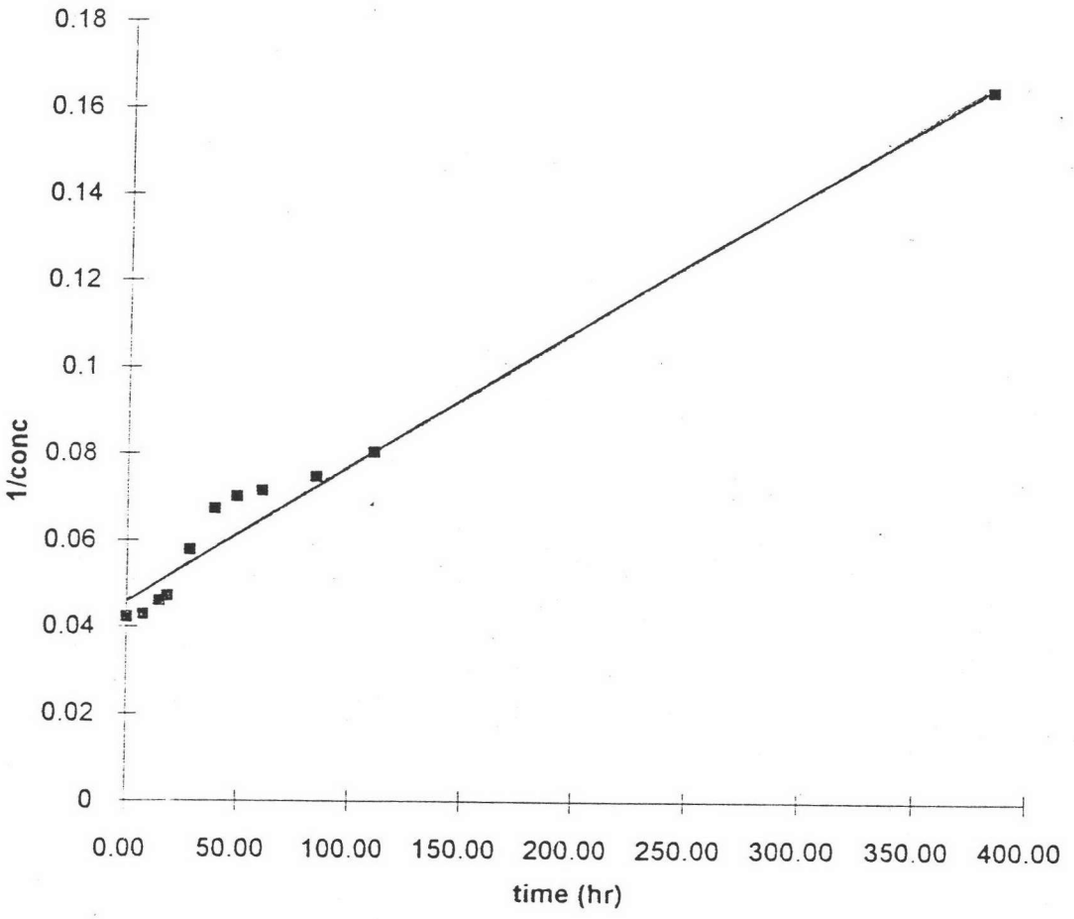
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(k)	21.72	24.17	23.70	25.18	23.69 ± 1.45
7.17	(k)	23.70	22.17	23.22	24.56	23.41 ± 1.00
14.50	(k)	20.43	22.59	22.98	21.17	21.79 ± 1.20
18.00	(k)	22.90	20.78	21.27	19.91	21.22 ± 1.26
28.08	(k)	19.29	16.64	16.86	16.54	17.33 ± 1.31
39.00	(k)	15.28	13.68	15.73	14.82	14.88 ± 0.88
48.67	(k)	15.49	13.68	13.71	14.28	14.29 ± 0.85
60.00	(l)	14.96	13.48	14.10	13.56	14.02 ± 0.68
84.25	(l)	14.68	13.03	12.50	13.40	13.40 ± 0.93
110.17	(l)	10.62	11.89	14.80	12.54	12.46 ± 1.75
381.08	(m)	5.745	6.609	5.757	6.365	6.119 ± 0.44

*calibration curves used are in parenthesis.

Zero-order : conc = 19.58- 0.0414time $r^2 = 0.6723$.

First-order : $\log conc = 1.299 - 1.460 \times 10^{-3} time$ $r^2 = 0.8624$.

Second-order : $1/conc = 0.0469 + 3.120 \times 10^{-4} time$ $r^2 = 0.9545$.



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 0.5 M).

pH 5 Phosphate Buffer (Ionic Strength = 0.8 M)

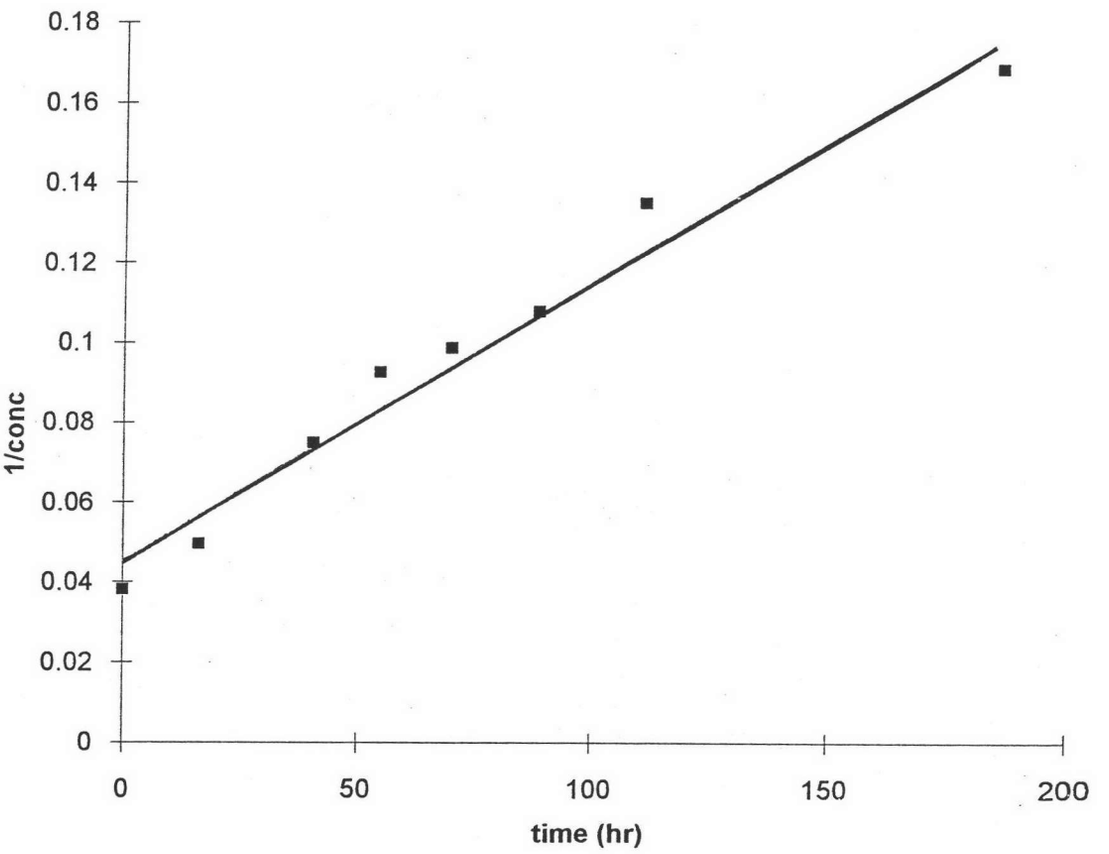
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)				Average Conc ± SD
0.00	(q) 26.47	25.27	26.79	26.18	26.18 ± 0.65
16.42	(q) 21.86	21.04	18.96	18.92	20.20 ± 1.49
40.58	(q) 13.84	13.45	12.57	13.61	13.37 ± 0.56
54.75	(q) 11.50	10.61	10.76	10.33	10.80 ± 0.50
69.92	(q) 10.50	9.760	10.25	10.10	10.15 ± 0.31
88.58	(q) 9.140	8.978	9.283	9.790	9.298 ± 0.35
111.25	(q) 7.299	7.645	7.323	7.424	7.423 ± 0.16
186.25	(r) 5.827	5.212	6.561	6.201	5.950 ± 0.58

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 19.90 - 0.0984\text{time}$ $r^2 = 0.7098.$

First-order : $\log \text{conc} = 1.302 - 3.376 \times 10^{-3}\text{time}$ $r^2 = 0.8647.$

Second-order : $1/\text{conc} = 0.0449 + 7.126 \times 10^{-4}\text{time}$ $r^2 = 0.9696.$



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 0.8 M).

pH 5 Phosphate Buffer (Ionic Strength = 1.0 M)

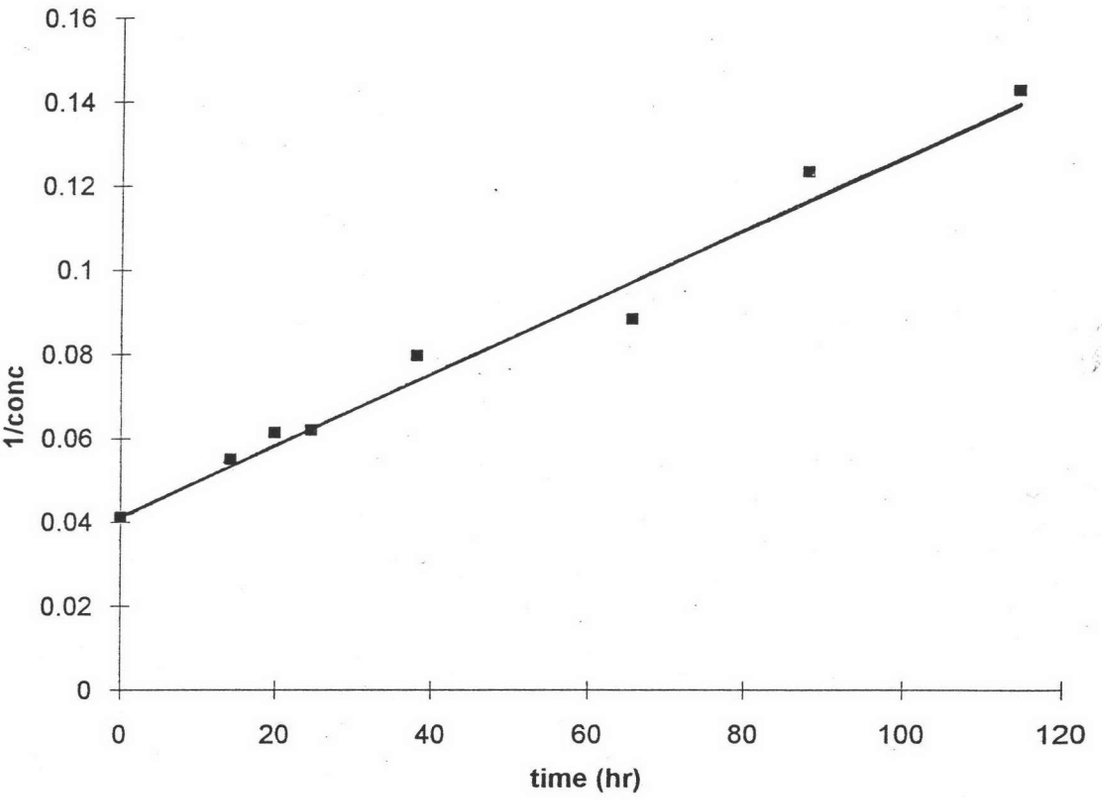
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(q)	24.36	23.28	21.08	28.32	24.26 ± 3.03
14.17	(q)	20.45	16.10	20.07	16.19	18.20 ± 2.38
19.83	(q)	15.31	17.33	15.44	17.14	16.30 ± 1.08
24.50	(r)	15.97	16.83	15.23	16.61	16.16 ± 0.72
38.00	(r)	10.52	13.96	12.64	13.10	12.56 ± 1.46
65.58	(r)	13.77	10.83	10.67	10.07	11.34 ± 1.66
87.92	(r)	8.787	7.340	8.281	8.138	8.137 ± 0.60
114.42	(r)	7.494	6.560	7.002	7.052	7.037 ± 0.38

*calibration curves used are in parenthesis.

