SECTION II-g

TESTING EFFICIENCY OF ANTACIDS IN THE PRESENCE OF SELECTED DRUGS

INTRODUCTION:

(A) Drugs Used Along with Antacids:

Drug therapy used in medically treated hospitalized patients suffering from duodenal ulcer disease has been reviewed by Roberts[220] and others. The information was obtained by the means of a medical audit of patient records indexed by the discharged diagnosis of duodenal ulcers. A total of 485 cases were abstracted.

The therapy consisted of a combination of drugs usually five or six per case. The most frequently used drugs were antacids, prescribed for 78.4% of the cases. Almost 70% of the patients received anticholinergics; analgesics-antipyretics, and sedatives were ordered for almost two-thirds of the sample. Tranquillizers and vitamins were prescribed for about 40% and 10% of the patients respectively. A number of gastrointestinal drugs, excluding antacids, were also prescribed.

It has been reported[87] that blood serum levels of vitamins A,B,B_2,B_6,C,D, nicotinic acid, and carotene were lower, and of vitamin B_{12}, and E were somewhat lower in ulcer patients. Multivitamin supplements were thus recommended during ulcer therapy.

It has also been noted that the incidence of ulcer was reduced by giving the rat intramuscular injections of a water-soluble vitamin A[88].

(B) Antacid Used with Drugs (Possibly Ulcerogenic):

The frequent association between peptic ulcer and treatment with certain drugs has given the impression that some drugs increase the incidence of peptic ulcer and associated dyspepsia in men.

It has now-a-days become a routine practice for many physicians to prescribe antacids when some of the drugs, possibly ulcerogenic, are prescribed.

All the Analgesics mentioned below are inhibitor of prostaglandin synthesis. As prostaglandins are involved in the control of gastric acid secretion, and regulate protective mechanisms in the gastric mucosa, interference with prostaglandin synthesis is a putative mechanism for the gastric effect of analgesics[221]. No member of this group of drugs seems immune from effects on the stomach. The best documented evidence relates to drugs which have been in longest use like aspirin, indomethacin, phenyl butazone and oxyphenbutazone. Work on these drugs has been reviewed by Davies[35].

Colchicine, sodium aminosalicylate (PAS), tolbutamide, and caffiene, as well as ethanol, have all been shown in experimental animals to reduce mucosal resistence to ulceration and to increase acid secretion. Theophylline and its derivatives, and reserpine may cause dyspepsia[222]. Ulceration of the small intestine is now well recognized as an adverse effect of enteric-coated potassium chloride preparations[223]. Localized ulceration may occur when the drugs remain in the oesophagus for longer than usual after being swallowed. Potassium preparations may cause oesophageal ulceration in this way, as may tetracycline[224] or clindamycin[225].

Adverse effect of following drugs in gastrointestinal tract has been reviewed by Scherer[22].

Generic Name	Adverse effect	Page No.
1. dipyridamole	GI distress	82
2. Pentaerythritol tetranitrate	"	83
3. Cyclandelate	"	83
4. Nicotinyl alcohol	GI disturbance	83
5. Bendroflumethiazide	Gastric irritation	97
6. Benzthiazide	"	97

Generic Name	Adverse effect	Page No.
7. Nadolol	GI disturbances	99
8. Amphetamines	"	104
9. Sulfamethoxazole	"	115
10. Sulfisoxazole	"	115
11. Sulfamethizole	"	115
12. Sulfacytine	"	115
13. Sodium nafcillin	oral route GI disturbance	126
14. Cephalosporins	GI bleeding	128
15. Isoniazid	GI distress	135
16. Rifampin	"	135
17. Pyrantel pamoate	GI disturbances	142
18. Floxuridine	GI hemorrhage	181
19. Methotrexate	GI ulcerations & bleeding	182
20. Biperiden	Gastric distress	196
21. Psychotherapeutic agents	GI disturbances	206-209
22. Niacin	Activation of peptic ulcer	241
23. Ibuprofen	GI distress	270
24. Fenoprofen calcium	"	270
25. Naproxen	GI bleeding	271

