SECTION III

GENERAL DISCUSSION AND SUMMARY

Peptic ulcer is the most common disease of the upper gastrointestinal system and affects one in ten persons. Antacids are used in the medical management of peptic ulcer, gastritis, food indiscretions, gastric distress, and discomfort associated with vague causes. Nonsystemic antacids ($Al(OH)_3$, $Mg(OH)_2$) are more often prescribed than the systemic antacids ($NaHCO_3$). The neutralization capacity of $Mg(OH)_2$ exceeds that of $Al(OH)_3$. Moreover magnesium hydroxide is rapidly reacting antacid. The acid neutralizing capacity and the cost effectiveness of liquid antacids are generally better than the tablet antacids.

It was therefore decided to prepare and evaluate suspensions containing magnesium hydroxide. Following points were considered for formulating antacid products: (a) meq of HCl neutralized by one dose (b) Maximum value of pH in the Rossett-Rice test (c) Speed of action, and (d) Duration of action.

Aqueous suspensions, oily suspensions, emulsion, aqueous suspensions containing coated particles, and granules containing $Mg(OH)_2$ were prepared and evaluated. Market products containing the mixture of $Mg(OH)_2$ and $Al(OH)_3$ were also evaluated.

Formulated antacids were evaluated by a modified U.S.P. acid-consuming capacity test and the Rossett-Rice test. There is a good relationship in vivo activity of an antacid and in vitro acid-consuming capacity. Rossett-Rice test attempts to simulate most of the in vivo conditions and so it was selected as a method for evaluating antacid products.

Aqueous $Mg(OH)_2$ suspensions were made by the use of various adjuvants. There is considerable inter-subject variation in the release of HCl in ulcer patient and so it was decided to carry out the in vitro test at different rates of addition of HCl (2 and 4 cc/min). Standard dose of antacid does not exist and so it was decided to test a formulation at different dosage levels both in the in vitro and in vivo test in pylorus-ligated rat.

The relationship between pH and time is non-linear in the in vitro test. Good linear relationship is obtained by plotting 1/TMEQ-NxRxT versus log pH (OBS) where, TMEQ is the total milliequivalents, N is the normality of HCl, R is the rate of addition of HCl and T is the time. Semilog or log-log plot of time and pH did not yield good results.

A mathematical equation is proposed to compute the values of pH at different times in the Rossett-Rice test.

$$pH\ (CALC) = 10^{Bo+B_1\left[\frac{1}{TMEQ-NxRxT}\right]}$$

where, pH (CALC) is the calculated pH, Bo is the intercept, B_1 is the slope. Other terms are as described previously.

Literature shows that the removal of stomach contents vary enormously in the living body and could scarcely be produced in a test in which conditions should be capable of standardization. An equation is proposed to calculate the values of corrected pH with an assumption that there is a negligible increase in the volume of stomach content because the gastric fluid is secreted and simultaneously the contents of stomach are evacuated.

$$\text{Corrected observed pH} = pH(OBS) + \log\left(\text{CpH (OBS)}\right) \frac{Vo}{Vo + RT}$$

where, pH (OBS) is the observed pH and Vo is the initial volume of liquid in the in vitro test.

A computer (PDP 11/34, D.E.C. Corp., U.S.A.) was used to solve above mentioned equations. The programme also contains a subroutine to perform linear regression between:

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

(b) 1/TMEQ-NxRxT and log CpH (OBS)

(c) pH (OBS) and pH (CALC), and

(d) CpH (OBS) and CpH (CALC)

The correlation obtained is reasonably good in all the parameters studied. It is proposed from these findings that the proposed equation can be used to calculate the values of pH in the Rossett-Rice test with good confidence level. The equation gives good results at different rates of addition of HCl and at different dosage levels in aqueous magnesium hydroxide suspensions.

The proposed equation was also tested for market products containing $Mg(OH)_2$ and $Al(OH)_3$. Aqueous $Al(OH)_3$ suspension, oily suspensions containing $Mg(OH)_2$, emulsion dosage form, and granules containing $Mg(OH)_2$. Good results were obtained in all the cases and it indicates flexibility of the equation.

