SECTION II-e

STUDY ON AQUEOUS SUSPENSIONS CONTAINING COATED MAGNESIUM HYDROXIDE PARTICLES

INTRODUCTION:

An attempt is made to prepare aqueous suspensions containing magnesium hydroxide having controlled release property. The main objective behind such formulations is (1) To prevent the dumping of magnesium hydroxide in the stomach and thereby to prevent excessive rise in the pH in the stomach. It has been previously noted that acid rebound may be observed when the stomach contents become alkaline. (2) less frequent dosing will require.

Takebe[203] and others reported a preparation of stable slow release powdered preparation containing antacid and anticholinergics.

Ogava[204] and others reported the preparation of antacids coated with a material soluble at pH less than 5 to 6. Sodium bicarbonate was spray coated with poly (dimethylaminoethyl methacrylate) in acetone-methanol.

Products capable of maintaining the pH of artificially prepared gastric juice at pH 3-5 for upto 24 hours have been reported[205]. The following method was used: The pectin was dissolved in water, followed by addition of magnesium oxide. The mixture was added to water and stirred until homogenous (exothermic). The mixture was then stirred for another one hour and then aluminium hydroxide gel was added. The mixture was then stirred till homogenous.

The preparation of hard, slow release antacid lozenges has been presented by Mitra[206]. He used sugar or sugar alcohol, a gel forming swelling agent (NaCMC), water insoluble lipids and antacids. The mixture was then made into lozenge on a tablet press. The lozenges were hard, beyond the normal scale range of a conventional tablet hardness tester. The average time for solution of the lozenge in the mouth was approximately 50 minutes.

Sustained release freeze dried antacid powder has been prepared containing inorganic acid neutralizers and water-absorbing polymers, such as gelatins and poly acrylic acid[207].

The duration of antacid product depends on the gastric residence time in addition to the type of antacid material present in the product.

It has been reported that the food of an ordinary mixed diet remains in the stomach for 2-6 hours[208]. Another study shows that the mean emptying time is 2.1 hour and the range is 1.5 to 3.3 hours[209]. It is noted that the duration of action of an antacid taken 1 hour after a meal was much greater then when taken on an empty stomach[210].

Fordtran[113,211] and coworkers concluded that combined

buffer capacity of the meal and antacid and increased retention of antacid, taken 1 hour after meal, accounted for longer duration of acid neutralization in the postcibal (3 hours) than in the fasted (20-40 minutes) state in duodenal or gastric ulcer patients.

It has been reported[138] that the curve for total acidity commences to rise a short time after the meal, and about 1 hour later reaches maximum which varies from 35 to 70 cc of 0.1N HCl in different persons. The curve maintained its maximum height for half an hour or less and then commence to decline reaching the resting level again from 2.5 to 3.0 hours after the ingestion of test meals.

The gastric emptying of antacid preparations and food was monitored by gamma camera by Wilson[212] and others. The results showed that the food remained in the stomach for more than 2 hours. The factors affecting stomach emptying are discussed by Banker and Rhodes[209].

The study of commercial antacid products containing mixture of $Al(OH)_3$ and $Mg(OH)_2$ indicated that the duration of action ranged from 34 to 78 minutes. Above mentioned reports indicate that there is a scope of formulating controlled release antacid preparation.

Patients should be advised to take antacids 1 hour after meals and at the bed time to enhance the effectiveness of preparation.

EXPERIMENTAL

(a) Preparation of magnesium hydroxide suspension containing uncoated particles:

Formulation number SU-1:

It contained 8% w/v of $Mg(OH)_2$, 1.05% w/v of cross-linked polyvinylpyrrolidone, 0.45% w/v of carboxymethyl cellulose sodium salt, 0.6% w/v of sodium benzoate, and distilled water to make 100 cc of the product.