Alterations in Bioavailability of Drugs due to Coadministered Antacids:

The pH at the absorption site is an important factor in drug absorption because many drugs are either weak organic acids or weak bases. In solution, organic electrolytes exists in a non-ionized (usually lipid-soluble) and an ionized (usually poorly lipid-soluble) form. The fraction of each species depends on the pH of the solution. Since the gastrointestinal barrier is much more permeable to uncharged lipid-soluble solutes, the absorption of weakly basic drugs such as antihistamines and antidepressant is favoured in the small intestine (alkaline pH) where drug exists largely in a non-ionized form. On the other hand, acidic gastric fluids tend to retard the absorption of weak bases but promote the absorption of weakly acidic drugs such as sulfonamides and non-steroidal anti-inflammatories.

Changes in the pH of the fluids in a given segment of tract may improve or impede the absorption of drugs. The bioavailability of a drug may change when administered with an antacid[226].

Any chemical change due to pH, complexation and enzymatic action that reduces the bioavailability of the drug should be prevented or minimized[227].

Tablet coatings sensitive to changes in pH (enteric coating) may be prematurely disintegrated or dissolved if the drug product is taken concurrently with antacids. Bisacodyl (Dulcolax^{R}) has an enteric coating which is dissolved by antacids, releasing the very irritating laxative drug in the stomach and causing irritation and nausea[228].

Regular administration of certain antacids can increase urine pH sufficiently to have pronounced effect on the kinetics of elimination of certain acidic and basic drugs[229].

Drugs, such as antacids that can alter gastric and intestinal pH, have complex and unpredictable effects on the absorption of other drugs. Antacids not only alter gastro intestinal pH but also chelates drugs (tetracyclines plus divalent-cation antacids)[230], precipitate drugs (ferrous sulphate plus calcium carbonate), or inhibit gastric emptying (aluminium hydroxide gel and phenobarbital and isoniazid)[231]. Examples of the effects of antacids on drug absorption are summarized in Table A.

TABLE A : Effects of antacids on absorption of some other drugs

Drug	Antacid type	Effect on absorption	Clinically important
Aminophylline	Mg-Al	Rate(not extent)	No
Atropine and hyoscine	Mg	Extent	Possibly
Chlordiazepoxide	Mg	Rate(not extent)	No
Clorazepate	Mg	Extent[a]	Yes
Cimetidine	Mg	Extent	Possibly[b]
Diazepam	Mg-Al	Rate(not extent)	No
Diflunisal	Al	Extent	Yes
Digoxin	Mg-Al	Extent	Uncertain
Indomethacin	Mg-Al	Extent	?
Levodopa	Mg-Al	Extent	?
Isoniazid	Al	Peak level	?
Nitrofurantoin	Mg	Peak level	?
Oral contraceptives	Mg	Adsorbed in vitro	?
Phenothiazines	Mg-Al	Adsorbed in vitro	?
Tetracyclines	Al	Adsorbed in vitro	Yes
Warfarin	Mg	Adsorbed in vitro	Yes

[a] Activity of drug depends on liberation of desmethyldiazepam in the acidic conditions of the gastric contents.

[b] Variable effects from person to person.

Ref. No. 232

Literature review shows that the absorption of following drugs is also adversely affected by the concomitantly administered antacids : Trimethoprim[233], Penicillin G[233], Nalidixic acid[17], Nitrofurantoin[234], chlorpromazine[235], Sulphadiazine sodium[236], quinine[236], Sodium pentobarbital[236], and Iron-salts[237].

It is concluded that the bioavailability of many drugs is altered in the presence of antacids. The effects on the neutralization of antacids in presence of drugs are not very well documented. It was therefore decided to study any changes in the neutralization behaviour of aqueous magnesium hydroxide suspension when concomitantly used with other drugs. Drugs, which are most often used, were selected for this study,viz: tranquillizer (diazepam), hypotensive drug (propanolol), Analgesic (dexamethasone), Vitamin (vitamin A tablet), Antibiotic (chloramphenicol), Analgesic and antipyretic (soluble aspirin), and Antituberculous drug (ethambutol).