Zero-order : conc = 20.27 - 0.1321time $r^2 = 0.8680$.

First-order : log conc = 1.324 - 4.439×10^{-3} time $r^2 = 0.9588$.

Second-order : $1/conc = 0.0420 + 8.682 \times 10^{-4}$ time $r^2 = 0.9806$.



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 1.0 M).

pH 5 Phosphate Buffer (Ionic Strength = 1.2 M)

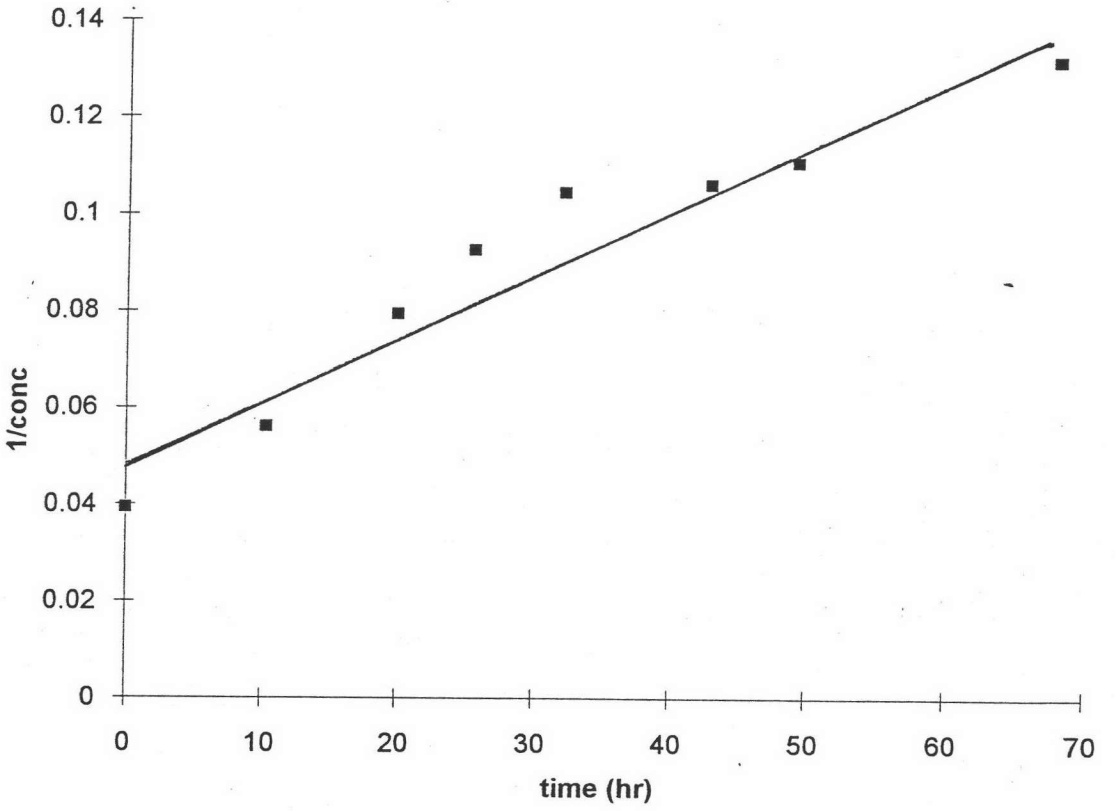
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(s)	25.51	25.02	25.73	25.42	25.42 ± 0.30
10.25	(s)	18.71	17.85	17.20	17.44	17.80 ± 0.66
20.00	(s)	12.90	12.95	11.91	12.73	12.62 ± 0.48
25.58	(s)	11.13	10.51	11.30	10.34	10.82 ± 0.47
32.17	(s)	9.662	9.889	9.436	9.426	9.603 ± 0.22
42.92	(t)	9.510	9.401	9.011	9.878	9.450 ± 0.36
49.25	(t)	9.101	8.945	8.561	9.694	9.075 ± 0.47
68.00	(t)	7.512	8.001	7.991	7.000	7.626 ± 0.48

*calibration curves used are in parenthesis.

Zero-order : $conc = 19.99 - 0.2318 time$ $r^2 = 0.7274.$

First-order : $\log conc = 1.298 - 7.232 \times 10^{-3} time$ $r^2 = 0.8383.$

Second-order : $1/conc = 0.0488 + 1.320 \times 10^{-4} time$ $r^2 = 0.9256.$



Second-order plot of ranitidine HCl degradation in pH 5 phosphate buffer (ionic strength = 1.2 M).

pH 12 Phosphate Buffer (Ionic Strength = 0.2 M)

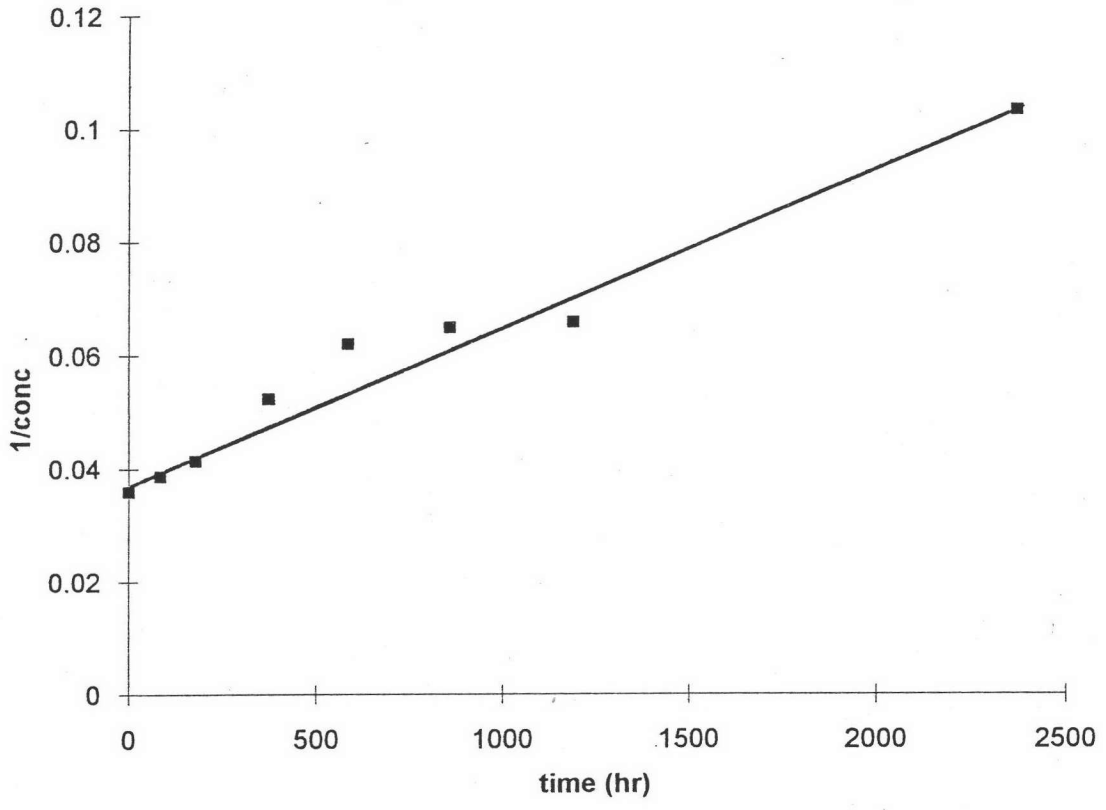
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	28.11	28.69	26.89	27.88	27.89 ± 0.75
86.67	(p)	25.16	28.04	24.17	26.30	25.92 ± 1.66
182.00	(q)	24.40	26.64	24.10	21.77	24.23 ± 1.91
373.92	(r)	21.33	17.73	18.07	19.26	19.10 ± 1.63
584.67	(s)	15.68	16.08	17.16	15.67	16.15 ± 0.70
857.67	(t)	15.97	14.07	15.47	16.20	15.59 ± 0.66
1,188.67	(u)	14.67	15.00	14.52	16.69	15.22 ± 1.00
2,366.17	(w)	9.997	9.425	9.422	10.00	9.615 ± 0.33

*calibration curves used are in parenthesis.

Zero-order : $conc = 24.26 - 7.168 \times 10^{-3} time$ $r^2 = 0.8010$.

First-order : $\log conc = 1.392 - 1.847 \times 10^{-4} time$ $r^2 = 0.9035$.

Second-order : $1/conc = 0.0387 + 2.731 \times 10^{-5} time$ $r^2 = 0.9634$.



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 0.2 M).

pH 12 Phosphate Buffer (Ionic Strength = 0.5 M)

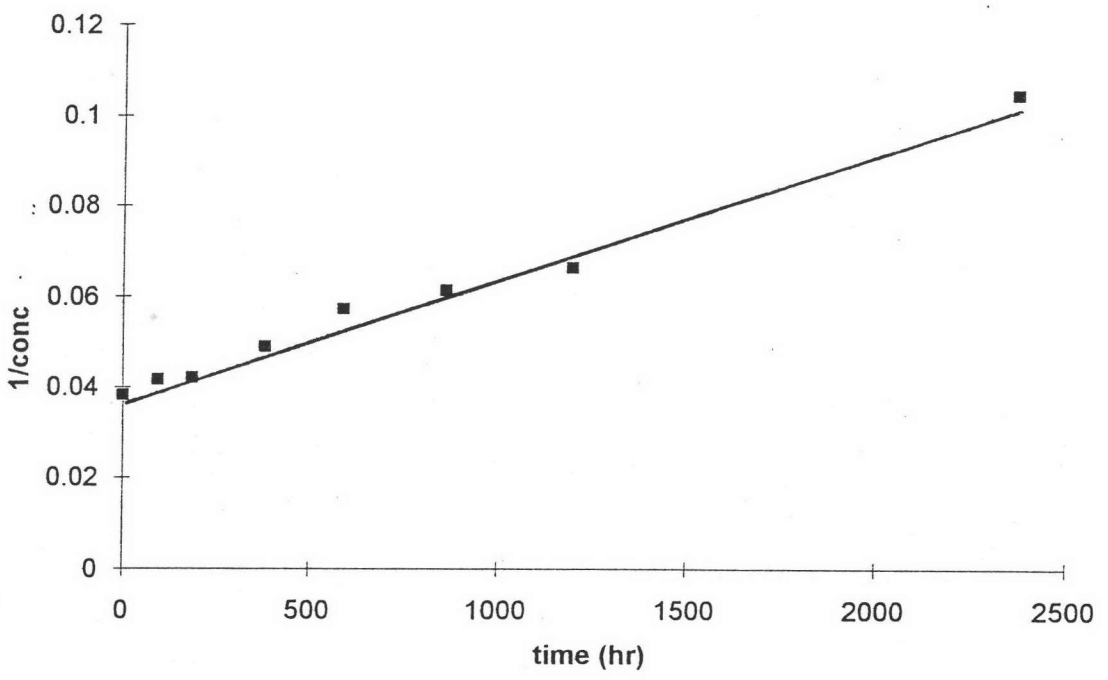
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	26.05	27.31	25.14	26.17	26.17 ± 0.89
94.33	(p)	22.97	26.14	24.85	22.16	24.03 ± 1.80
187.67	(q)	22.21	24.62	22.50	25.61	23.74 ± 1.65
381.67	(r)	20.96	19.54	21.46	19.84	20.45 ± 0.91
592.58	(s)	16.98	16.52	17.03	19.36	17.49 ± 1.28
865.00	(t)	18.30	17.67	14.03	15.24	16.31 ± 2.01
1,196.67	(u)	16.57	15.01	14.40	14.42	15.70 ± 1.61
2,370.58	(w)	10.19	10.14	8.269	9.810	9.602 ± 0.90

*calibration curves used are in parenthesis.

