SECTION 2-f

PREPARATION AND EVALUATION OF GRANULES CONTAINING MAGNESIUM HYDROXIDE

INTRODUCTION:

An attempt is made to formulate controlled release antacid preparations in the form of granules. Literature review shows that little emphasis has been given to antacid products in granular form.

Long-lasting antacid preparations were prepared by coating granules (diameter 1 mm, length 2-3 mm) using solution of ethyl cellulose in dichloro methane-ethyl alcohol-acetone (6:2:2). The amount of ethyl cellulose in the granule was about 4%[216].

Sustained release preparation of magnesium trisilicate were prepared by EL-Samaligy[217] and others. They concluded that methocel, ethocel, and silicone oil retarded the antacid efficiency of magnesium trisilicate as a function of concentration. The order of retardation was silicone oil > ethaocel > methocel. The ethocel and silicone oil retarded the magnesium trisilicate activity too much while 2% methocel exhibited retardation suitable for sustained-release preparation.

A method to prepare granular, reactive, high purity magnesium hydroxide that does not disintegrate readily has been presented by Suehiro[218]. He prepared it by a two-

stage process. In the first stage crystalline magnesium hydroxide was prepared by adding seed crystals during precipitation and in the second stage additional gelatinous magnesium hydroxide was precipitated on crystal form to act as a binder during drying at > 200°.

It is thought that it will be easier to prepare antacid products, with controlled release properties, in solid dosage form and therefore it was decided to prepare antacids in granular form. The surface area exposed for solvent action will be very much lower with the granular product as compared to the surface area available in light and fluffy magnesium hydroxide present in powder form or in the suspension form. It is expected that the maximum pH, in the vitro test, will be lower with granular antacid products.

The neutralization power of magnesium hydroxide is high as compared to that of other conventional antacids and so it was selected for formulating controlled release preparation.

The main advantages of this type of product are as follows:

(i) The process of manufacture is simple and it does not require any special equipments.

(2) Reproducible results can be easily obtained.

(3) Antacid products free of sodium, saccharin, and hexitols can be formulated. It has been reported[219] that long term use of hexitols, specifically sorbitol requires further study before it can be recommended. The problems with diabetes and caries are mentioned in the report.

(4) Magnesium hydroxide is stable at higher temperature and so the total milliequivalents of dried products will not change after drying granules, while the activity of aluminium hydroxide will be adversely affected after drying.

(5) The final product is in dry form and so its stability will be better as compared to that of liquid products.

EXPERIMENTAL

(A) Preparation of binder solution:

(1) Polyvinylpyrrolidone - 3% w/v

Three grams of polyvinylpyrrolidone was dissolved in 100 cc of distilled water by stirring on a magnetic stirrer.

(2) (a) Tragacanth - 3% w/v.

(b) Sodium salt of carboxymethyl cellulose - 0.5% w/v

(c) Ispaghula (dispersible grade) - 1% w/v

Dispersible grade of ispaghula was first prepared by a procedure reported in the chapter of aqueous suspensions containing magnesium hydroxide.

Accurately weighed tragacanth, sodium salt of carboxymethyl cellulose and ispaghula were separately wetted with sufficient quantity of glycerin in 250-cc beakers. Distilled water, in sufficient quantity, was added to the mixture while stirring and the dispersions were set aside for about 12 hours. The dispersions were individually stirred on a magnetic stirrer, at moderate speed, to yeild uniform products.

(3) Hydroxypropylmethylcellulose - 0.1% w/v

Hundred mg of hydroxypropylmethylcellulose was first wetted with sufficient quantity of PEG 400 and then 100 cc

of cold distilled water was slowly added while stirring. The dispersion was then heated to 80° on a water-bath cum magnetic stirrer while stirring at moderate speed. The mixture was stirred till homogenous and then gradually cooled to 40° while stirring.

(4) Starch paste - 5% w/v

Nine grams of starch powder was transferred to a 250-cc beaker containing 20-cc of cold distilled water. The mixture was stirred well with a glass rod until a uniform suspension without lumps was formed.

One hundred sixty cc of cold distilled water was transferred to a 500-cc beaker and heated until started boiling. The beaker was removed from fire and the starch suspension was added to the boiling water and stirred vigorously with a glass rod till gel became translucent.