EXPERIMENTAL

Magnesium hydroxide powder was prepared from light magnesium oxide by a method reported in the chapter of aqueous magnesium hydroxide suspensions.

Forty grams of magnesium hydroxide powder (160 mesh) was slowly added to a 1000-cc beaker containing about 200-cc of distilled water. It was then stirred with a glass rod till an uniform dispersion resulted. About 300 cc of distilled water was gradually added to the dispersion while stirring with a glass rod. The aqueous magnesium hydroxide suspension was then repeatedly passed through a homogenizer. The final volume was adjusted with the sufficient quantity of distilled water and the suspension was stirred till it became uniform.

The modified acid-consuming capacity test and the Rossett-Rice test were performed as reported in the chapter of aqueous magnesium hydroxide suspensions. The rate of addition of 0.1 N HCl was kept at 4.0 cc/min because it simulates vivo conditions. Ten cc of suspensions were used in the Rossett-Rice test.

Drugs used along with the magnesium hydroxide suspension in the modified acid-consuming capacity test and Rossett-Rice test were as follows:

(a) Sample No. FD-1 : Aqueous $Mg(OH)_2$ suspension 8% w/v (P)

(b) Sample No. FD-2 : P + Diazepam (5mg) tablet.

(c) Sample No. FD-3 : P + Propanolol (40mg) tablet.

(d) Sample No. FD-4 : P + Dexamethazone (0.5mg) tablet.

(e) Sample No. FD-5 : P + Vitamin A (50,000 i.u.) tablet.

(f) Sample No. FD-6 : P + Chloramphenicol (250 mg) dragee.

(g) Sample No. FD-7 : P + Soluble aspirin (500 mg) tablet.

(h) Sample No. FD-8 : P + Ethambutol (800 mg) tablet.

Following procedure was used for the addition of drug into water and HCl mixture used in the Rossett-Rice test.

The tablets were first powdered in a glass mortar and then passed through a 120 mesh hand screen. Fine powder was then transferred to a 50-cc beaker and 2 cc of ethanol was added to wet all the particles. It was followed by the addition of 20 cc of distilled water. The dispersion was then transferred to a 400-cc beaker containing 70 cc of 0.1N HCl. The 50-cc beaker was rinsed with 5 cc of distilled water and the contents were transferred to the beaker containing HCl. It was then stirred for 2 minutes on a magnetic stirrer. The Rossett-Rice test was then continued as reported in the chapter of aqueous magnesium hydroxide suspension. The pH (OBS) -Time profile for different samples appears in Tables VII-1 to VII-8.

RESULTS AND DISCUSSION

Aqueous magnesium hydroxide suspension containing only $Mg(OH)_2$ and distilled water was used to see any change in the neutralization pattern of antacid suspension when combined with other drugs. In this case a change, if at all there is any, in the neutralization pattern will be solely due to drug-antacid combination and not due to any other reason like antacid-adjuvant combination.

There is no appreciable change in the value of Rossett-Rice time (the time for which the pH was maintained above 2.5 in the test), when selected drugs were combined and tested with aqueous magnesium hydroxide suspension.

The pH (OBS) was 4.0 in the in vitro test at 37, 36, 38, 33, 34, 34, 40, and 42 minutes respectively with sample numbers FD-1 to FD-8. The times at which pH (OBS) returned to 2.5 were 51 and 49 minutes respectively with FD-7 and FD-8. The change in pH (OBS) was sudden in the case of FD-8 while it was gradual in the case of FD-7 especially in the later stages of the in vitro test. This behaviour might be due to the buffering action provided by soluble aspirin tablet.