Zero-order : $conc = 23.89 - 6.723 \times 10^{-3}time$ $r^2 = 0.9061$.

First-order : $\log conc = 1.390 - 1.790 \times 10^{-4}time$ $r^2 = 0.9728$.

Second-order : $1/conc = 0.0382 + 2.715 \times 10^{-5}time$ $r^2 = 0.9895$.



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 0.5 M).

pH 12 Phosphate Buffer (Ionic Strength = 0.8 M)

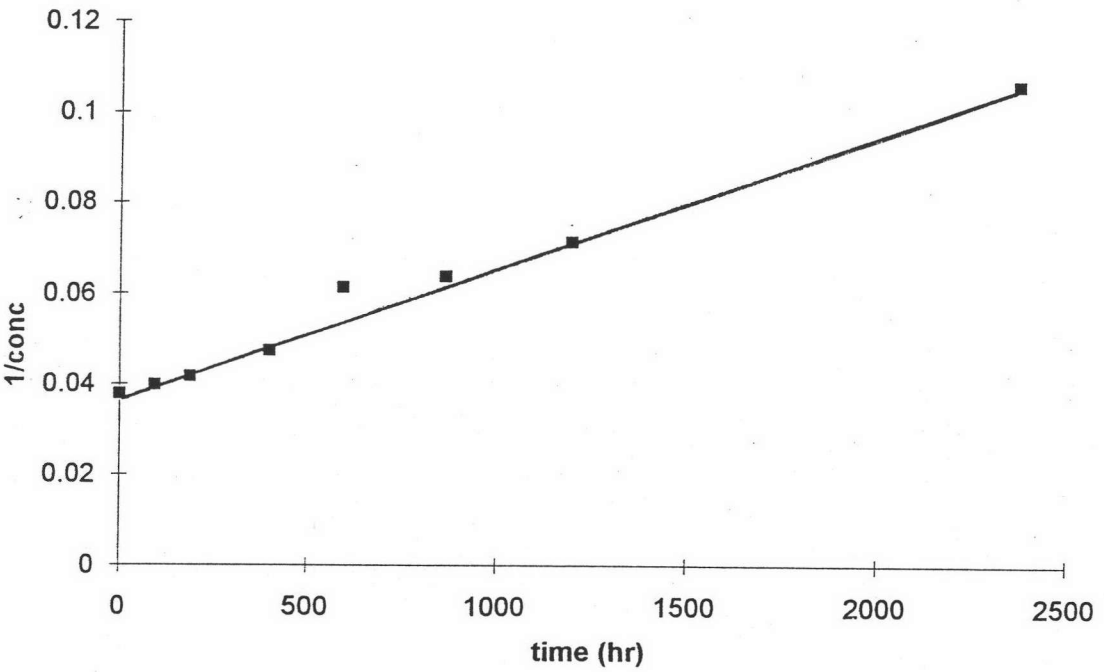
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	27.39	25.91	26.11	26.48	26.47 ± 0.66
94.33	(p)	24.61	24.91	25.63	25.21	25.09 ± 0.43
189.67	(q)	24.16	23.52	24.28	24.00	23.99 ± 0.33
401.50	(r)	19.54	21.23	23.26	20.43	21.11 ± 1.59
592.58	(s)	17.60	16.11	15.85	15.62	16.30 ± 0.89
865.00	(t)	15.66	15.98	16.24	14.88	15.69 ± 0.59
1,196.58	(u)	14.00	13.50	14.30	14.32	14.03 ± 0.38
2,370.00	(w)	9.136	9.897	9.696	9.066	9.449 ± 0.41

*calibration curves used are in parenthesis.

Zero-order : $conc = 24.15 - 7.191 \times 10^{-3 \times time}$ $r^2 = 0.8629.$

First-order : $\log conc = 1.393 - 1.906 \times 10^{-4 \times time}$ $r^2 = 0.9439.$

Second-order : $1/conc = 0.0380 + 2.889 \times 10^{-5 \times time}$ $r^2 = 0.9860.$



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 0.8 M).

pH 12 Phosphate Buffer (Ionic Strength = 1.0 M)

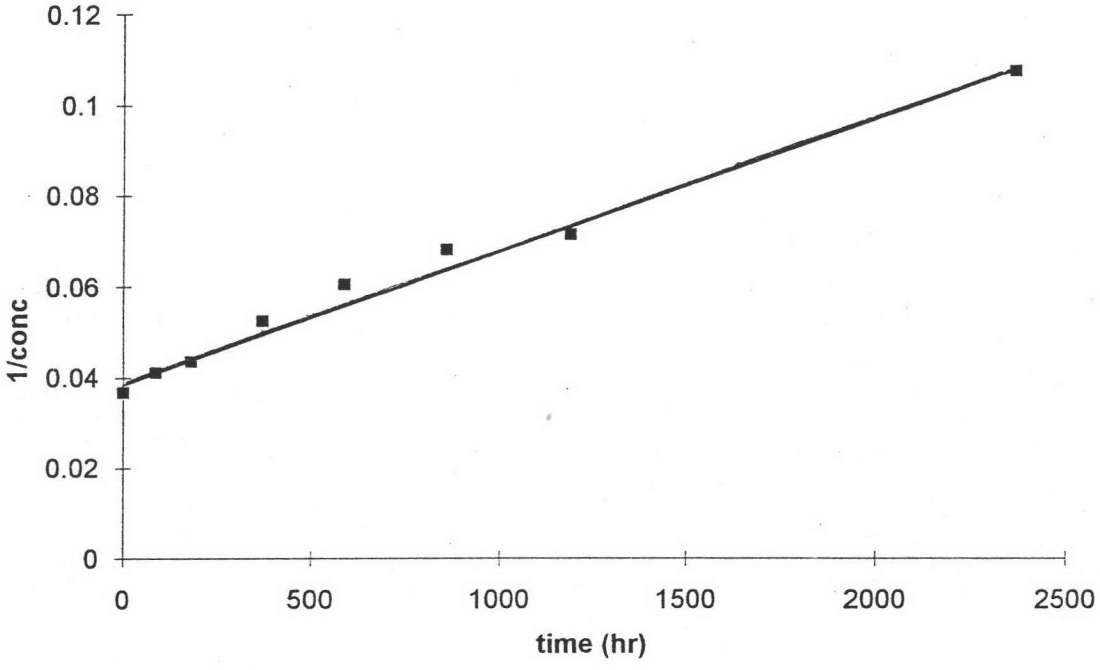
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	27.91	25.90	27.97	27.27	27.26 ± 0.96
86.67	(p)	24.18	23.84	25.01	24.17	24.30 ± 0.50
182.00	(q)	21.89	24.03	21.96	24.02	22.98 ± 1.21
373.92	(r)	21.33	17.73	18.07	19.26	19.10 ± 1.63
584.92	(s)	15.80	17.60	16.22	16.54	16.54 ± 0.77
857.67	(t)	14.27	15.02	15.08	14.42	14.70 ± 0.41
1,188.25	(u)	14.50	16.23	12.56	12.83	14.03 ± 1.70
2,362.08	(w)	9.223	9.460	8.752	9.928	9.341 ± 0.49

*calibration curves used are in parenthesis.

Zero-order : $conc = 23.47 - 7.006 \times 10^{-3} time$ $r^2 = 0.8306.$

First-order : $\log conc = 1.378 - 1.881 \times 10^{-4} time$ $r^2 = 0.9312.$

Second-order : $1/conc = 0.0397 + 2.894 \times 10^{-5} time$ $r^2 = 0.9858.$



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 1.0 M).

pH 12 Phosphate Buffer (Ionic Strength = 1.2 M)

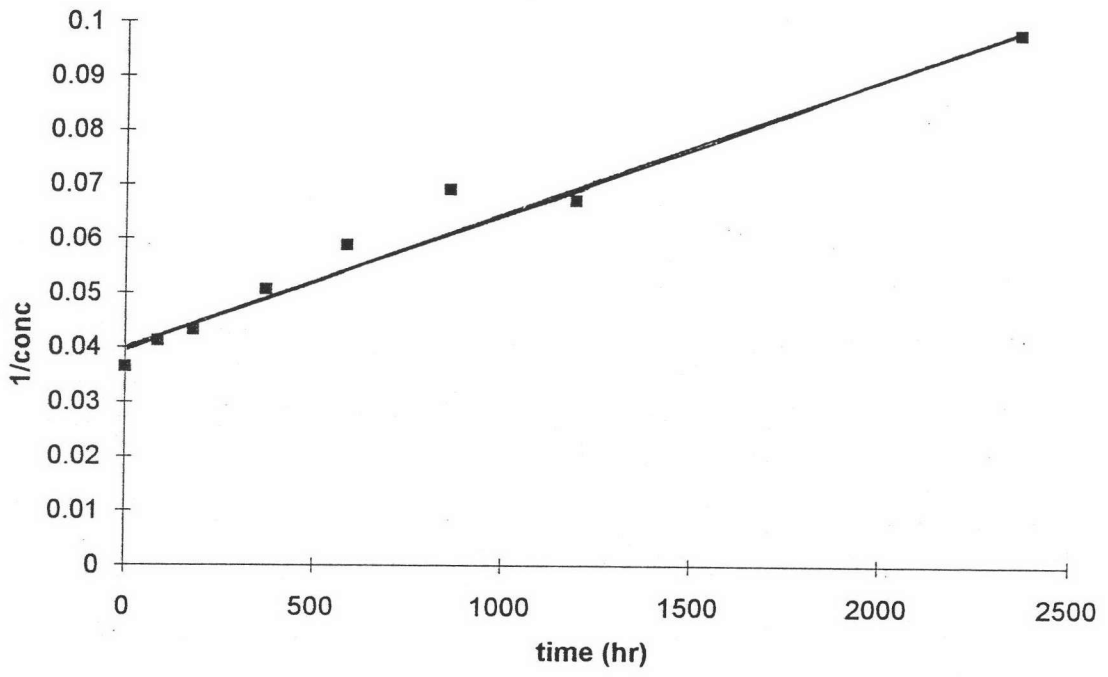
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	27.46	26.02	28.87	27.44	27.45 ± 1.16
94.33	(p)	22.14	25.13	25.29	24.57	24.28 ± 1.46
189.67	(q)	23.94	21.60	24.49	22.60	23.16 ± 1.31
401.50	(r)	21.31	17.62	19.47	20.77	19.79 ± 1.64
592.58	(s)	17.49	17.10	16.46	17.02	17.02 ± 0.42
865.00	(t)	14.94	14.75	12.60	15.76	14.51 ± 1.35
1,196.58	(u)	14.95	15.51	15.00	14.34	14.95 ± 0.48
2,370.00	(w)	9.802	10.27	10.89	10.06	10.26 ± 0.46

*calibration curves used are in parenthesis.