Accurately weighed NaCMC was first wetted with sufficient quantity of 70% aqueous sorbitol solution. Cross-linked polyvinylpyrrolidone was separately dispersed in 35 cc of distilled water. The dispersion was gradually added to NaCMC while stirring. The mixture was stored undisturbed for about 15 hours. A dispersion of $Mg(OH)_2$ (8 gms in 40 cc water) was gradually added to the dispersion of polymers. Solution of sodium benzoate was then stirred in . The mixture was stirred on a magnetic stirrer for about 20 minutes.

(b) Preparation of aqueous dispersions containing waxy materials by melting method:

The preparations contained following material in addition to the materials present in formulation number SU-1.

(1) Formulation number SU-2: Glyceryl monostearate (self emulsifying) 2% w/v

(2) Formulation number SU-3: Stearyl alcohol 1% w/v,

(3) Formulation number SU-4: Beeswax 3% w/v, and

(4) Formulation number SU-5: Cetyl alcohol 1% w/v.

Double strength dispersion of cross-linked PVP and NaCMC was first prepared by a method described in the formulation number SU-1.

$Mg(OH)_2$ powder was dispersed in 40 cc of distilled water and heated to 80° on a water bath. The hot aqueous dispersion was then added to the melted waxy material (80°) with continuous stirring. The mixture was heated at 80°, while stirring, for about 15 minutes. The preparation was cooled to the room temperature while stirring on a magnetic stirrer. Double strength dispersion of cross-linked PVP and NaCMC (50 cc) and the aqueous solution of sodium benzoate were gradually mixed, one after another, with the above dispersion. Sufficient quantity of distilled water was added to adjust the final volume to 100 cc. The suspension was then stirred for about 5 minutes on a magnetic stirrer.

(c) Preparation of aqueous dispersion containing ethyl cellulose:

Formulation Number SU-6: The preparation was

prepared using 2% w/v of ethyl cellulose, and 20 cc of ethanol per 100 cc of product in addition to the ingredients present in formulation number SU-1.

The dispersion of $Mg(OH)_2$ in water (8 gms in 50 cc) was heated to 50° on a water bath. Ethyl cellulose was separately dissolved in ethanol and heated to 50° on a water bath. The hot alcoholic solution of ethyl cellulose was then added dropwise to the hot aqueous dispersion. The mixture was stirred on a magnetic stirrer at 50° till the ethanol completely evaporated. The mixture was then gradually cooled to the room temperature while stirring. Double strength dispersion of cross-linked PVP and NaCMC (50 cc) and the aqueous solution of sodium benzoate were then gradually mixed, one after another, with the above dispertion. Sufficient quantity of distilled water was added to adjust the final volume to 100 cc. The suspension was then stirred for about 5 minutes on a magnetic stirrer. The methodology reported earlier[213] was adopted with minor modifications.

(d) Preparation of aqueous dispersion containing encapsulating agent:

Formulation number SU-7: The preparation was prepared using 0.04% w/v of sodium lauryl sulphate, 1.5% w/v of ethyl cellulose, and chloroform 50 cc per 100 cc of the final product in addition to the ingredients present in formulation number SU-1.

Magnesium hydroxide powder was dispersed uniformely in 1.5% solution of ethyl cellulose in chloroform. The dispersion of $Mg(OH)_2$ and the solution of sodium lauryl sulphate were separately heated to 40° on a water bath. The dispersion was then added dropwise to the aqueous solution. The hot dispersion was stirred till all the chloroform evaporated. The mixture was gradually cooled to the room temperature while stirring continuously. Double strength dispersion of cross-linked PVP and NaCMC (50 cc) and the aqueous solution of sodium benzoate were then gradually mixed, one after another, with the dispersion. The final volume was adjusted using sufficient quantity of distilled water. The homogeneous dispersion was obtained after stirring for 5 minutes on a magnetic stirrer. The procedure is adapted from the method of Mortada[214].

(e) Preparation of aqueous dispersion containing cellulose acetate and PEG 400:

Formulation number SU-8: The preparation was prepared using 1.05% w/v of cellulose acetate, 0.45% PEG 400, and 70 cc of CH_2Cl_2 per 100 cc of the product in addition to the ingredients present in the formulation number SU-1.