The maximum value of pH (OBS) reached in the Rossett -Rice test were nearly the same however the change in pH(OBS)

with respect to the time, in the in vitro test, was different in different drug-antacid combination. This is reflected into the values of area under the curve of time in minutes versus pH (OBS).

The AUC was calculated by using a programme, written for a programmable calculator, mentioned in the chapter of aqueous magnesium hydroxide suspensions. There is no appreciable change in the values of AUC in the sample numbers 2,3,7, and 8 while there was slight decrease in the values of AUC for the sample numbers FD-4 to 6 as compared to the value of AUC of plain magnesium hydroxide suepension (FD-1). pH (OBS) remained above 2.5, in the in vitro test, for 47 minutes in the case of sample numbers FD-4 to 6 and it remained above 2.5 for 49 minutes for FD-1.

It is thus concluded that there is no appreciable change in the neutralization capacity of aqueous magnesium hydroxide suspension when combined with selected drugs.

It is not advisable to administer drugs along with antacid materials because it has been reported that there is serious alterations in the biological availability of drugs when concomitantly given with antacids. It is thus pharmacist's duty to fix the dosage regimen so that there is a difference of 2 hours between the administration of the

drug and the antacid to avert any change in the biological availability of drugs generally administered along with antacids in peptic ulcer patients.

The equations proposed in the chapter of aqueous magnesium hydroxide suspensions were used to calculate the calculated and the corrected values of pH. The linear regression was performed between:

(1) 1/TMEQ-NxRxT and log pH (OBS)

(2) 1/TMEQ-NxRxT and log pH (CALC)

(3) pH (OBS) and pH (CALC), and

(4) Corrected observed pH and corrected calculated pH by the use of a computer programme mentioned in the chapter of aqueous magnesium hydroxide suspensions.

The results for FD-1 to FD-8 are mentioned in Tables VII-1 to VII-8. The values of 1/TMEQ-NxRxT and log pH (OBS) for all the samples are tabulated in Tables VII-9 and VII-10.

The results indicate that there is good correlation especially between 1/TMEQ-NxRxT and log pH (OBS), and pH (OBS) and pH (CALC). The advantages and applications of equations mentioned in the chapter of aqueous magnesium hydroxide suspensions are also applicable even when some other drugs are combined with the antacid suspension in the in vitro test.

TABLE VII-1

(1) Formulation number : FD-1
(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) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 301.65 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.55	8.88	8.53	8.84
2	8.55	8.81	8.51	8.76
4	8.50	8.65	8.43	8.58
7	8.50	8.41	8.39	8.30
11	8.45	8.05	8.28	7.90
15	8.25	7.66	8.04	7.46
19	8.10	7.23	7.84	6.98
21	7.85	6.99	7.57	6.72
23	7.40	6.75	7.11	6.45
25	7.10	6.49	6.79	6.16
27	6.70	6.21	6.37	5.86
29	5.85	5.92	5.50	5.55
31	4.70	5.61	4.34	5.22
33	4.40	5.28	4.02	4.87
35	4.20	4.94	3.81	4.51
37	4.00	4.57	3.59	4.13
39	3.60	4.19	3.18	3.73
41	3.35	3.78	2.91	3.32
43	3.15	3.36	2.70	2.89
45	2.90	2.92	2.44	2.46
47	2.70	2.46	2.23	2.03
49	2.55	2.00	2.06	1.59