Zero-order : $\text{conc} = 23.63 - 6.673 \times 10^{-3}\text{time}$ $r^2 = 0.8138.$

First-order : $\log \text{conc} = 1.379 - 1.719 \times 10^{-4}\text{time}$ $r^2 = 0.9054.$

Second-order : $1/\text{conc} = 0.0403 + 2.503 \times 10^{-5}\text{time}$ $r^2 = 0.9641.$



Second-order plot of ranitidine HCl degradation in pH 12 phosphate buffer (ionic strength = 1.2 M).

APPENDIX VI

Effect of Solvent Polarity on

Ranitidine HCl Degradation

20% Methanol

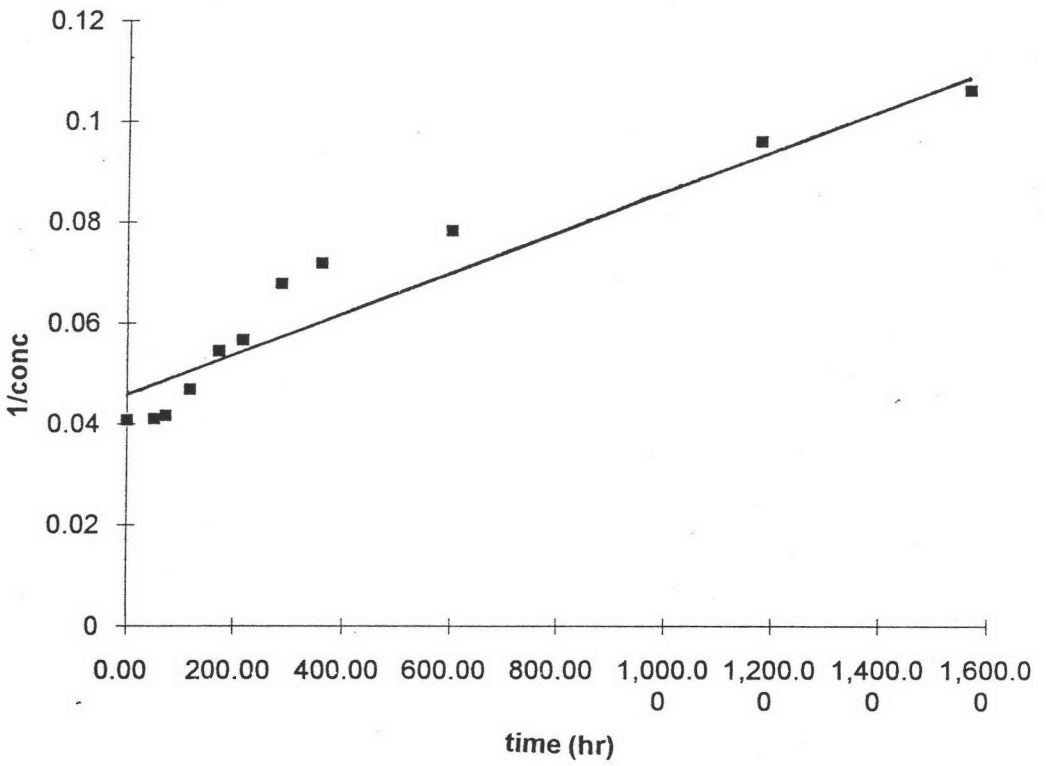
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(0)	24.98	23.44	25.06	24.50	24.50 ± 0.75
51.17	(p)	24.45	23.46	24.01	25.45	24.34 ± 0.84
71.50	(p)	25.90	21.79	22.86	25.48	24.01 ± 2.00
118.00	(p)	20.70	23.57	19.83	21.30	21.35 ± 1.60
172.17	(q)	17.84	18.46	19.05	18.07	18.36 ± 0.53
215.17	(q)	17.56	16.73	18.11	18.19	17.65 ± 0.67
286.67	(q)	14.24	15.34	15.06	14.43	14.77 ± 0.52
359.67	(r)	12.67	14.11	15.20	13.73	13.93 ± 1.04
601.25	(t)	12.49	13.05	12.89	12.67	12.78 ± 0.24
1,177.50	(u)	10.07	10.17	10.85	10.66	10.44 ± 0.38
1,563.00	(v)	9.136	10.09	9.092	9.437	9.439 ± 0.46

*calibration curves are used in parenthesis.

Zero-order : $\text{conc} = 21.34 - 9.355 \times 10^{-3}\text{time}$ $r^2 = 0.7211.$

First-order : $\log \text{conc} = 1.330 - 2.651 \times 10^{-4}\text{time}$ $r^2 = 0.8246.$

Second-order : $1/\text{conc} = 0.0459 + 4.240 \times 10^{-5}\text{time}$ $r^2 = 0.9127.$



Second-order plot of ranitidine HCl degradation in 20% methanol.

40% Methanol

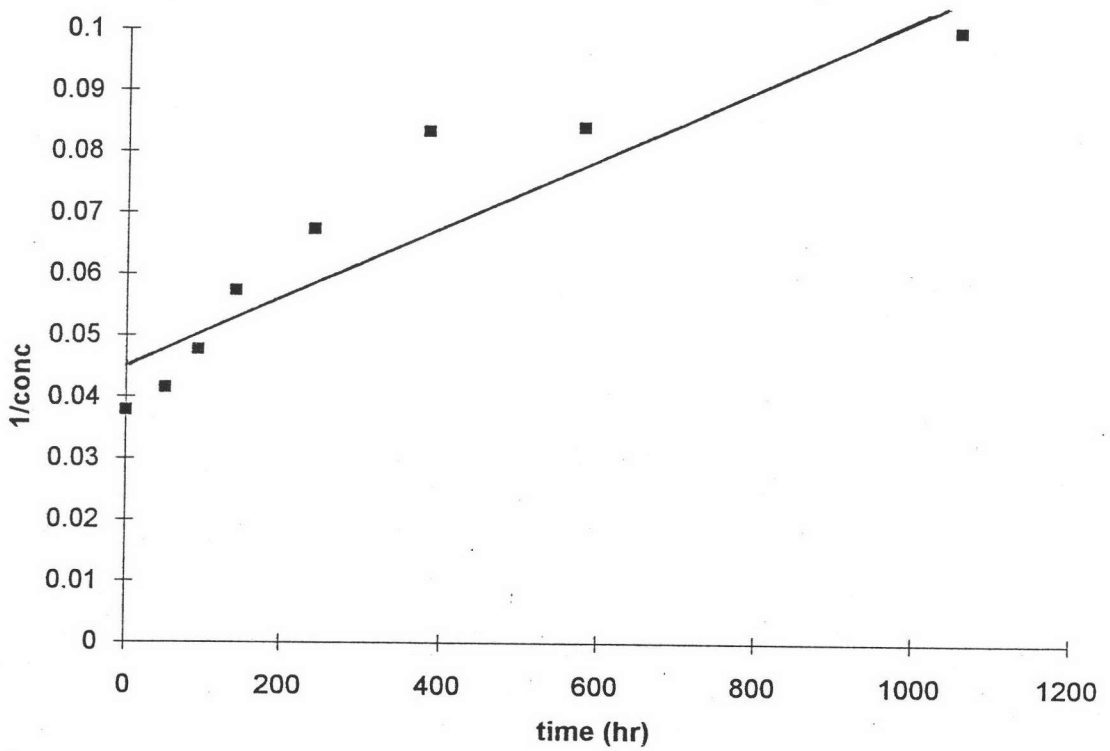
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(q)	27.45	23.13	27.96	27.18	26.43 ± 2.22
51.00	(q)	24.94	24.34	23.17	23.92	24.09 ± 0.74
93.83	(q)	21.17	21.97	17.68	23.00	20.96 ± 2.31
141.25	(q)	16.10	18.68	16.79	18.25	17.46 ± 1.24
238.67	(r)	14.64	15.27	14.60	14.85	14.84 ± 0.31
381.75	(s)	12.08	11.77	12.19	12.02	12.02 ± 0.18
578.67	(t)	11.62	11.75	12.84	11.52	11.93 ± 0.61
1,055.83	(u)	10.00	9.664	10.15	10.39	10.05 ± 0.30

*calibration curves are used in parenthesis.

Zero-order : conc = 21.74 - 0.0142time $r^2 = 0.6856$.

First-order : $\log conc = 1.334 - 3.848 \times 10^{-4} time$ $r^2 = 0.7758$.

Second-order : $1/conc = 0.0461 + 5.873 \times 10^{-5} time$ $r^2 = 0.8568$.



Second-order plot of ranitidine HCl degradation in 40% methanol.

60% Methanol

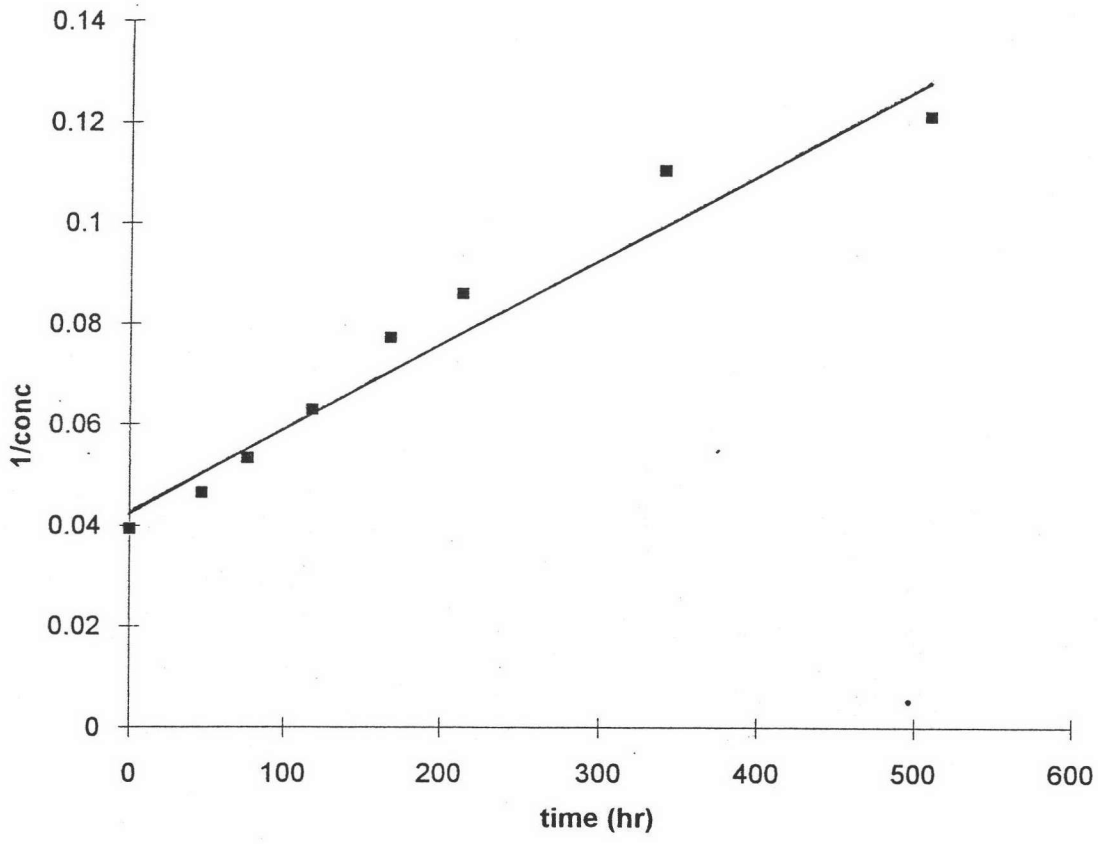
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(q)	23.59	26.84	25.93	25.46	25.46 ± 1.37
47.00	(q)	22.98	23.35	20.66	19.13	21.53 ± 1.99
76.50	(q)	18.39	18.18	19.44	19.04	18.76 ± 0.58
117.50	(r)	15.70	16.91	15.13	15.92	15.92 ± 0.74
167.67	(r)	12.45	13.01	13.97	12.49	12.98 ± 0.71
213.75	(r)	11.59	11.65	12.32	11.05	11.65 ± 0.52
339.67	(s)	10.49	9.149	9.830	9.810	9.810 ± 0.55
508.00	(t)	7.501	8.510	8.125	8.952	8.272 ± 0.62

*calibration curves are used in parenthesis.