Cellulose acetate and PEG 400 were dissolved in CH_2Cl_2 by overnight soaking. The dispersion of $Mg(OH)_2$ in

water, previously heated to 40°, was then added gradually to hot (40°) solution of celluiose acetate and PEG 400. The mixture was stirred till all CH_2Cl_2 evaporated, in a water bath maintained at 40°. The dispersion was gradually cooled to the room temperature. Cross-linked PVP, NaCMC, sodium benzoate and balance distilled water were then added as described in the previous formulation. The methodology reported earlier by Teeuwes[215] was adopted with minor modifications.

The modified acid-consuming capacity test and the Rossett-Rice test were performed as reported in the chapter of aqueous dispersion of magnesium hydroxide.

RESULTS AND DISCUSSION

The Rossett-Rice times, the time for which the pH was maintained above 2.5 in the in vitro test, for the formulation numbers SU-1, and SU-3 to SU-7 were 45, 44, 44, 47, 43 and 50 minutes respectively and the maximum value of pH in the in vitro test were 8.72, 8.8, 8.65, 8.75, 8.72 and 8.75 respectively. It is concluded that the formulations which contained stearyl alcohol, bees wax, cetyl alcohol and ethyl cellulose do not show controlled release properties. The areas under the curve of time in minutes versus pH are 322, 314, 261, 317, 262 and 340 respectively for the formulation numbers SU-1 and SU-3 to SU-7. It can be concluded that the pH (OBS) was controlled to some extent in the in vitro test in the formulation number SU-4 containing beeswax and formulation number SU-6 containing ethyl cellulose. Microscopic examination of suspensions showed discontinues coats on some of the particles. It seems that the amount of coating agent was insufficient to coat completely light and fluffy particles of magnesium hydroxide or the process needs modification .

The Rossett-Rice time was 33 minutes in the formulation number SU-2 containing self emulsifying grade of glyceryl monostearate. The addition of 0.1N HCl was stopped after 33rd minute in the in vitro test to check whether any

further amount of antacid material was released later or not. The pH (OBS) was then recorded at different times. The readings were found to be as follows: 2.95 at 45th minute, 3.2 at 50th minute, 3.35 at 55th minute, 3.9 at 70th minute, 4.0 at 75th minute and 7.4 after storage of 8 hours. Thirty cc of 0.1N HCl was required to bring down the pH to 2.5 after 8 hours of storage. The release pattern in the formulation number SU-2 indicates that the magnesium hydroxide was released at a controlled rate in the in vitro test. The area under the curve of time in minute versus pH was 208 for the formulation number SU-2. It seems that glyceryl mono stearate (self emulsifying) is a suitable substance for formulating controlled release aqueous antacid suspension. Long acting concentrated aqueous antacid suspensions could be formulated by the use of blend of coated and uncoated particles.

The Rossett-Rice time was 33 minutes in the formulation number SU-8 containing cellulose acetate and PEG 400. The maximum value of pH in the in vitro test was 8.3. The addition of 0.1N HCl was stopped in this formulation with a intention to study the release pattern in the later period of in vitro test. The pH (OBS) was recorded at different times. The pH (OBS) changed to 2.6 after stirring for another 50 minutes. This indicates that there was no further release

of magnesium hydroxide after 33rd minute. This behaviour may be due to slow diffusion of 0.1N HCl through swellable film of cellulose acetate and PEG 400. The area under the curve of time in minute versus pH (OBS) was 164, which is significantly lower as compared to the suspension containing uncoated particles. It seems that the concentration and method are unsuitable for formulating controlled release preparation.

The equations proposed in the chapter of aqueous suspensions containing magnesium hydroxide were applied to these formulations and the results are tabulated in Tables V-1 to V-8.