(5) Cellulose acetate 2.8% w/v and PEG 400 1.2% w/v

Accurately weighed cellulose acetate and PEG 400 were dissolved in a blend of dichloromethane and methanol (8:2) by overnight soaking. The mixture was stirred with a glass rod till homogenous. The volume was adjusted to 100 cc by adding sufficient quantity of a blend of solvents.

(6) Ethyl cellulose - 4% w/v

Four grams of ethyl cellulose was dissolved in 100 cc of chloroform by stirring on a water bath. The final volume was adjusted to 100 cc when the solution was complete.

(B) Preparation of the granules:

Sufficient quantity of granulating agent was added to magnesium hydroxide powder (160 mesh), contained in a stainless steel pan, to prepare a coherent mass of suitable consistency for granulation. The wet mass was then passed through a No. 20 mesh hand screen onto a piece of paper. The wet granules were dried in a forced-air drying oven at 55°. The dried granules were shifted through a No. 20 mesh screen and the fraction retained on a No. 36 mesh screen was used for evaluation.

The amount of binder solution required per 10 gm of magnesium hydroxide powderis as follows:

Formulation No. G1	:	13.5 cc of PVP solution.
Formulation No. G2	:	15.0 cc of tragacanth dispersion.
Formulation No. G3	:	15.0 cc of sodium carboxymethyl cellulose solution.
Formulation No. G4	:	14.0 cc of ispaghula dispersion.
Formulation No. G5	:	14.0 cc of hydroxypropylmethyl-cellulose solution.

Formulation No. G6 : 20 cc of starch paste.

Formulation No. G7 : 14 cc of cellulose acetate and PEG 400 solution.

Formulation No. G8 : 12 cc of ethyl cellulose solution.

The modified acid-consuming capacity test (to find total milliequivalents of HCl neutralized by one dose) and the Rossett-Rice test were performed as reported in the chapter of aqueous suspension containing magnesium hydroxide.

RESULTS AND DISCUSSION

The maximum value of pH (OBS) in the Rossett-Rice test ranged from 2.5 to 4.0 in the case of granules containing magnesium hydroxide. Earlier it has been noted that the maximum value of pH (OBS) was greater than 8.5 in most of the aqueous magnesium hydroxide suspensions.

Acid rebound is a major disadvantage of aqueous magnesium hydroxide suspension because the pH (OBS) was on the alkaline side in the in vitro test. It is expected from the pH (OBS) range observed in the in vitro test that there would not be any acid rebound if the granular preparations containing magnesium hydroxide were consumed.

The values of maximum pH reached and the pH (OBS) -time profile are tabulated in Tables VI-1 to VI-8 for different granular preparations containing magnesium hydroxide. The first reading of pH (OBS) is the maximum pH reached in the in vitro test.

The maximum pH (OBS) in the granules containing ethyl cellulose was only 2.5 in the in vitro test and so the Rossett-Rice time (the time during which the pH was maintained above 2.5 in the test) is equal to zero minute. Thus it is concluded that the release of magnesium hydroxide was

retarded to a great extent. The pH (OBS) was 2.5 at the end of 10th minute. The experiment was continued to see any further release of antacid material in the next 26 minutes. The pH (OBS)-time profile is recorded in the TableVI-8. The addition of HCl was stopped at the end of 36th minute but the stirring was continued for another 24 minutes. The pH (OBS) was 4.4 at the end of 60th minute. Twelve cc of 0.1N HCl was required to bring down the pH to 2.5. An ideal antacid is one which buffer the artificial gastric juice at about pH 3.5. It can be concluded that the concentration of ethyl cellulose seems to be unsuitable for formulating an ideal antacid.

The maximum pH (OBS), reached in the in vitro test, in the case of granules containing cellulose acetate and PEG 400 was 2.75, the Rossett-Rice time was 31 minutes, and the area under the curve (AUC) of time in minutes versus pH (OBS) was 83.7 min x pH. The addition of 0.1N HCl was stopped when the pH (OBS) returned to 2.5 (36th minute) and then the mixture was stirred for another 24 minutes. The pH (OBS) raised to 3.1 at the end of 60th minute and 8 cc of 0.1N HCl was required to bring down the pH (OBS) to 2.5. It is thus concluded that very little extra magnesium hydroxide was released after 36th minute. There is definite retardation in the release of magnesium hydroxide, but it is not as great as ethyl cellulose.

The maximum pH (OBS) was far less than 3.5 and so it is also not an ideal preparation.