Zero-order : $conc = 21.71 - 0.3180 time$ $r^2 = 0.8007.$

First-order : $\log conc = 1.339 - 9.578 \times 10^{-4} time$ $r^2 = 0.9003.$

Second-order : $1/conc = 0.0430 + 1.656 \times 10^{-4} time$ $r^2 = 0.9683.$



Second-order plot of ranitidine HCl degradation in 60% methanol.

80% Methanol

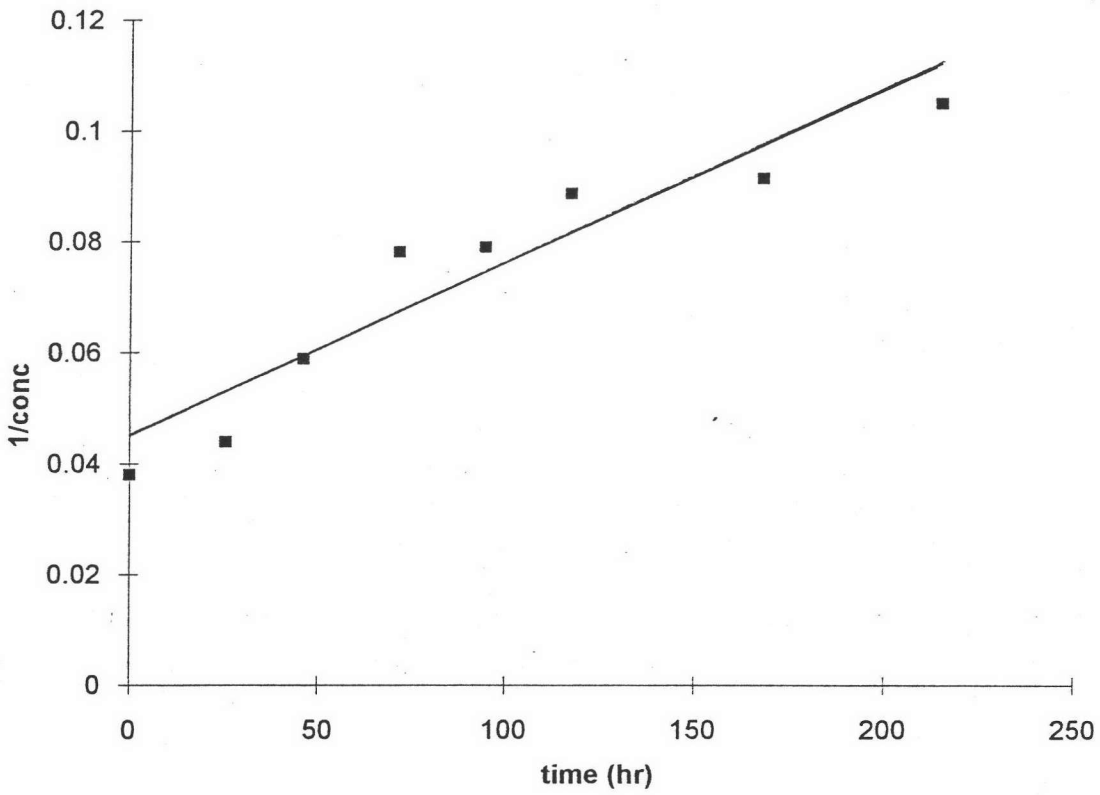
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)				Average Conc ± SD
0.00	(q) 28.29	26.57	24.00	26.28	26.28 ± 1.76
25.75	(r) 23.09	22.47	22.77	22.78	22.78 ± 0.25
46.00	(r) 16.23	16.28	19.11	16.32	17.00 ± 1.42
71.67	(r) 13.70	13.26	11.32	13.00	12.82 ± 1.04
98.67	(r) 12.04	13.33	12.46	12.87	12.68 ± 0.55
117.25	(r) 11.30	12.50	10.36	11.00	11.29 ± 0.90
167.83	(s) 10.97	10.56	11.23	11.11	10.97 ± 0.29
214.58	(s) 9.691	9.436	9.125	10.00	9.563 ± 0.37

*calibration curves are used in parenthesis.

Zero-order : $\text{conc} = 22.12 - 0.0720\text{time}$ $r^2 = 0.7466.$

First-order : $\log \text{conc} = 1.345 - 1.986 \times 10^{-4}\text{time}$ $r^2 = 0.8276.$

Second-order : $1/\text{conc} = 0.0443 + 3.084 \times 10^{-4}\text{time}$ $r^2 = 0.8981.$



Second-order plot of ranitidine HCl degradation in 80% methanol.

100% Methanol

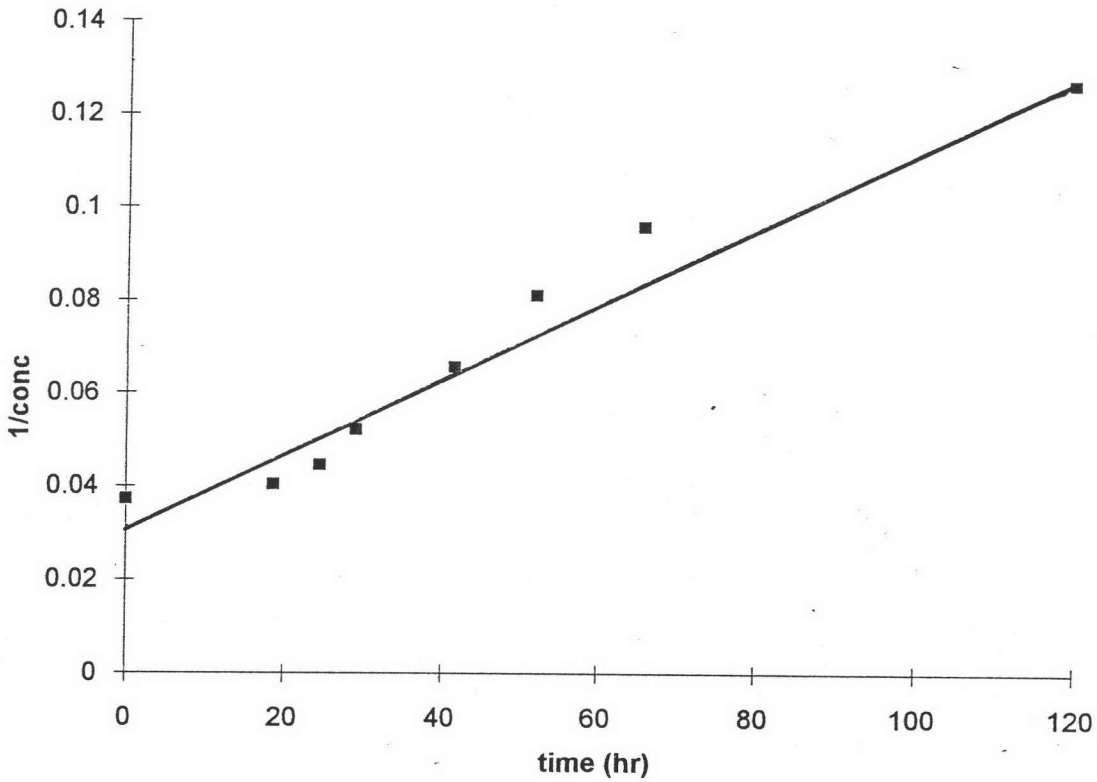
Time (hr)	Concentration of Ranitidine HCl Remaining * (mg/ml)					Average Conc ± SD
0.00	(o)	26.20	27.63	26.90	26.94	26.92 ± 0.58
18.67	(p)	25.56	25.64	23.04	24.75	24.75 ± 1.21
24.50	(p)	22.15	23.69	21.57	22.47	22.47 ± 0.89
29.00	(p)	19.90	18.98	18.79	19.22	19.22 ± 0.48
41.50	(p)	15.24	15.27	15.50	15.01	15.26 ± 0.20
52.00	(p)	12.32	12.48	12.32	12.37	12.37 ± 0.08
65.67	(p)	10.26	10.40	10.70	10.46	10.46 ± 0.18
119.58	(q)	8.377	8.030	7.906	7.399	7.928 ± 0.40

*calibration curves are used in parenthesis.

Zero-order : $conc = 25.01 - 0.1730 time$ $r^2 = 0.8270.$

First-order : $\log conc = 1.424 - 4.950 \times 10^{-3} time$ $r^2 = 0.9066.$

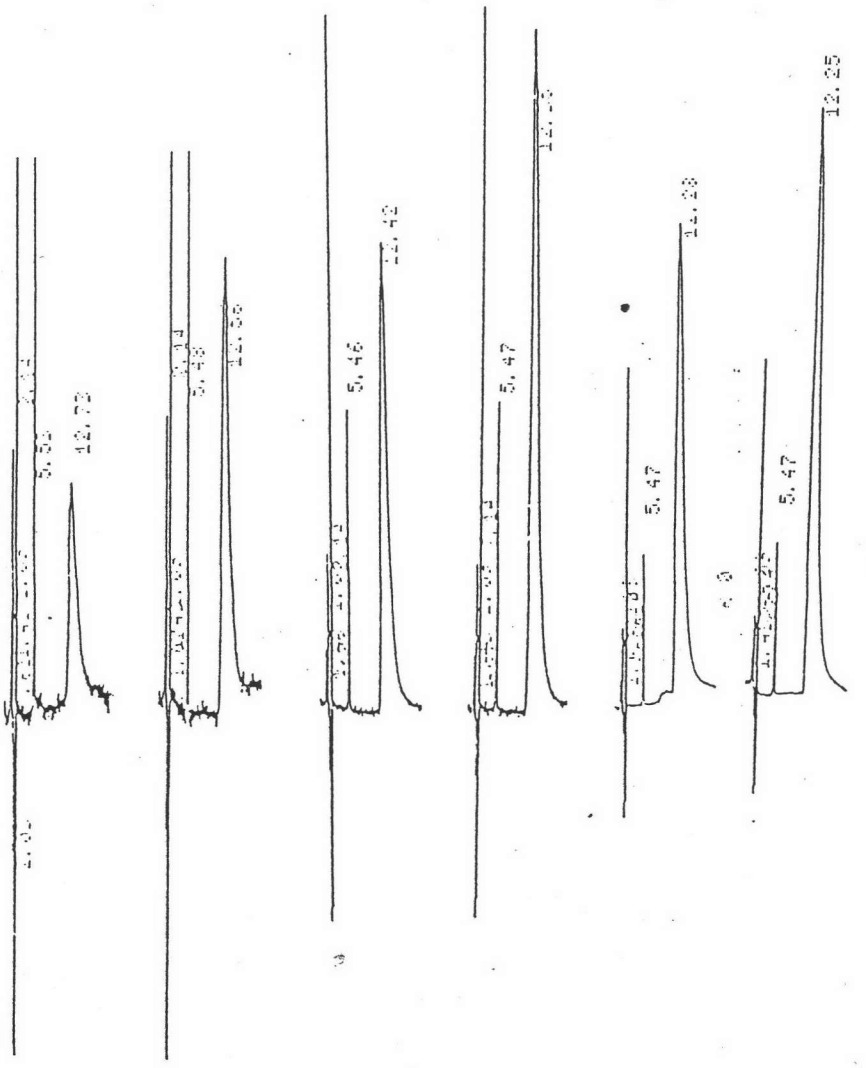
Second-order : $1/conc = 0.0312 + 8.325 \times 10^{-4} time$ $r^2 = 0.9571.$



Second-order plot of ranitidine HCl degradation in 100% methanol.