The value of correlation coefficient between:

(1) 1/TMEQ-NxRxT and log pH (OBS) is 0.9834,

(2) 1/TMEQ-NxRxT and log corrected pH (OBS) is 0.9855,

(3) Uncorrected observed pH and uncorrected calculated pH is 0.976, and

(4) Corrected observed pH and corrected calculated pH is 0.9767 for the formulation number SU-2 containing self emulsifying glyceryl monostearate. The total number of observations were 17. The results indicate that the

proposed equation gives satisfactory results in the preparation containing self emulsifying glyceryl monostearate. The values of regression analysis for other formulations are tabulated in Tables V-1 to V-8.

It seems that it is difficult to prepare controlled release aqueous preparation containing magnesium hydroxide as antacid material as there are lots of variables and limitations and so other methods should to tried to obtain a good controlled release antacid preparation. The duration of antacid action can be increased by formulating concentrated antacid preparations or by using a higher dose of an antacid product containing a blend of coated and uncoated particles.

TABLE V-1

(1)	Formulation number	: SU-1
(2)	The amount used for in vitro test	: 10 cc
(3)	The total milliequivalents (TMEQ)	: 26.14
(4)	The normality of HCl (N)	: 0.100
(5)	The rate of addition of HCl (R)	: 4.0 cc/min
(6)	The time to reach maximum pH (TM)	: 3 min
(7)	Total number of observations	: 23
(8)	Area under the curve (AUC)	: 322.68 min x ph

Time (min)	pH (OBS)	pH (CALC)	CpH(OBS)	CpH(CALC)
3	8.72	10.18	8.67	10.19
5	8.72	9.98	8.64	9.96
7	8.72	9.77	8.61	9.72
9	8.70	9.55	8.56	9.48
11	8.70	9.32	8.53	9.22
13	8.65	9.08	8.46	8.95
15	8.60	8.83	8.39	8.66
17	8.60	8.56	8.37	8.37
19	8.55	8.28	8.29	8.06
21	8.50	7.99	8.22	7.73
23	8.45	7.68	8.16	7.39
25	8.40	7.35	8.09	7.03
27	8.20	7.00	7.87	6.66
29	8.00	6.64	7.65	6.26
31	7.70	6.26	7.34	5.85
33	6.70	5.85	6.32	5.42
35	5.70	5.42	5.31	4.97
37	4.75	4.97	4.34	4.51
39	4.20	4.50	3.78	4.02
41	3.55	4.01	3.11	3.52
43	3.10	3.50	2.65	3.02
45	2.70	2.97	2.24	2.50
47	2.50	2.43	2.03	1.99

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.266 B_1 = -6.463 r = -0.9651

SE = 0.0495 I_o = 1.019

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = .1.303 B_1 = -7.366 r = -0.9690

SE = 0.0530 I_o = 1.021

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.1297 B_1 = 0.9795 r = 0.9385

SE = 0.8415

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = -0.0205 B_1 = 1.0021 r = 0.9423

SE = 0.8706

TABLE V-2

(1)	Formulation number	:	SU-2
(2)	The amount used for in vitro test	:	10 cc
(3)	The total milliequivalents (TMEQ)	:	24.00
(4)	The normality of HCl (N)	:	0.100
(5)	The rate of addition of HCl (R)	:	4cc/min
(6)	The time to reach maximum pH (TM)	:	3 min
(7)	Total number of observations	:	17
(8)	Area under the curve (AUC)	:	207.07 minxpH

Time (min)	pH (OBS)	pH (CALC)	CpH(OBS)	CpH (CALC)
3	8.55	9.53	8.50	9.56
5	8.50	9.15	8.42	9.13
7	8.45	8.75	8.34	8.69
9	8.35	8.34	8.21	8.24
11	8.20	7.92	8.03	7.78
13	8.00	7.49	7.81	7.30
15	7.80	7.04	7.59	6.82
17	7.50	6.59	7.27	6.33
19	6.65	6.12	6.39	5.83
21	6.00	5.65	5.72	5.33
23	5.10	5.16	4.81	4.82
25	4.25	4.67	3.94	4.31
27	3.80	4.18	3.47	3.81
29	3.35	3.68	3.00	3.30
31	2.95	3.19	2.59	2.81
33	2.70	2.70	2.32	2.34
35	2.50	2.23	2.11	1.89