The maximum pH (OBS) reached in the Rossett-Rice test was 2.95, the Rossett-Rice time was 24 minutes, and the AUC was 63.5, in the case of granules containing ispaghula. The preparation was stirred for total one hour like previous formulations. Twenty cc of 0.1N HCl was required to bring down the pH to 2.5. The result indicates that part of the magnesium hydroxide was not released during 60 minutes.

It is concluded from the values of maximum pH (OBS) reached in the in vitro test that ethyl cellulose, cellulose acetate, and ispaghula are unsuitable for formulating an ideal, controlled release antacid formulation at the concentration levels used.

The maximum values of pH (OBS) reached in the in vitro test were 4.2, 3.6 and 4.0, the Rossett-Rice times were 43, 44, and 48 minutes, and the AUC were 136, 120, and 150 respectively with the granules prepared using polyvinyl-pyrrolidone, tragacanth and CMCNa respectively. The addition of 0.1 N HCl was stopped when the pH (OBS) returned to 2.5 i.e. after 43, 44, and 48 minutes respectively with granules containing polyvinylpyrrolidone, tragacanth, and CMCNa. The

mixtures were stirred for total one hour and then 0.1 N HCl was added to bring down the pH to 2.5. Amount of HCl required were 12, 12 and zero cc respectively with polyvinylpyrrolidone, tragacanth, and CMCNa. It is concluded that all the three preparations satisfies ideal requirements of antacids. All the magnesium hydroxide was released within first 48 minutes in the case of granules containing CMCNa, while in the case of granules containing polyvinylpyrrolidone and tragacanth all the magnesium hydroxide was released within 60 minutes in the in vitro test. The chances of acid rebound with these preparations are minimum because the maximum pH (OBS) is on the acidic side during neutralization of HCl by antacid material. It seems that these three substances are suitable for formulating controlled release antacid preparations in granular form.

The equations proposed in the chapter of aqueous suspensions containing magnesium hydroxide were used to calculate the calculated and corrected values of pH for the products in granular form. The computer programme was also used to perform linear regression between 1/TMEQ-NxRxT and log pH (OBS), 1/TMEQ-NxRxT and log pH (corrected), pH (OBS) and pH (CALC), and corrected observed pH and corrected calculated pH. The results obtained from computer output are tabulated in Tables VI-1 to VI-10.

The values of correlation coefficient between 1/TMEQ-NxRxT and log pH (OBS) ranged from 0.969 to 0.984. The values of 1/TMEQ-NxRxT and log pH (OBS) are tabulated in Tables VI-9 and VI-10 for all the products studied. It is concluded from the values of correlation coefficient that a near linear relationship exist between 1/TMEQ-NxRxT and log pH (OBS). The time required to reach pH 2.5 or 2.0 can be easily found out if the Rossett-Rice test is terminated earlier at about pH 3.0.

The values of correlation coefficient between 1/TMEQ-NXRxT and log pH (corrected) ranged from 0.979 to 0.991. The results appear in Tables VI-1 to VI-7.

The values of correlation coefficient between the pH (OBS) and pH (CALC) ranged from 0.967 to 0.985. It is concluded that the proposed equation can be used to calculate the values of pH with good confidence. It is possible to calculate the time at which the pH will be 2.5 or 2.0 in the in vitro test if the test is terminated earlier.

The values of correlation coefficient between corrected observed pH and corrected calculated pH ranged from 0.973 to 0.993. The results appear in Tables VI-1 to VI-7.

The advantages and the applications of equation proposed in the chapter of aqueous suspension containing magnesium hydroxide are also applicable to the granular preparations containing magnesium hydroxide. In addition to that, these preparations will help in preventing acid rebound in the stomach because the values of maximum pH (OBS) in the in vitro test were less than 4.2.

The pH (OBS) was controlled in these preparations may be because the magnesium hydroxide was gradually released from the surface of granules throughout the in vitro test, as the granules does not contain any disintegrating agent. The release of magnesium hydroxide can be further retarded by compressing the granules into tablet.