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

Bo = 1.184 B_1 = -6.187 r = -0.9696
SE = 0.0468 I_o = 0.9520

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

Bo = 1.218 B_1 = -7.110 r = -0.9747
SE = 0.0489 I_o = 0.9507

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

Bo = 0.5745 B_1 = 0.9019 r = 0.9741
SE = 0.4921

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

Bo = 0.4824 B_1 = 0.9118 r = 0.9786
SE = 0.4778

TABLE VII-2

(1) Formulation number : FD-2
(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) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 313.23 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.62	9.19	8.60	9.16
2	8.62	9.11	8.58	9.07
4	8.62	8.95	8.55	8.89
7	8.60	8.70	8.49	8.61
11	8.55	8.34	8.38	8.19
15	8.40	7.93	8.19	7.74
19	8.15	7.49	7.89	7.24
21	8.00	7.25	7.72	6.98
23	7.90	6.99	7.61	6.70
25	7.80	6.72	7.49	6.40
27	7.60	6.44	7.27	6.09
29	6.90	6.14	6.55	5.76
31	6.00	5.82	5.64	5.42
33	4.60	5.48	4.22	5.06
35	4.10	5.12	3.71	4.69
37	3.80	4.74	3.39	4.29
39	3.60	4.35	3.18	3.88
41	3.50	3.92	3.06	3.45
43	3.30	3.48	2.85	3.01
45	2.90	3.02	2.44	2.56
47	2.80	2.55	2.33	2.10
49	2.55	2.06	2.06	1.65

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

Bo = 1.196 B_1 = -6.089 r = -0.9634
SE = 0.0516 I_o = 0.9667

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

Bo= 1.229 B_1 = -6.980 r = -0.9689
SE = 0.0543 I_o = 0.9658

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

Bo = 0.5449 B_1 = 0.9097 r = 0.9635
SE = 0.6029

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

Bo = 0.4343 B_1 = 0.9228 r = 0.9686
SE = 0.5971

TABLE VII-3

(1) Formulation number : FD-3
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 26.2
(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) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 319.87 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.60	9.30	8.58	9.28
4	8.55	9.08	8.56	9.20
7	8.55	8.83	8.44	8.74
11	8.50	8.47	8.33	8.34
15	8.35	8.08	8.14	7.89
19	8.25	7.64	7.99	7.40
21	8.20	7.40	7.92	7.14
23	8.15	7.15	7.86	6.86
25	8.00	6.88	7.69	6.56
27	7.65	6.60	7.32	6.25
29	7.20	6.29	6.85	5.93
31	6.55	5.97	6.19	5.58
33	5.40	5.63	5.02	5.22
35	4.60	5.27	4.21	4.84
37	4.20	4.89	3.79	4.43
39	3.85	4.48	3.43	4.01
41	3.45	4.05	3.01	3.57
43	3.25	3.60	2.80	3.12
45	3.00	3.12	2.54	2.65
47	2.75	2.62	2.28	2.17
49	2.50	2.11	2.01	1.69

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

Bo = 1.189 B_1 = -5.706 r = -0.9714
SE = 0.0448 I_o = 0.9720

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

Bo = 1.221 B_1 = -6.551 r = -0.9763
SE = 0.0466 I_o = 0.9715

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

Bo = 0.3815 B_1 = 0.9382 r = 0.9638
SE = 0.6028

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

Bo = 0.2688 B_1 = 0.9531 r = 0.9686
SE = 0.6012

TABLE VII-4

(1) Formulation number : FD-4
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 25.4
(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) : 5 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 253.3 minx pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
5	8.30	7.77	8.22	7.65
7	8.20	7.63	8.09	7.49
9	8.20	7.48	8.06	7.32
11	8.20	7.32	8.03	7.15
13	8.20	7.15	8.01	6.96
15	7.50	6.98	7.29	6.76
17	7.00	6.79	6.77	6.56
19	6.70	6.59	6.44	6.34
21	6.30	6.39	6.02	6.11
23	6.00	6.16	5.71	5.86
25	5.90	5.93	5.59	5.60
27	5.30	5.68	4.97	5.33
29	4.70	5.41	4.35	5.04
31	4.40	5.12	4.04	4.74
33	4.00	4.82	3.62	4.41
35	3.90	4.49	3.51	4.07
37	3.70	4.14	3.29	3.71
39	3.50	3.77	3.08	3.33
41	3.40	3.38	2.96	2.93
43	3.00	2.96	2.55	2.52
45	2.75	2.52	2.29	2.09
47	2.55	2.06	2.08	1.66

