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Original Research Article

Comparison of two marketed effervescent fast relief formulations for antacid activity-an *in vitro* study

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ABSTRACT

Background: Hyper-acidity is excessive formation of acid (pH=1.5-3.5) in the stomach by parietal cells which causes a burning sensation in the chest. The preservation of gastric acid insult is crucial because of the implications of hyperacidity in gastroesophageal reflux disease (GERD), peptic ulcers and duodenal ulcers. Acidity is controlled by use of some over-the-counter (OTC) antacid formulations containing magnesium or aluminum hydroxides.
Methods: In the present study, the preliminary antacid test (PAT), the pH acid neutralizing capacity (ANC), acid neutralizing potential (ANP) along with buffering capacity of two well-known quick release formulations (F1 [Digene Ultra Fizz] and F2 [a standard, commercially available product]) were determined.
Results: According to US pharmacopeia USP, both the antacid formulations passed the PAT test. PAT results revealed that the pH of the acid-antacid solution was higher in F1 (8.20±0.02) as compared to F2, (6.53±0.01). The ANC results revealed that F1 (46.89±0.6 mEq/dosage) had higher neutralizing capacity as compared to F2(30.12±1.3 mEq/dosage). Higher ANP was observed for F1 (245 mins), and it was 2.7 times that of F2 (90 min). The onset of action for both the antacids was <2 seconds. Additionally, buffering capacity was evidently observed during ANP analysis in the case of F1. Independent T test performed for all the tests revealed that the data obtained was highly significant ($p<0.01$).
Conclusions: F1 showed high antacid and buffering properties when tested *in vitro*. The present study highlights the need for future research on specific OTC non-prescribed antacid formulations with respect to their price, efficacy and side effects.

Keywords: Acid neutralizing capacity, Acid neutralizing potential, Preliminary antacid test

INTRODUCTION

Excessive formation of acid in the stomach by parietal cells causes a burning sensation in the chest, along with reflux termed hyperacidity. Commonly available treatment includes gastric acid blockers, proton pump inhibitors, tissue lining protection drugs, over-the-counter antacids and antibiotics for hyperacidity due to *Helicobacter pylori*.[1,2] Antacids are weak bases (hydroxide, citrate, carbonate, bicarbonate) combined with metallic ions (aluminum, calcium), classified as systemic or non-systemic, and are capable of neutralizing gastric acidity.[3] Variables that affect a patient's imbalance between acid secreting mechanism of stomach and protective mechanisms of the gastric mucosa are faulty eating habits, smoking, tobacco chewing, stress, improper sleep, and anxiety.[4,5]

The easy and inevitable use of antacids and treatment regimens suggests their long-term use. This can inadvertently affect the gastric mucosa causing alkalosis

and retention of fluid. A study conducted by Rana et al suggested that prolonged use of an effervescent antacid shows no side effect till 30 days.[4]

This study is an extended research to our previously published work on different antacid formulations.[6] In this paper, we aimed to determine the pH of F1 to frequently used antacid powder F2 and to study the antacid properties of both the marketed formulations. The need for evaluating different antacid formulations rely on the fact that medical institutions should be aware of composition, efficacy, dosage and side effects of different antacid formulations. Digene Ultra Fizz (F1), a product of Abbott India, is a combination of Svarjiksara (sodium bicarbonate), Nimbukamlam (citric acid) and Khatikachurna (calcium carbonate). F1, an over-the-counter OTC non-prescription drug, provides symptomatic relief from heartburn, acid indigestion, and sour stomach. F2, a marketed product is a combination of Svarjiksara (Shudh) and Nimbukamlam (Shushkam). Common antacid formulations contain tartaric acid, citric acid, sodium-bi-carbonate and sodium carbonate.[7]

Citric acid (Nimbukamlam) is essentially added to the antacid formulation to aid gas removal, flatulence relief, and relief from abdominal discomfort. Baking soda and citric acid together has potential to control and neutralize acidity.[8] Sodium bicarbonate (Svarjiksara) used in antacid formulations reacts with acid and forms NACl, H_2O, and CO_2. Sodium chloride is the effect of neutralized acid and CO_2 relieves abdominal discomfort.[3] Calcium carbonate (Khatikachurna) is a potent, rapid and inexpensive acid neutralizer and has been known to prevent constipation.[9]

Liquid gels or quick release antacid formulations are more effective as compared to antacids in tablet form available in the Indian pharmaceutical market to ensure instant relief from heart burn and acidity. Various brands of OTC antacids are available in the market, with reports suggesting disparity in performance amongst these formulations. Acid neutralizing capacity and buffering capacity of any antacid explains the efficiency of the antacid performance *in vivo*. New formulations are created to tackle the pre-existing side effects of any antacid available in market and to meet new demands in terms of symptomatic and quick relief. In the current study, a marketed antacid fizz formulation, F2 was used as a standard to compare the preliminary antacid test, acid neutralizing capacity and acid neutralizing potential of F1, Digene Ultra Fizz, an antacid product of Abbot India limited.