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.471 B_1 = -11.232 r = -0.9834

SE = 0.0367 I_o = 1.003

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.530 B_1 = -12.547 r = -0.9855

SE = 0.0383 I_o = 1.008

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.1349 B_1 = 0.9751 r = 0.9760

SE = 0.5242

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = 0.0639 B_1 = 0.9867 r = 0.9767

SE = 0.5448

TABLE V-3

(1)	Formulation number	: SU-3
(2)	The amount used for in vitro test	: 10 cc
(3)	The total milliequivalents (TMEQ)	: 26.00
(4)	The normality of HCl (N)	: 0.100
(5)	The rate of addition of HCl (R)	: 4.0 cc/min
(6)	The time to reach maximum pH (TM)	: 3 min
(7)	Total number of observations	: 22
(8)	Area under the curve (AUC)	: 314.26 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
3	8.80	10.45	8.75	10.49
5	8.80	10.22	8.72	10.23
7	8.78	9.98	8.67	9.96
9	8.70	9.73	8.56	9.67
11	8.70	9.47	8.53	9.38
13	8.70	9.19	8.51	9.07
15	8.65	8.91	8.44	8.75
17	8.65	8.60	8.42	8.41
19	8.60	8.29	8.34	8.06
21	8.50	7.96	8.22	7.69
23	8.45	7.61	8.16	7.31
25	8.30	7.24	7.99	6.91
27	8.20	6.86	7.87	6.50
29	8.00	6.45	7.65	6.06
31	7.70	6.03	7.34	5.62
33	6.75	5.59	6.37	5.15
35	5.70	5.13	5.31	4.67
37	4.30	4.65	3.89	4.17
39	3.65	4.15	3.23	3.67
41	3.10	3.63	2.66	3.15
43	2.65	3.10	2.20	2.64
45	2.50	2.57	2.04	2.13

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.309 B_1 = -7.191 r = -0.9490

SE = 0.0602 I_o = 1.032

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.350 B_1 = -8.174 r = -0.9531

SE = 0.0654 I_o = 1.036

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.1272 B_1 =0.9797 r= 0.9172

SE = 0.9967

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = -0.0528 B_1 = 1.006 r = 0.9214

SE = 1.038

TABLE V-4

(1) Formulation number : SU-5
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 24.4
(4) The normality of HCl (N) : 0.100
(5) The rate of addition of HCl (R) : 4.0 cc/min
(6) The time to reach maximum pH (TM) : 4 min
(7) Total number of observations : 21
(8) Area under the curve (AUC) : 261.96 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
4	8.65	9.25	8.58	9.22
5	8.62	9.14	8.54	9.09
7	8.62	8.91	8.51	8.83
9	8.62	8.67	8.48	8.56
11	8.40	8.41	8.23	8.28
13	8.30	8.15	8.11	7.98
15	8.25	7.87	8.04	7.67
17	8.15	7.57	7.92	7.34
19	8.10	7.26	7.84	7.00
21	7.95	6.93	7.67	6.65
23	7.70	6.59	7.41	6.27
25	6.50	6.22	6.19	5.88
27	6.00	5.84	5.67	5.48
29	5.00	5.44	4.65	5.05
31	4.25	5.02	3.89	4.61
33	3.95	4.58	3.57	4.15
35	3.60	4.11	3.21	3.68
37	3.30	3.63	2.89	3.20
39	3.00	3.14	2.58	2.71
41	2.75	2.63	2.31	2.22
43	2.55	2.12	2.10	1.74

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.261 B_1 = -6.731 r = -0.9746
SE = 0.0441 I_o = 0.9857

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.298 B_1 = -7.620 r = -0.9785
SE = 0.0.458 I_o = 0.9865