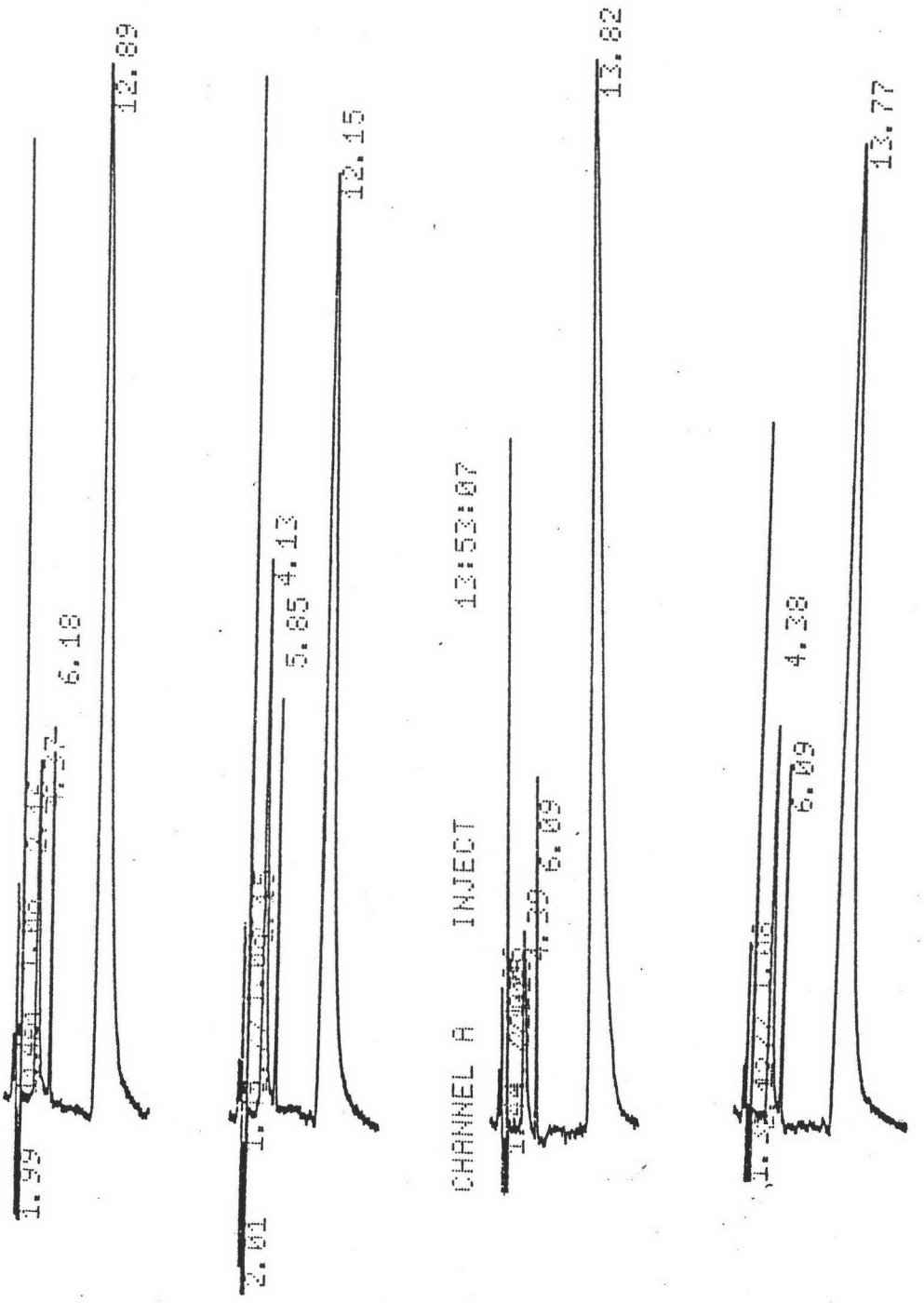
APPENDIX VII

HPLC Chromatograms of Ranitidine HCl



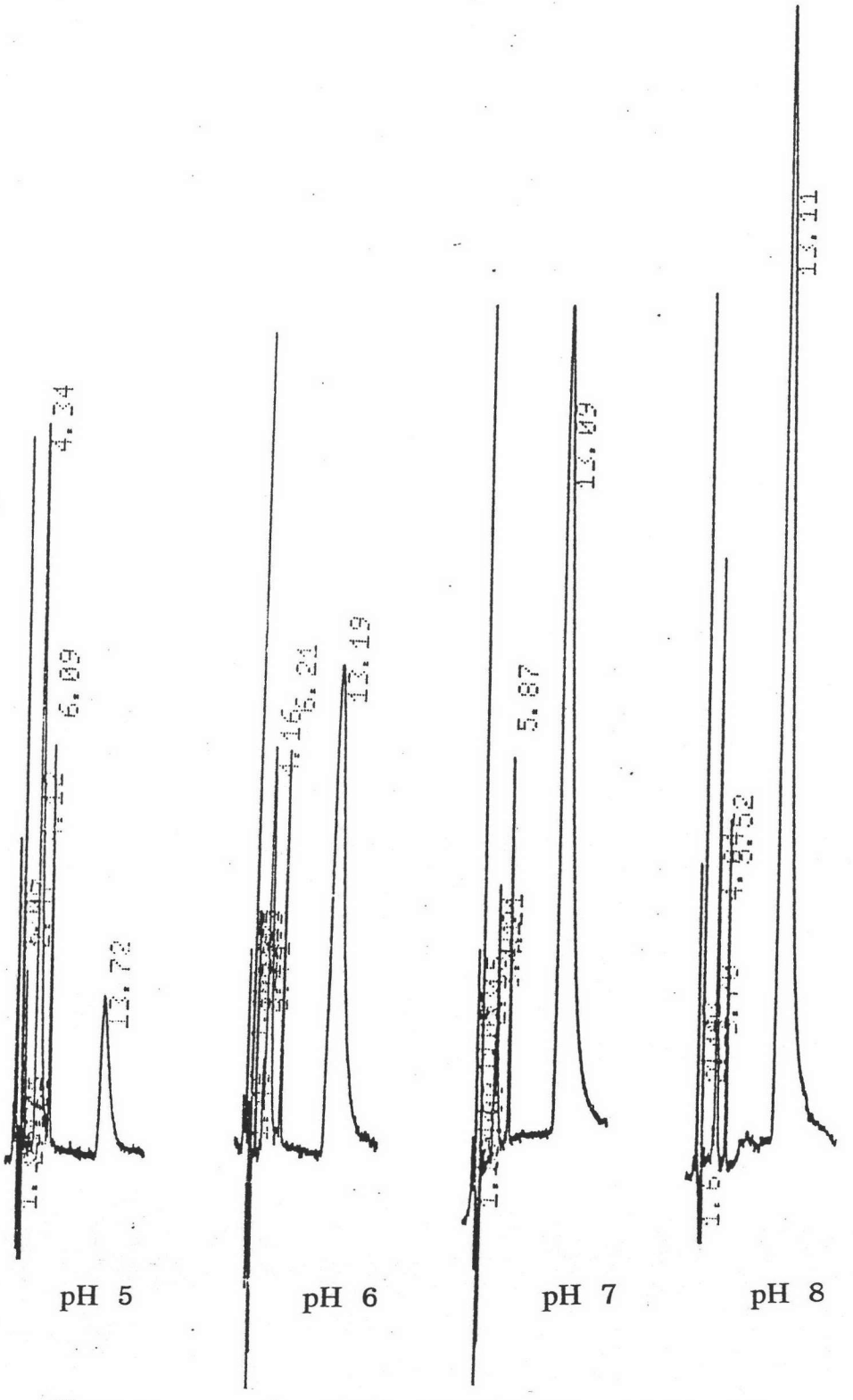
High performance liquid chromatogram of caffeine (retention time 5.47 min) and ranitidine HCl (retention time 12.43 min) at 262 nm. Each sample contained fix concentration of 0.4 mcg/ml caffeine as internal standard and various concentrations of ranitidine HCl as follows:

A	= 4 mcg/ml	B	= 8 mcg/ml	C	= 16 mcg/ml
D	= 24 mcg/ml	E	= 32 mcg/ml	F	= 40 mcg/ml

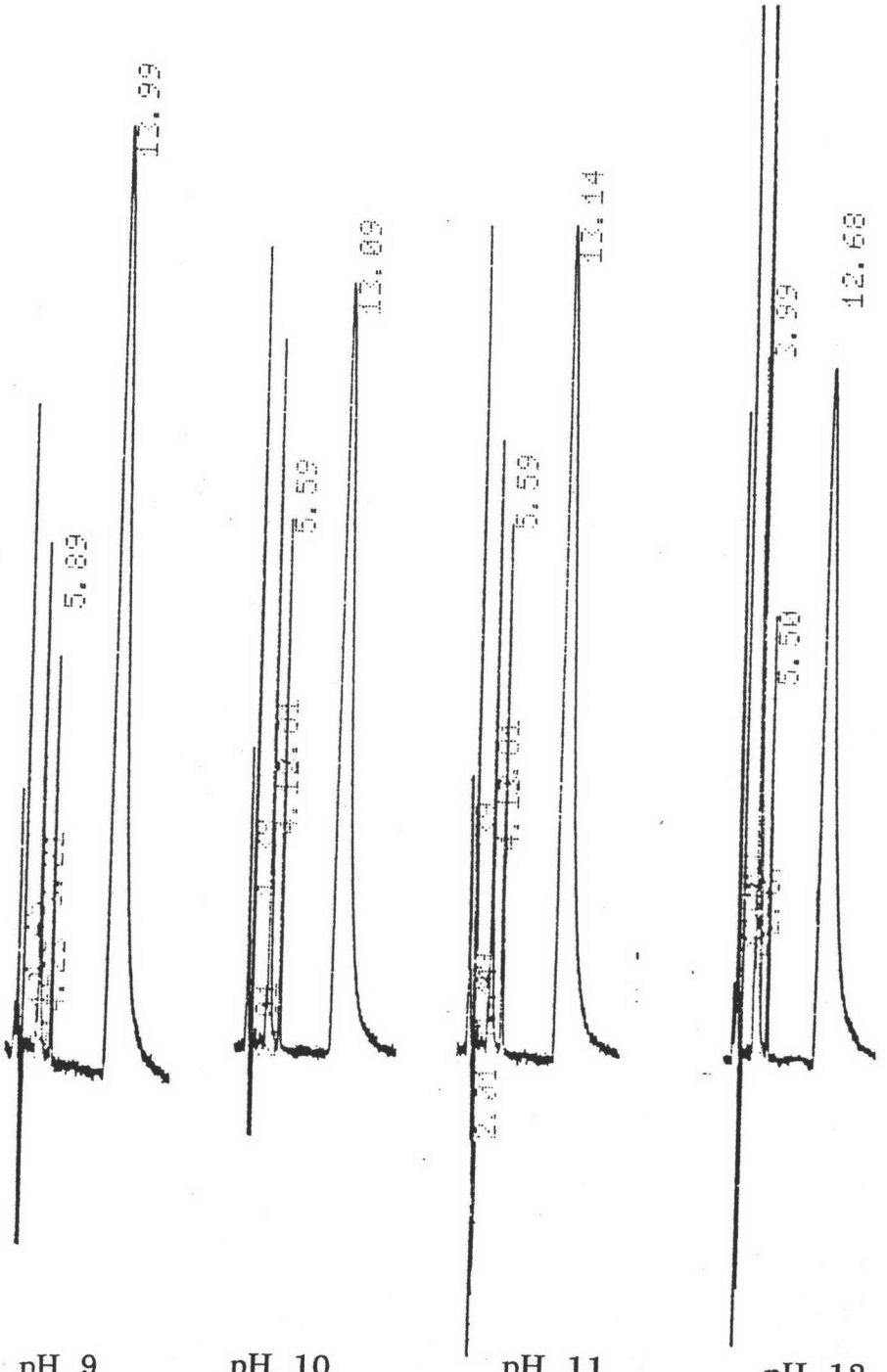


pH 1 pH 2 pH 3 pH 4

Chromatogram of ranitidine HCl (12.15 - 14.68 min) , its internal standard (5.85 - 6.32 min) and its degradation products (4.13 - 4.47 min) in pH 1 , 2 , 3 and 4 phosphate buffers.