Following applications of proposed equation are proposed:

(1) The time of in vitro analysis can be shortened if the in vitro test is terminated earlier. It is then possible to calculate the time at which the pH will be 2.5, 2.0, or 1.5. Large number of products thus can be compared in reasonably short period.

(2) Dosage regimen of an antacid can be easily fixed for the ulcer patients. The proposed equation can be used for any product and for any patient because terms like 'TMEQ' and 'R' are included into the equation.

The use of reasonably cheap programmable calculator is also demonstrated to solve equation to calculate pH (CALC). Another programme is presented to calculate the area under the curve (AUC) of time in minute versus pH. The use of programmable calculator is proposed for the academic and research institutes.

It is possible to select a good antacid formula if the values of TMEQ, AUC, and Rossett-Rice time (RRT - The time for which the pH was maintained above 2.5 in test) are available.

Two disadvantages were seen with commercial antacid products containing the mixture of $Al(OH)_3$ and $Mg(OH)_2$:

(a) The maximum value of pH in the in vitro test was less than 4 in 8 out of 9 products, and

(b) The maximum pH was attained after 22 to 30 minutes in 5 products, which indicates slow onset of action.

Oily suspensions can be used to control the maximum pH reached in the in vitro test. The onset of action, RRT, and TMEQ can be controlled by selecting proper HLB value of

emulsifiers. The maximum pH in the in vitro test was in between 4 and 6 in selected oily suspensions. These formulations will naturally possess more antipeptic activity than most of the commercial products studied. It is concluded that the dumping of $Mg(OH)_2$ in the stomach can be controlled by formulating it into an oily suspension form.

Olive oil, saffola oil, and arachis oil were tested for antiulcer activity in pylorus-ligated rat. It is concluded that the saffola oil and arachis oil possess protective action against gastric ulcer in pylorus-ligated rat. Suspensions containing these oils will be possessing better protective action against ulcer formation as compared to the aqueous suspension of antacids.

An attempt was made to control the maximum pH in the in vitro test by the use of suspension containing coated particles but the method tried did not give promising results. It seems that it is difficult to prepare controlled release aqueous $Mg(OH)_2$ suspensions by traditional methods.

Magnesium hydroxide was formulated as granules, using various binders, to obtain controlled release. The results indicate that it is possible to prevent dumping of $Mg(OH)_2$ by making proper selection of binding agent. The Rossett-Rice

time was significantly unaffected with granules prepared using CMC Na, PVP and tragacanth. Cellulose acetate, ethyl cellulose and ispaghula are unsuitable binders because formulations containing these binders do not satisfy the ideal requirements for an antacid (e.g. an ideal antacid must raise the pH above 3).

To assess the effect of adjuvants on the neutralization behaviour in vivo testing was performed with selected antacid preparations in pylorus-ligated rat. The results show that the action is directly proportional to the dose (or TMEQ) both in the in vitro test and in vivo test. The Rossett-Rice time is directly proportional to the dose. Better in vivo activity is shown by the oily suspensions which might be due to the protective action exerted by the oil present into oily antacid suspension.

Efforts should be first made to assess an antacid activity by the use of modified acid-consuming capacity test and the Rossett-Rice test. It is proposed that in vivo study, in pylorus-ligated rat, should be carried out only for the products showing similar in vitro characters. The differences observed, in the in vivo test, between products containing the same amount of antacid material might be due to the difference in actual formulations of the products.

It is thus concluded that selection of adjuvants plays a major role in the formulation of antacid products. Rat is proposed as an experimental animal because large number of rats can be used for drawing conclusions. It was found unnecessary to carry out bioavailability study in human volunteers because antacids are not intended for absorption in the body.

The neutralization behaviour of aqueous $Mg(OH)_2$ suspensions was not appreciably altered in the in vitro test when the test was performed in the presence of drugs. Results show that there is no appreciable change in the antacid activity when some drugs are given along with antacids. The proposed equation gives satisfactory results when drugs are concomitantly used with antacids. It is thus possible to predict the changes in pH in ulcer patients taking more than one drugs.