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.4120 B_1 = 0.9288 r = 0.9723
SE = 0.5379

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo= 0.3239 B_1 = 0.9399 r = 0.9751
SE = 0.5390

TABLE V-5

(1) Formulation number : SU-5
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 26.6
(4) The normality of HCl (N) : 0.100
(5) The rate of addition of HCl (R) : 4.0 cc/min
(6) The time to reach maximum pH (TM) : 4 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 317.62 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
5	8.75	10.31	8.67	10.31
7	8.75	10.08	8.64	10.06
9	8.75	9.85	8.61	9.79
11	8.75	9.60	8.58	9.51
13	8.70	9.34	8.51	9.21
15	8.70	9.06	8.49	8.91
17	8.65	8.78	8.42	8.59
19	8.60	8.48	8.34	8.26
21	8.60	8.16	8.32	7.91
23	8.50	7.83	8.21	7.55
25	8.40	7.49	8.09	7.17
27	8.30	7.12	7.97	6.77
29	8.20	6.74	7.85	6.36
31	7.90	6.34	7.54	5.93
33	7.10	5.92	6.72	5.49
35	5.95	5.48	5.56	5.02
37	4.90	5.02	4.49	4.55
39	4.10	4.54	3.68	4.05
41	3.55	4.04	3.11	3.55
43	3.10	3.52	2.65	3.04
45	2.75	3.00	2.29	2.53
47	2.50	2.47	2.03	2.03

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.301 B_1 = -7.096 r = -0.9609
SE = 0.0532 I_o = 1.035

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.341 B_1 = -8.069 r = -0.9647
SE = 0.0573 I_o = 1.038

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.1589 B_1 = 0.9749 r = 0.9318
SE = 0.9041

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = 0.0069 B_1 = 0.9976 r = 0.9348
SE = 0.9410

TABLE V-6

(1)	Formulation number	: SU-6
(2)	The amount used for in vitro test	: 10 cc
(3)	The total milliequivalents (TMEQ)	: 26.3
(4)	The normality of HCl (N)	: 0.100
(5)	The rate of addition of HCl (R)	: 4.0 cc/min
(6)	The time to reach maximum pH (TM)	: 3 min
(7)	Total number of observations	: 21
(8)	Area under the curve (AUC)	: 262 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
3	8.72	9.61	8.67	9.62
5	8.70	9.33	8.62	9.31
7	8.60	9.05	8.49	8.99
9	8.60	8.75	8.46	8.65
11	8.50	8.45	8.33	8.31
13	8.50	8.13	8.31	7.96
15	8.45	7.80	8.24	7.59
17	8.30	7.45	8.09	7.22
19	8.20	7.10	7.94	6.83
21	8.10	6.73	7.82	6.43
23	7.50	6.35	7.21	6.02
25	6.40	5.96	6.09	5.60
27	5.20	5.56	4.87	5.18
29	4.40	5.14	4.05	4.74
31	4.00	4.71	3.64	4.29
33	3.55	4.27	3.17	3.85
35	3.30	3.83	2.91	3.39
37	3.10	3.38	2.69	2.94
39	2.80	2.92	2.38	2.50
41	2.65	2.47	2.21	2.07
43	2.50	2.03	2.05	1.65

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.367 B_1 = -9.643 r = -0.9669
SE = 0.0540 I_o = 1.000

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.418 B_1 = -10.914 r = -0.9716
SE = 0.0563 I_o = 1.003

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.4898 B_1 = 0.9129 r = 0.9611
SE = 0.6733

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = 0.3838 B_1 = 0.9265 r = 0.9641
SE = 0.6844