TABLE VI-1

(1)	Formulation number	:	G 1
(2)	The amount used for in vitro test	:	850 mg
(3)	The total milliequivalents (TMEQ)	:	27.00
(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)	:	5 min
(7)	Total number of observations	:	20
(8)	Area under the curve (AUC)	:	135.86 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
5	4.20	3.88	4.12	3.74
7	3.90	3.84	3.79	3.68
9	3.90	3.80	3.76	3.63
11	3.90	3.76	3.73	3.57
13	3.80	3.71	3.61	3.51
15	3.60	3.66	3.39	3.45
17	3.45	3.60	3.22	3.38
19	3.45	3.55	3.19	3.31
21	3.40	3.49	3.12	3.23
23	3.35	3.42	3.06	3.15
25	3.30	3.35	2.99	3.06
27	3.20	3.28	2.87	2.97
29	3.10	3.20	2.75	2.87
31	3.00	3.11	2.64	2.76
33	2.95	3.01	2.57	2.65
35	2.90	2.91	2.51	2.53
37	2.85	2.80	2.44	2.39
39	2.70	2.68	2.28	2.25
41	2.58	2.54	2.14	2.10
43	2.50	2.39	2.05	1.93

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

Bo = 0.7242 B_1 = -3.380 r = -0.9766

SE = 0.0141 I_o = 0.5990

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

Bo = 0.7567 B_1 = -4.607 r = -0.9797

SE = 0.0179 I_o = 0.5861

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

Bo = 0.2859 B_1 = 0.9126 r = 0.9727

SE = 0.1080

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

Bo = 0.2750 B_1 = 0.9073 r = 0.9755

SE = 0.1248

TABLE VI-2

(1)	Formulation number	:	G 2
(2)	The amount used for in vitro test	:	850 mg
(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)	:	11 min
(7)	Total number of observations	:	17
(8)	Area under the curve (AUC)	:	119.94 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
11	3.60	3.56	3.43	3.36
13	3.60	3.53	3.41	3.31
15	3.55	3.49	3.34	3.26
17	3.50	3.45	3.27	3.21
19	3.45	3.41	3.19	3.15
21	3.40	3.36	3.12	3.09
23	3.30	3.31	3.01	3.03
25	3.25	3.25	2.94	2.96
27	3.10	3.19	2.77	2.88
29	3.00	3.13	2.65	2.80
31	3.00	3.06	2.64	2.71
33	2.95	2.98	2.57	2.61
35	2.85	2.89	2.46	2.51
37	2.75	2.80	2.34	2.40
39	2.70	2.69	2.28	2.27
41	2.60	2.57	2.16	2.13
43	2.54	2.44	2.09	1.98

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

Bo = 0.6649 B_1 = -2.4411 r = -0.9846

SE = 0.0091 I_o = 0.5710

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

Bo = 0.6835 B_1 = -3.405 r = -0.9854

SE = 0.0124 I_o = 0.5525

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

Bo = 0.1580 B_1 = 0.9491 r = 0.9855

SE = 0.0607

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

Bo = 0.1618 B_1 = 0.9416 r = 0.9864

SE = 0.0723

TABLE VI-3

(1) Formulation number : G 3
(2) The amount used for in vitro test : 850 mg
(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) : 5 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 150.04 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
5	4.00	3.79	3.92	3.62
7	3.80	3.76	3.69	3.59
9	4.00	3.74	3.86	3.55
11	3.75	3.71	3.58	3.51
13	3.65	3.68	3.46	3.47
15	3.65	3.65	3.44	3.43
17	3.55	3.62	3.32	3.39
19	3.50	3.58	3.24	3.34
21	3.40	3.54	3.12	3.29
23	3.38	3.50	3.09	3.23
25	3.38	3.45	3.07	3.17
27	3.38	3.40	3.05	3.10
29	3.30	3.35	2.95	3.03
31	3.30	3.29	2.94	2.96
33	3.15	3.22	2.77	2.87
35	3.12	3.15	2.73	2.78
37	3.10	3.07	2.69	2.68
39	3.00	2.98	2.58	2.57
41	2.90	2.88	2.46	2.45
43	2.80	2.77	2.35	2.31
45	2.65	2.64	2.19	2.16
47	2.52	2.49	2.05	1.99

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

Bo = 0.6620 B_1 = -2.047 r =-0.9794
SE = 0.0111 I_o = 0.5848

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

Bo = 0.6781 B_1 = -2.925 r = -0.9806
SE = 0.0154 I_o = 0.5678

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

Bo = 0.2328 B_1 = 0.9297 r = 0.9736
SE = 0.0899

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

Bo = 0.2508 B_1 = 0.9161 r = 0.9739
SE = 0.1135

TABLE VI-4

(1)	Formulation number	:	G 4
(2)	The amount used for in vitro test	:	800 mg
(3)	The total milliequivalents (TMEQ)	:	23.48
(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)	:	9 min
(7)	Total number of observations	:	10
(8)	Area under the curve (AUC)	:	63.52 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
9	2.95	3.00	2.81	2.85
11	2.95	2.96	2.78	2.79
13	2.95	2.92	2.76	2.73
15	2.95	2.88	2.74	2.67
17	2.80	2.83	2.57	2.60
19	2.80	2.78	2.54	2.53
21	2.70	2.72	2.42	2.45
23	2.65	2.66	2.36	2.36
25	2.60	2.59	2.29	2.27
27	2.50	2.51	2.17	2.18