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

Bo = 1.116 B_1 = -5.294 r= -0.9641
SE = 0.0465 I_o = 0.9082

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

Bo = 1.144 B_1 = -6.098 r = -0.9700
SE = 0.04881 I_o = 0.9043

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

Bo = 0.8525 B_1 = 0.8362 r = 0.9706
SE = 0.4309

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

Bo = 0.7663 B_1 = 0.8416 r = 0.9758
SE = 0.4148

TABLE VII-5

(1)	Formulation number	:	FD-5
(2)	The amount used for in vitro test	:	10 cc
(3)	The total milliequivalents (TMEQ)	:	25.7
(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)	:	1 min
(7)	Total number of observations	:	22
(8)	Area under the curve (AUC)	:	285.17 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.50	8.77	8.48	8.73
2	8.50	8.69	8.46	8.64
4	8.50	8.53	8.43	8.46
7	8.40	8.28	8.29	8.17
11	8.35	7.91	8.18	7.76
15	8.00	7.50	7.79	7.30
17	7.80	7.28	7.57	7.05
19	7.65	7.04	7.39	6.79
21	7.50	6.80	7.22	6.52
23	6.90	6.54	6.61	6.24
25	6.60	6.26	6.29	5.94
27	5.90	5.97	5.57	5.62
29	5.50	5.66	5.15	5.29
31	4.80	5.34	4.44	4.94
33	4.30	4.99	3.92	4.57
35	3.85	4.62	3.46	4.19
37	3.60	4.24	3.19	3.79
39	3.40	3.83	2.98	3.38
41	3.20	3.40	2.76	2.95
43	3.00	2.95	2.55	2.51
45	2.70	2.49	2.24	2.06
47	2.50	2.02	2.03	1.62

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

Bo = 1.181 B_1 = -6.047 r = -0.9770

SE = 0.0401 I_o = 0.9466

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

Bo = 1.215 B_1 = -6.936 r = -0.9810

SE = 0.0417 I_o = 0.9454

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

Bo = 0.4636 B_1 = 0.9200 r = 0.9829

SE = 0.3943

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

Bo = 0.3905 B_1 = 0.9279 r = 0.9862

SE = 0.3774

TABLE VII-6

(1) Formulation number : FD-6
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 25.2
(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) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 291.05 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.45	8.95	8.43	8.91
2	8.55	8.87	8.51	8.83
4	8.55	8.71	8.48	8.64
7	8.50	8.45	8.39	8.35
11	8.40	8.07	8.23	7.93
15	8.25	7.66	8.04	7.46
17	8.00	7.43	7.77	7.21
19	7.90	7.19	7.64	6.94
21	7.75	6.94	7.47	6.66
23	7.65	6.67	7.36	6.37
25	7.25	6.39	6.94	6.06
27	6.35	6.09	6.02	5.73
29	5.85	5.76	5.50	5.39
31	4.65	5.42	4.29	5.02
33	4.30	5.06	3.92	4.64
35	3.80	4.68	3.41	4.24
37	3.50	4.27	3.09	3.82
39	3.30	3.84	2.88	3.38
41	3.15	3.39	2.71	2.93
43	2.85	2.92	2.40	2.47
45	2.60	2.43	2.14	2.00
47	2.50	1.93	2.03	1.54