TABLE V-7

(1)	Formulation number	: SU-7
(2)	The amount used for in vitro test	: 10 cc
(3)	The total milliequivalents (TMEQ)	: 26.5
(4)	The normality of HCl (N)	: 0.100
(5)	The rate of addition of HCl (R)	: 4.0 cc/min
(6)	The time to reach maximum pH (TM)	: 4 min
(7)	Total number of observations	: 20
(8)	Area under the curve (AUC)	: 340.4 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
4	8.75	10.67	8.68	10.68
8	8.75	10.26	8.62	10.22
14	8.75	9.58	8.55	9.45
16	8.70	9.33	8.48	9.17
18	8.70	9.07	8.46	8.88
20	8.70	8.79	8.43	8.57
22	8.65	8.49	8.37	8.25
24	8.60	8.18	8.30	7.90
26	8.55	7.86	8.23	7.54
28	8.40	7.51	8.07	7.17
30	8.10	7.14	7.75	6.77
32	8.00	6.75	7.63	6.35
34	7.50	6.34	7.11	5.91
36	6.75	5.90	6.35	5.45
38	6.10	5.44	5.69	4.97
40	4.80	4.95	4.37	4.47
42	4.00	4.44	3.56	3.94
44	3.45	3.90	2.99	3.41
46	3.00	3.34	2.53	2.86
48	2.65	2.77	2.17	2.31

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.271 B_1 = -6.051 r = -0.9588
SE = 0.0508 I_o = 1.042

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.304 B_1 = -6.871 r = -0.9625
SE = 0.0549 I_o = 1.045

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.0766 B_1 = 0.9877 r = 0.9293
SE = 0.0881

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = -0.0841 B_1 = 1.0121 r = 0.9329
SE = 0.9208

TABLE V-8

(1)	Formulation number	:	SU-8
(2)	The amount used for in vitro test	:	10 cc
(3)	The total milliequivalents (TMEQ)	:	21.6
(4)	The normality of HCl (N)	:	0.100
(5)	The rate of addition of HCl (R)	:	4.0 cc/min
(6)	The time to reach maximum pH (TM)	:	3 min
(7)	Total number of observations	:	16
(8)	Area under the curve (AUC)	:	164.95 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
3	8.30	7.72	8.25	7.67
5	8.20	7.42	8.12	7.34
7	8.00	7.10	7.89	6.99
9	7.70	6.78	7.56	6.63
11	7.50	6.44	7.33	6.26
13	6.60	6.09	6.41	5.88
15	5.65	5.72	5.44	5.48
17	4.65	5.34	4.42	5.07
19	3.95	4.94	3.69	4.65
21	3.70	4.54	3.42	4.23
23	3.35	4.12	3.06	3.79
25	3.10	3.69	2.79	3.35
27	2.95	3.25	2.62	2.90
29	2.85	2.80	2.50	2.46
31	2.65	2.36	2.29	2.03
33	2.50	1.92	2.12	1.61

(a) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log pH (OBS)

Bo = 1.310 B_1 = -8.633 r = -0.9413

SE = -0.0688 I_o = 0.9110

(b) Correlation and regression coefficients for 1/(TMEQ-NxRxT) and log CpH

Bo = 1.359 B_1 = -9.685 r = -0.9493

SE = 0.0713 I_o = 0.9111

(c) Correlation and regression coefficients for pH (OBS) and pH (CALC)

Bo = 0.9784 B_1 = 0.7905 r = 0.9593

SE = 0.5426

(d) Correlation and regression coefficients for CpH (OBS) and CpH (CALC)

Bo = 0.8768 B_1 = 0.7995 r = 0.9659

SE = 0.5220

TABLE V-9

VALUES OF 1/TMEQ-NxRxT, (x) and LOG pH (OBS), (y)