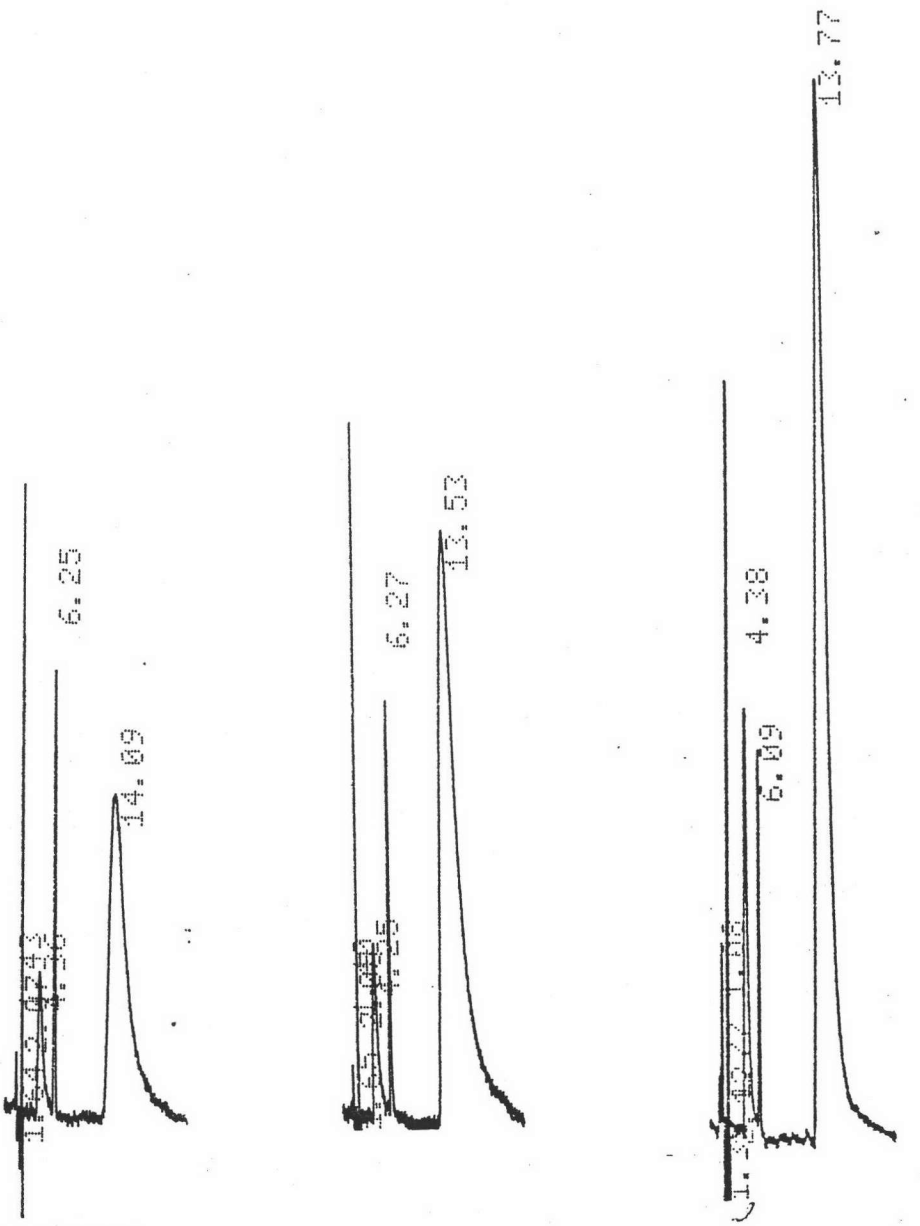


Chromatogram of ranitidine HCl (12.76 - 13.72 min), its internal standard (5.52 - 6.09 min) and its degradation products (4.34 - 4.21 min) in pH 5, 6, 7 and 8 phosphate buffers.

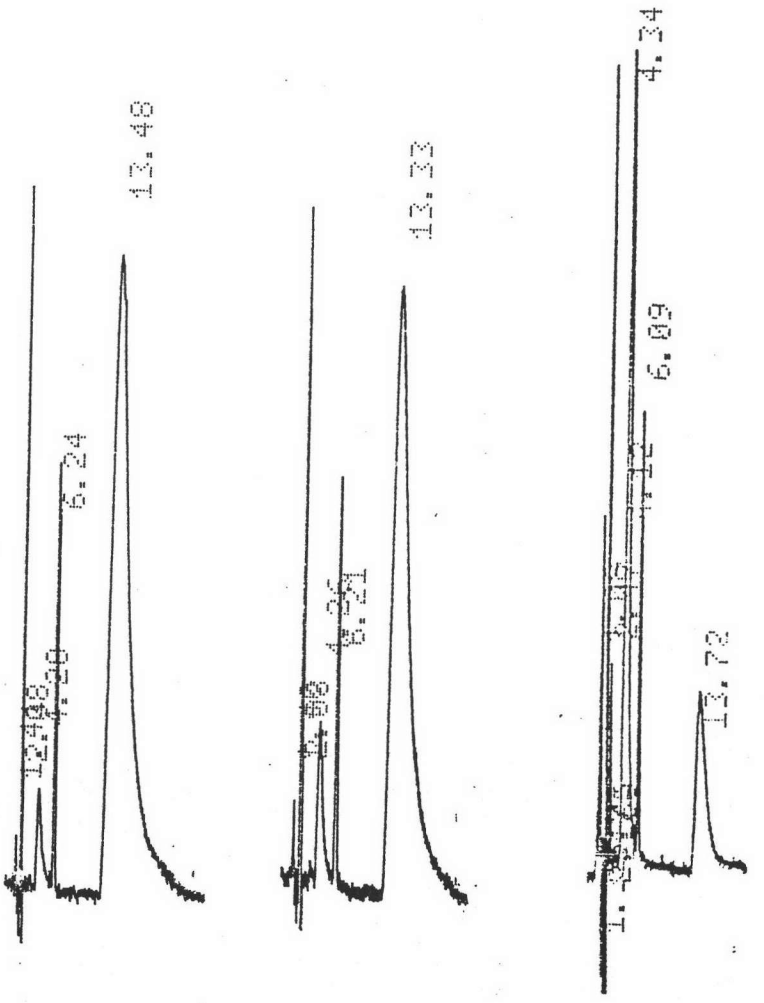


pH 9 pH 10 pH 11 pH 12

Chromatogram of ranitidine HCl (12.68 - 14.33 min) , its internal standard (5.50 - 5.94 min) and its degradation products (3.21 - 4.28 min) in pH 9 , 10 , 11 , and 12 phosphate buffers.

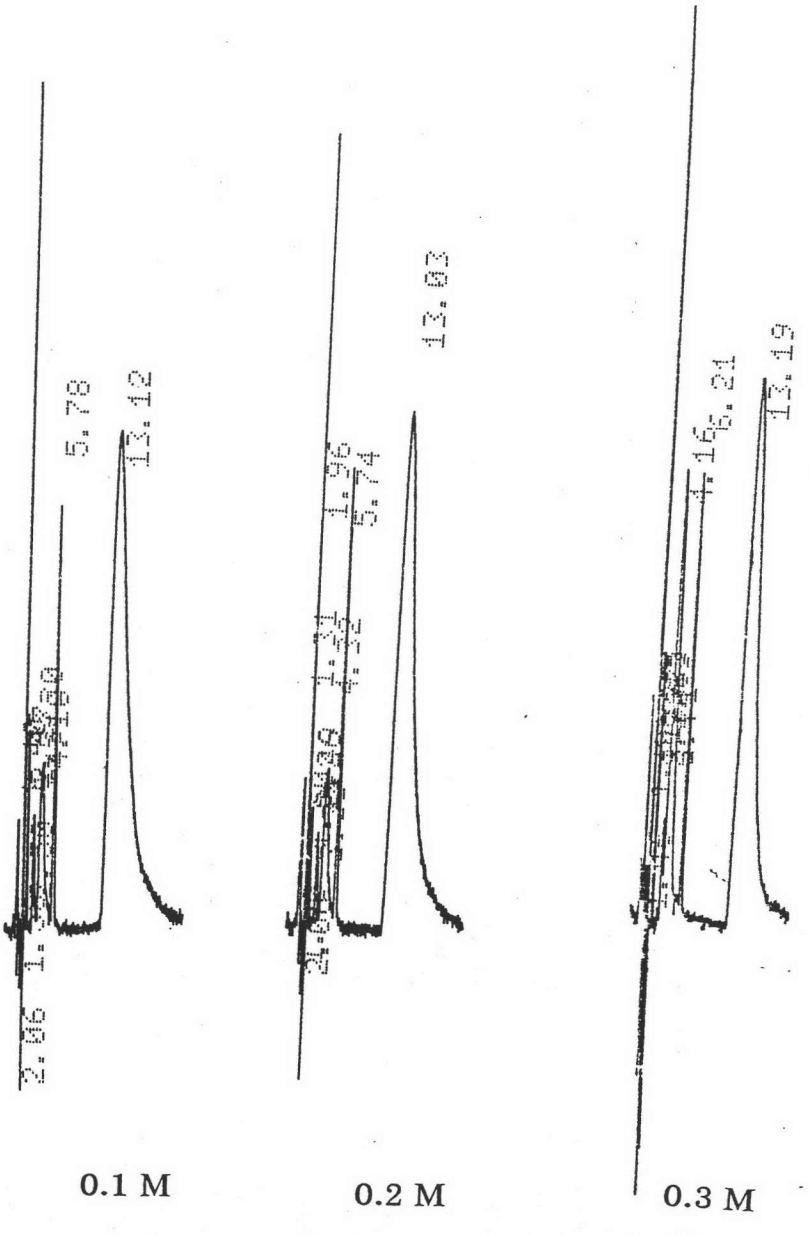


Chromatogram of ranitidine HCl (13.53–14.09 min), its internal standard (6.09–6.25 min) and its degradation products (4.25–4.38 min) in pH 4 phosphate buffer with 0.1, 0.2 and 0.4 M buffer concentrations.