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

Bo = 1.183 B_1 = -5.747 r_- = -0.9677
SE = 0.0497 I_o = 0.9553

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

Bo = 1.215 B_1 = -6.587 r = -0.9726
SE = 0.0522 I_o = 0.9543

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

Bo = 0.5414 B_1 = 0.9074 r = 0.9725
SE = 0.5181

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

Bo = 0.4463 B_1 = 0.9181 r = 0.9768
SE = 0.5064

TABLE VII-7

(1) Formulation number : FD-7
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 26.4
(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 (T_M) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 326.52 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.60	9.06	8.58	9.02
2	8.60	9.00	8.56	8,95
4	8.60	8.87	8.53	8.80
7	8.55	8.65	8.44	8.55
9	8.50	8.50	8.36	8.38
13	8.40	8.17	8.21	8.01
17	8.20	7.81	7.97	7.59
21	8.15	7.40	7.87	7.14
25	7.80	6.93	7.49	6.62
27	7.25	6.68	6.92	6.35
29	7.00	6.41	6.65	6.05
31	6.45	6.12	6.09	5.74
33	5.90	5.82	5.52	5.41
35	5.10	5.49	4.71	5.06
37	4.50	5.14	4.09	4.69
39	4.10	4.76	3.68	4.29
41	3.70	4.36	3.26	3.88
43	3.45	3.93	3.00	3.44
45	3.00	3.47	2.54	2.98
47	2.80	2.99	2.33	2.51
49	2.70	2.49	2.21	2.03
51	2.50	1.97	2.00	1.55

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

Bo = 1.156 B_1 = -5.168 r = -0.9747
SE = 0.0424 I_o = 0.9603

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

Bo = 1.184 B_1 = -5.962 r = -0.9789
SE = 0.0445 I_o = 0.9588

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

Bo = 0.4004 B_1 = 0.9336 r = 0.9776
SE = 0.4644

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

Bo = 0.3108 B_1 = 0.9444 r = 0.9815
SE = 0.4506

TABLE VII-8

(1) Formulation number : FD-8
(2) The amount used for in vitro test : 10 cc
(3) The total milliequivalents (TMEQ) : 25.2
(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) : 1 min
(7) Total number of observations : 22
(8) Area under the curve (AUC) : 352.82 min x pH

Time (min)	pH (OBS)	pH (CALC)	CpH (OBS)	CpH (CALC)
1	8.65	9.55	8.63	9.53
2	8.65	9.50	8.61	9.47
4	8.65	9.38	8.58	9.33
7	8.65	9.19	8.54	9.12
11	8.55	8.92	8.38	8.80
15	8.50	8.61	8.29	8.45
19	8.35	8.26	8.09	8.05
21	8.20	8.06	7.92	7.83
23	8.20	7.85	7.91	7.60
25	8.10	7.63	7.79	7.35
27	8.00	7.39	7.67	7.08
29	7.80	7.12	7.45	6.79
31	7.40	6.84	7.04	6.48
33	7.00	6.53	6.62	6.14
35	6.90	6.20	6.51	5.78
37	6.65	5.83	6.24	5.39
39	6.10	5.44	5.68	4.96
41	5.80	5.00	5.36	4.51
43	5.40	4.52	4.95	4.01
45	3.50	4.00	3.04	3.48
47	2.75	3.43	2.28	2.92
49	2.45	2.82	1.96	2.32