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

Bo = 0.6134 B_1 = -2.7003 r = -0.9795

SE = 0.0056 I_o = 0.4984

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

Bo = 0.6616 B_1 = -4.108 r = -0.9911

SE = 0.0055 I_o = 0.4865

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

Bo = 0.1114 B_1 = 0.9599 r = 0.9772

SE = 0.0368

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

Bo = 0.0448 B_1 = 0.9823 r = 0.9899

SE = 0.0340

TABLE VI-5

(1)	Formulation number	:	G 5
(2)	The amount used for in vitro test	:	800 mg
(3)	The total milliequivalents (TMEQ)	:	22.84
(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)	:	11 min
(7)	Total number of observations	:	14
(8)	Area under the curve (AUC)	:	93.05 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS))	CpH (CALC)
11	3.10	3.15	2.93	2.95
13	3.10	3.13	2.91	2.92
15	3.05	3.10	2.84	2.88
17	3.05	3.07	2.82	2.84
19	3.05	3.04	2.79	2.79
21	3.05	3.01	2.77	2.75
23	3.00	2.97	2.71	2.70
25	2.95	2.93	2.64	2.64
27	2.90	2.89	2.57	2.57
29	2.90	2.84	2.55	2.50
31	2.85	2.78	2.49	2.42
33	2.70	2.71	2.32	2.33
35	2.60	2.64	2.21	2.23
37	2.50	2.55	2.09	2.12

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

Bo = 0.5690 B_1 = -1.309 r = -0.9771

SE = 0.0065 I_o = 0.5117

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

Bo = 0.5809 B_1 = -2.051 r = -0.9936

SE = 0.0053 I_o = 0.4911

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

Bo = 0.08911 B_1 = 0.9693 r = 0.9763

SE = 0.04256

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

Bo = 0.00631 B_1 = 0.9975 r = 0.9936

SE = 0.0308

TABLE VI-6

(1)	Formulation number	: G 6
(2)	The amount used for in vitro test	: 800 mg
(3)	The total milliequivalents (TMEQ)	: 25.00
(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)	: 6 min
(7)	Total number of observations	: 14
(8)	Area under the curve (AUC)	: 82.23 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
6	3.30	3.20	3.20	3.07
7	3.25	3.18	3.14	3.05
9	3.20	3.14	3.06	2.99
11	3.10	3.10	2.93	2.94
13	3.00	3.06	2.81	2.88
15	2.90	3.02	2.69	2.81
17	2.87	2.97	2.64	2.74
19	2.87	2.91	2.61	2.67
21	2.87	2.86	2.59	2.59
23	2.82	2.80	2.53	2.51
25	2.76	2.73	2.45	2.42
27	2.66	2.66	2.33	2.33
29	2.60	2.58	2.25	2.23
31	2.51	2.49	2.15	2.12

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

Bo = 0.6412 B_1 = -3.077 r =-0.9699

SE = 0.0090 I_o = 0.5181

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

Bo = 0.6917 B_1 = -4.609 r = -0.9789

SE = 1.132 I_o = 0.5073

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

Bo = 0.2284 B_1 = 0.9211 r = 0.9673

SE = 0.0603

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

Bo = 0.1831 B_1 = 0.9310 r = 0.9760

TABLE VI-7

(1)	Formulation number	:	G 7
(2)	The amount used for in vitro test	:	800 mg
(3)	The total milliequivalents (TMEQ)	:	24.8
(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)	:	7 min
(7)	Total number of observations	:	15
(8)	Area under the curve (AUC)	:	83.7 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
7	2.72	2.73	2.61	2.58
9	2.72	2.72	2.58	2.56
11	2.72	2.71	2.55	2.54
13	2.72	2.71	2.53	2.51
15	2.70	2.70	2.49	2.49
17	2.70	2.68	2.47	2.46
19	2.65	2.67	2.39	2.44
21	2.65	2.66	2.37	2.41
23	2.65	2.65	2.36	2.37
25	2.62	2.63	2.31	2.34
27	2.60	2.61	2.27	2.30
29	2.60	2.59	2.25	2.25
31	2.60	2.57	2.24	2.21
33	2.55	2.55	2.17	2.15
35	2.50	2.52	2.11	2.09