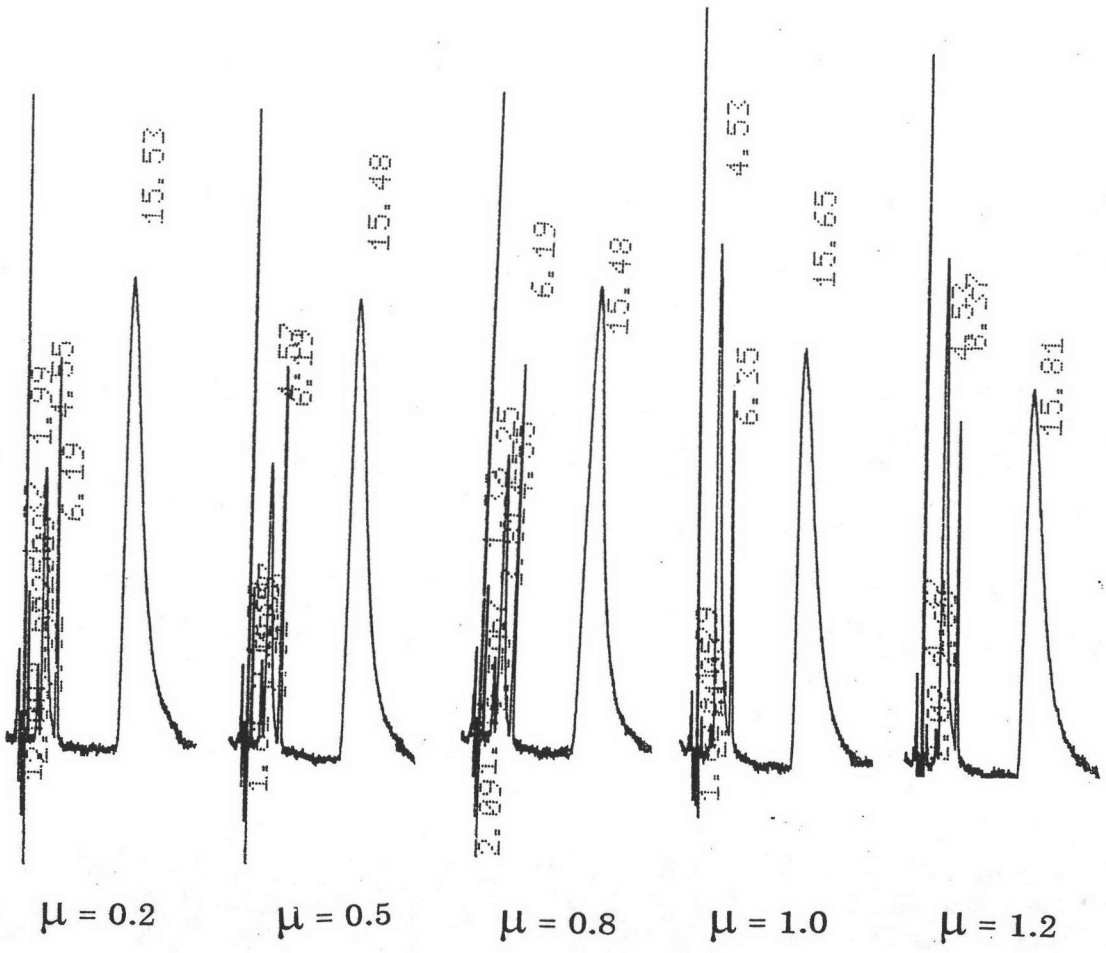


0.1 M 0.2 M 0.4 M

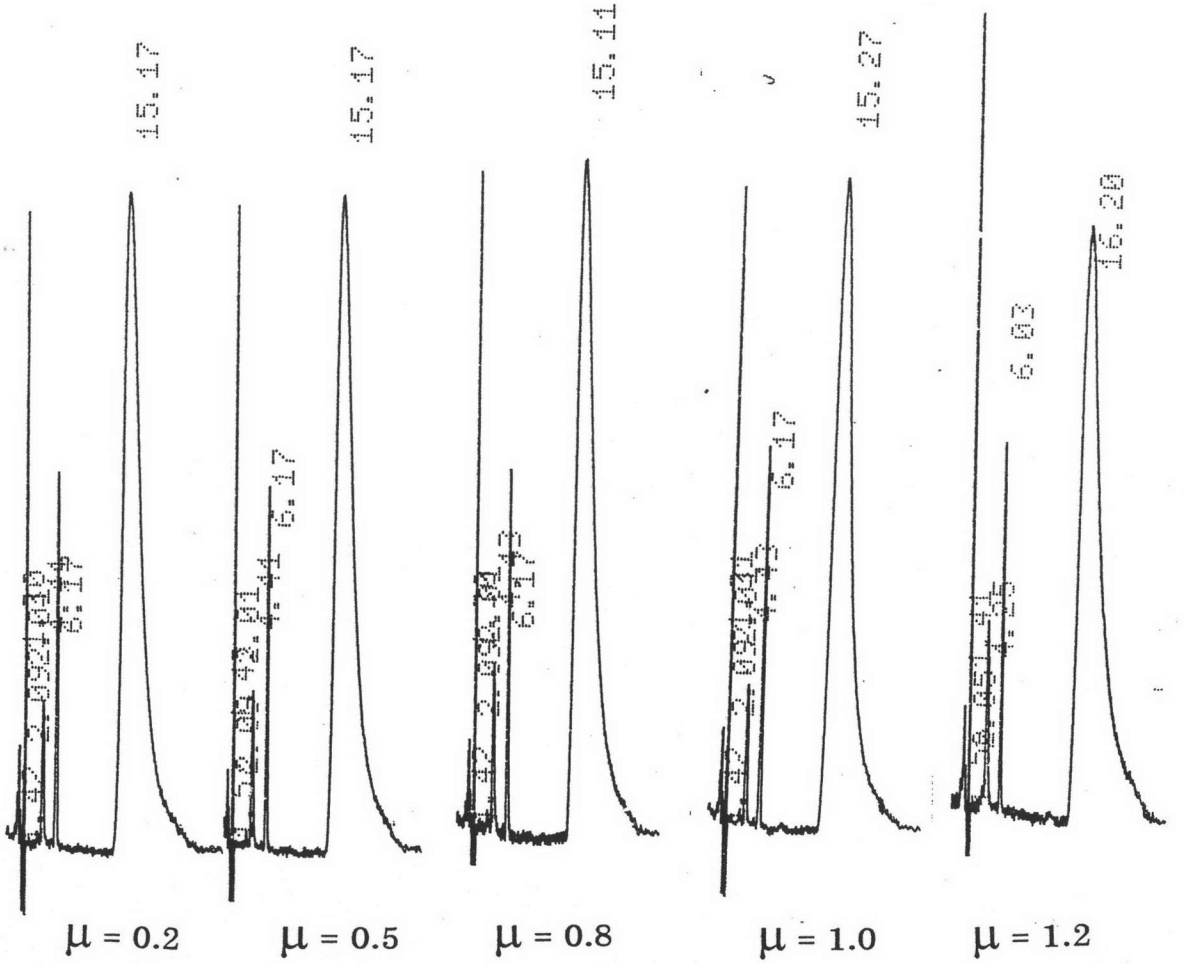
Chromatogram of ranitidine HCl (13.48–13.72 min), its internal standard (6.09–6.24 min) and its degradation products (4.20–4.34 min) in pH 5 phosphate buffer 0.1, 0.2 and 0.4 M buffer concentrations .



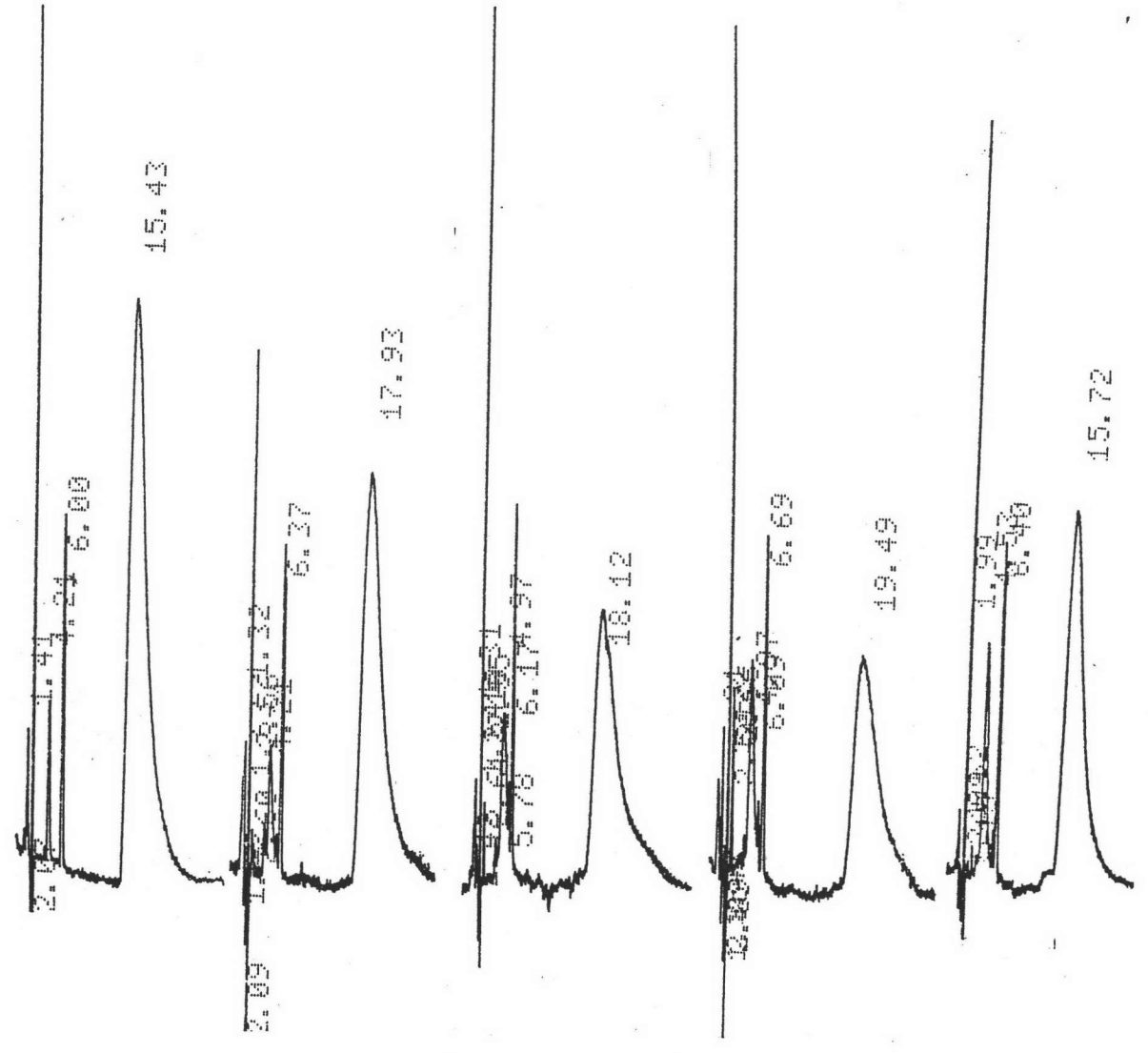
Chromatogram of ranitidine HCl (13.03–13.19 min), its internal standard (5.74–6.21 min) and its degradation products (4.10–4.32 min) in pH 6 phosphate buffer 0.1, 0.2 and 0.3 M buffer concentrations .



Chromatogram of ranitidine HCl (15.48–15.81 min), its internal standard (6.19–6.37 min) and its degradation products (4.53–4.57 min) in pH 5 phosphate buffers at ionic strength 0.2–1.2.



Chromatogram of ranitidine HCl (15.11–16.20 min), its internal standard (6.03–6.17 min) and its degradation products (4.14–4.43 min) in pH 12 phosphate buffers at ionic strength 0.2–1.2.



20 % methanol 40 % methanol 60 % methanol 80 % methanol 100 %methanol

Chromatogram of ranitidine HCl (15.43–19.49 min), its internal standard (6.00–6.69 min) and its degradation products (4.21–6.40 min) in 20, 40, 60, 80 and 100 % methanol.

VITA

Miss Kanokwan Thiengthawat was born on 21st September, 1968 in Bangkok, Thailand. She got a B. Sc. in Pharmacy from the Faculty of Pharmaceutical Sciences, Chulalongkorn University in 1992. She had worked in Siam Pharmaceutical factory after she left the University for one year. At present, she has studied for the Master Degree in Pharmaceutical Sciences at Chulalognkorn University since 1993.