Data From Table V-1		Table V-2		Table V-3		Table V-4	
X	Y	X	Y	X	Y	X	Y
0.0414	0.9405	0.0438	0.9319	0.0403	0.9444	0.0438	0.9370
0.0428	0.9405	0.0454	0.9294	0.0416	0.9444	0.0446	0.9355
0.0443	0.9395	0.0471	0.9268	0.0431	0.9434	0.0462	0.9355
0.0459	0.9395	0.0490	0.9216	0.0446	0.9395	0.0480	0.9355
0.0477	0.9370	0.0510	0.9138	0.0462	0.9395	0.0500	0.9242
0.0496	0.9344	0.0531	0.9030	0.0480	0.9395	0.0520	0.9190
0.0517	0.9344	0.0555	0.8920	0.0500	0.9370	0.0543	0.9164
0.0539	0.9319	0.0581	0.8750	0.0520	0.9370	0.0568	0.9111
0.0563	0.9294	0.0609	0.8228	0.0543	0.9344	0.0595	0.9084
0.0590	0.9268	0.0641	0.7781	0.0568	0.9294	0.0625	0.9003
0.0619	0.9242	0.0675	0.7075	0.0595	0.9268	0.0657	0.8864
0.0651	0.9138	0.0714	0.6283	0.0625	0.9190	0.0694	0.8129
0.0687	0.9030	0.0757	0.5797	0.0657	0.9138	0.0735	0.7781
0.0727	0.8864	0.0806	0.5250	0.0694	0.9030	0.0781	0.6989
0.0772	0.8260	0.0862	0.4698	0.0735	0.8864	0.0833	0.6283
0.0823	0.7558	0.0925	0.4313	0.0781	0.8293	0.0892	0.5965
0.0881	0.6766	0.1000	0.3979	0.0833	0.7588	0.0961	0.5563
(.0948	0.6232			0.0892	0.6334	0.1041	0.5185
(.1026	0.5502			0.0961	0.5622	0.1136	0.4771
(.1118	0.4913			0.1041	0.4913	0.1250	0.4393
(.1228	0.4313			0.1136	0.4232	0.1388	0.4065
(.1362	0.3979			0.1250	0.3979		

TABLE V-10

VALUES OF 1/TMEQ-NxRxT, (x) and LOG pH (OBS), (y)

Data from							
Table V-5		Table V-6		Table V-7		Table V-8	
X	Y	X	Y	X	Y	X	Y
0.0406	0.9420	0.0398	0.9405	0.0401	0.9420	0.0490	0.9190
0.0420	0.9420	0.0411	0.9395	0.0429	0.9420	0.0510	0.9138
0.043-	0.9420	0.0425	0.9344	0.0478	0.9420	0.0531	0.9030
0.0450	0.9420	0.0440	0.9344	0.0497	0.9395	0.0555	0.8864
0.0467	0.9395	0.0456	0.9294	0.0518	0.9395	0.0581	0.8750
0.0505	0.9370	0.0492	0.9268	0.0540	0.9395	0.0609	0.8195
0.0526	0.9344	0.0512	0.9190	0.0540	0.9395	0.0641	0.7520
0.0549	0.9344	0.0534	0.9138	0.0564	0.9370	0.0675	0.6674
0.0574	0.9294	0.0558	0.9084	0.0591	0.9344	0.0714	0.5965
0.0602	0.9242	0.0584	0.8750	0.0621	0.9319	0.0757	0.5682
0.0632	0.9190	0.0613	0.8061	0.0653	0.9242	0.0806	0.5250
0.0666	0.9138	0.0645	0.7160	0.0689	0.9084	0.0862	0.4913
0.0704	0.8976	0.0680	0.6434	0.0729	0.9030	0.0925	0.4698
0.0746	0.8512	0.0719	0.6020	0.0775	0.8750	0.1000	0.4548
0.0793	0.7745	0.0763	0.5502	0.0826	0.8293	0.1086	0.4232
0.0847	0.6901	0.0813	0.5185	0.0884	0.7853	0.1190	0.3979
0.0909	0.6127	0.0869	0.4913	0.0952	0.6812		
0.098C	0.5502	0.0934	0.4471	0.1030	0.6020		
0.1063	0.4913	0.1010	0.4232	0.1123	0.5378		
0.1162	0.4393	0.1098	0.3979	0.1234	0.4771		
0.1282	0.3979			0.1369	0.4232		