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

Bo = 0.4704 B_1 = -0.7495 r = -0.9787

SE = 0.0024 I_o = 0.4402

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

Bo = 0.4976 B_1 = -1.907 r= -0.9877

SE = 0.0046 I_o = 0. 4207

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

Bo = 0.1096 B_1 = 0.9585 r = 0.9784

SE = 0.0143

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

Bo = 0.0819 B_1 = 0.9654 r = 0.9876

SE = 0.02463

TABLE VI-8

(1)	Formulation number	:	G8
(2)	The amount used for in vitro test	:	850 mg
(3)	The total milliequivalents (TMEQ)	:	25.3
(4)	The normality of HCl (N)	:	0.100
(5)	The rate of addition HCl (R)	:	4.0 cc/min
(6)	The time to reach maximum pH (TM)	:	11 min
(7)	Total number of observations	:	8

Time (min)	pH (OBS)
11	2.50
14	2.45
17	2.42
20	2.42
23	2.41
26	2.40
29	2.36
32	2.32

TABLE VI-9

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

Data from							
Table VI-1		Table VI-2		Table VI-3		Table VI-4	
X	Y	X	Y	X	Y	X	Y
0.0400	0.6232	0.0462	0.5563	0.0408	0.6020	0.0442	0.5185
0.0413	0.5910	0.0480	0.5563	0.0421	0.5797	0.0450	0.5118
0.0427	0.5910	0.0500	0.5502	0.0436	0.6020	0.0467	0.5051
0.0442	0.5910	0.0520	0.5440	0.0452	0.5740	0.0485	0.4913
0.0458	0.5797	0.0543	0.5378	0.0469	0.5622	0.0505	0.4771
0.0476	0.5563	0.0568	0.5314	0.0487	0.5622	0.0526	0.4623
0.0495	0.5378	0.0595	0.5185	0.0506	0.5502	0.0549	0.4578
0.0515	0.5378	0.0625	0.5118	0.0529	0.5440	0.0574	0.4578
0.0537	0.5314	0.0657	0.4913	0.0552	0.5314	0.0602	0.4578
0.0561	0.5250	0.0694	0.4771	0.0578	0.5289	0.0632	0.4502
0.0588	0.5185	0.0735	0.4771	0.0606	0.5289	0.0666	0.4409
0.0617	0.5051	0.0781	0.4698	0.0636	0.5289	0.0704	0.4248
0.0649	0.4913	0.0833	0.4548	0.0671	0.5185	0.0746	0.4149
0.0684	0.4771	0.0892	0.4393	0.0709	0.5185	0.0793	0.3996
0.0724	0.4698	0.0961	0.4313	0.0751	0.4983		
0.0769	0.4623	0.1041	0.4149	0.0800	0.4941		
0.0819	0.4548	0.1136	0.4048	0.0854	0.4913		
0.0877	0.4313			0.0917	0.4771		
0.0943	0.4116			0.0990	0.4623		
0.1020	0.3979			0.1075	0.4471		
				0.1176	0.4232		
				0.1298	0.4014		

TABLE VI-10

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

Data from					
Table VI-5		Table VI-6		Table VI-7	
X	Y	X	Y	X	Y
0.0542	0.4913	0.0453	0.4345	0.0503	0.4698
0.0566	0.4913	0.0471	0.4345	0.0524	0.4698
0.0593	0.4842	0.0490	0.4345	0.0547	0.4698
0.0623	0.4842	0.0510	0.4345	0.0572	0.4698
0.0656	0.4842	0.0531	0.4313	0.0599	0.4471
0.0692	0.4842	0.0555	0.4313	0.0629	0.4471
0.0733	0.4771	0.0581	0.4232	0.0663	0.4313
0.0778	0.4698	0.0641	0.4232	0.0700	0.4232
0.0830	0.4623	0.0675	0.4183	0.0741	0.4149
0.0889	0.4623	0.0714	0.4149	0.0788	0.3979
0.0957	0.4548	0.0806	0.4149		
0.1037	0.4313	0.0862	0.4065		
0.1131	0.4149	0.0925	0.3979		
0.1243	0.3979				