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

Bo = 1.134 B_1 = -3.834 r = -0.9580
SE = 0.0443 I_o = 0.9825

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

Bo = 1.157 B_1 = -4.435 r = -0.9612
SE = 0.0497 I_o = 0.9819

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

Bo = -0.2990 B_1 = 1.040 r = 0.9551
SE = 0.6094

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

Bo = -0.4562 B_1 = 1.0659 r = 0.9614
SE = 0.6135

TABLE VII-9

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

Data from							
Table VII-1		Table VII-2		Table VII-3		Table VII-4	
X	Y	X	Y	X	Y	X	Y
0.0381	0.9319	0.0383	0.9355	0.0387	0.9344	0.0427	0.9190
0.0387	0.9319	0.0389	0.9355	0.0393	0.9344	0.0442	0.9138
0.0400	0.9294	0.0401	0.9355	0.0406	0.9319	0.0458	0.9138
0.0420	0.9294	0.0421	0.9344	0.0427	0.9319	0.0476	0.9138
0.0450	0.9268	0.0452	0.9319	0.0458	0.9294	0.0495	0.9138
0.0485	0.9165	0.0487	0.9242	0.0495	0.9216	0.0515	0.8750
0.0526	0.9084	0.0529	0.9111	0.0537	0.9164	0.0537	0.8450
0.0549	0.8948	0.0552	0.9030	0.0561	0.9138	0.0561	0.8260
0.0574	0.8692	0.0578	0.8976	0.0588	0.9111	0.0588	0.7993
0.0602	0.8512	0.0606	0.8920	0.0617	0.9030	0.0617	0.7781
0.0632	0.8260	0.0636	0.8808	0.0649	0.8836	0.0649	0.7708
0.0666	0.7671	0.0671	0.8388	0.0684	0.9573	0.0684	0.7242
0.0704	0.6720	0.0709	0.7781	0.0724	0.8162	0.0724	0.6720
0.0746	0.6434	0.0751	0.6627	0.0769	0.7323	0.0769	0.6434
0.0793	0.6232	0.0800	0.6127	0.0819	0.6627	0.0819	0.6020
0.0847	0.6020	0.0854	0.5797	0.0877	0.6232	0.0877	0.5910
0.0909	0.5563	0.0917	0.5563	0.0943	0.5854	0.0943	0.5682
0.0980	0.5250	0.0990	0.5440	0.1020	0.5378	0.1020	0.5440
0.1063	0.4983	0.1075	0.5185	0.1111	0.5118	0.1111	0.5314
0.1162	0.4623	0.1176	0.4623	0.1219	0.4771	0.1219	0.4771
0.1282	0.4313	0.1298	0.4471	0.1351	0.4393	0.1351	0.4393
0.1428	0.4065	0.1449	0.4065	0.1515	0.3979	0.1515	0.4065

TABLE VII-10

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

Data from							
Table VII-5		Table VII-6		Table VII-7		Table VII-8	
X	Y	X	Y	X	Y	X	Y
0.0395	0.9294	0.0403	0.9268	0.0384	0.9344	0.0403	0.9370
0.0401	0.9294	0.0409	0.9319	0.0390	0.9344	0.0409	0.9370
0.0414	0.9294	0.0423	0.9319	0.0403	0.9344	0.0423	0.9370
0.0436	0.9242	0.0446	0.9294	0.0423	0.9319	0.0446	0.9370
0.0469	0.9216	0.0480	0.9242	0.0438	0.9294	0.0480	0.9319
0.0507	0.9030	0.0520	0.9164	0.0471	0.9242	0.0520	0.9294
0.0529	0.8920	0.0543	0.9030	0.0510	0.9138	0.0568	0.9216
0.0552	0.8836	0.0568	0.8976	0.0555	0.9111	0.0595	0.9138
0.0578	0.8750	0.0595	0.8893	0.0609	0.8920	0.0624	0.9138
0.0606	0.8388	0.0624	0.8836	0.0641	0.8603	0.0657	0.9084
0.0636	0.8195	0.0657	0.8603	0.0675	0.8450	0.0694	0.9030
0.0671	0.7708	0.0694	0.8027	0.0714	0.8095	0.0735	0.8920
0.0709	0.7403	0.0735	0.7671	0.0757	0.7708	0.0781	0.8692
0.0751	0.6812	0.0781	0.6674	0.0806	0.7075	0.0833	0.8450
0.0799	0.6334	0.0833	0.6334	0.0862	0.6532	0.0892	0.8388
0.0854	0.5854	0.0892	0.5797	0.0925	0.6127	0.0961	0.8228
0.0917	0.5563	0.0961	0.5440	0.1000	0.5682	0.1041	0.7853
0.0990	0.5314	0.1041	0.5185	0.1086	0.5378	0.1136	0.7634
0.1075	0.5051	0.1136	0.4983	0.1190	0.4771	0.1250	0.7323
0.1176	0.4771	0.1250	0.4548	0.1315	0.4471	0.1388	0.5440
0.1298	0.4313	0.1388	0.4149	0.1470	0.4313	0.1562	0.4393
0.1449	0.3979	0.1562	0.3979	0.1666	0.3979	0.1785	0.3891