METHODS

In the current study, *in vitro* tests were conducted to compare the antacid properties of Digene Ultra Fizz (F1) with those of the reference standard F2. The experiments were conducted in the Department of Animal Biotechnology and biochemistry and department of chemistry (FDA approved) in Kelkar Education Trust's scientific research centre (DSIR Recognized), Mulund, Mumbai. In December 2019, Digene Ultra Fizz (F1) and F2 were obtained from Abbott India Ltd. HCL and NaOH used were of analytical grade.

Calibration of pH meter

The pH Meter (Lab India solutions, India) used was calibrated using buffer tablets of known pH procured from Himedia, India. Buffer tablet of pH 4.0 was dissolved in 100 ml of distilled water and the pH was calibrated to 4. The pH meter was also calibrated at pH 7 using buffer tablet. Operation of pH meter at 1.0 was checked using 0.1M HCl.[10]

Preparation and standardization NaOH[11]

20gm of NaOH was weighed and added to 1000ml distilled water to obtain 0.5N NaOH. Further, it was standardized with Potassium hydrogen phthalate (KHPh). 0.26 g of KHPh was added to 50ml of distilled water and 2-3 drops of phenolphthalein were added and it was titrated using prepared NaOH solution till the solution turned light pink in color, and the volume of NaOH was noted down. The normality of NaOH was calculated using the formula given below,

Normality of NaOH = (Weight of KHPh×1000)/(Volume of NaOH in ml×204.22).[12]

Preparation of standardized HCl

81.8 mL of HCL was added to 1000 ml of distilled water to obtain a solution of 1 N HCl. This solution was standardized using a previously prepared NaOH solution. 10 ml of HCl was taken in a flask to which 2-drops of phenolphthalein indicator was added. The solution was titrated using NaOH solution of known normality until the endpoint of colorless to pink was observed and noted. The normality of HCl was then calculated using the formula given below,

Normality of HCl=(Normality of NaoH×Volume of NaOH in mL)/Volume of HCL in mL.[12]

Preliminary antacid test

According to USP, a standard antacid preparation should comply with preliminary antacid test (PAT) requirements. During the test the antacid solution should raise the pH of the acid-antacid solution above 3.5.[13] For estimating the PAT the samples were prepared by adding one packet each of the products in a 100 ml conical flask containing 10ml of distilled water. The solution was stirred at 300±30 RPM till the reaction subsided. Then volume was made up to 40 ml using distilled water and was stirred at 300±30 RPM for a minute.

The test was performed according to US pharmacopeia (USP) national formulary.[14] In order to determine the PAT,

10 ml of 0.5M HCl was added to the solution of antacid prepared above while stirring on a magnetic stirrer at 300±30 RPM for 10 minutes. After 10 min, the pH was recorded using a pH meter calibrated at pH 1.0, 4.0 and 7.0. The pH of the solution was noted, and the samples were processed for ANC and ANP if the PAT showed a result of pH above 3.5 (food and drug administration, HHS, part 331).[6]

Acid neutralizing capacity

Various *invitro* tests are available to evaluate the performance of antacids such as acid neutralizing capacity (ANC), pH stat, among others.[15] ANC is a measure to determine ability of an antacid to neutralize acid and is expressed as number of milli-equivalents of HCl that can be neutralized by one standard dose of antacid preparation.[16]

For estimating ANC of samples, one packet each of the products was added in a 100 ml conical flask containing 10ml of distilled water and the solution was stirred at 300±30 RPM till the reaction subsided. The volume was then made up to 70 ml with distilled water while stirring at 300±30 RPM on a magnetic stirrer. The stirring was followed for another one minute.

To study the ANC of the antacid formulations, 60 ml of 1.0 HCl was added to the 70 ml antacid-water solution. The stirring was continued for another 10 min at 300±30 RPM on a magnetic stirrer. The unutilized HCl from the flask was back titrated using 0.5 N NaOH standardized with KHPh-potassium hydrogen phthalate. Titration was completed within 5 min and the endpoint was noted when the pH of 3.5 and below was obtained. The ANC was stated as mEq of acid neutralized by the given antacid solution.

Total mEq of antacid sample=(60.0 ml) (Normality of HCl)-(ml of NaOH required for neutralization) (Normality of NaOH).

The experiments were conducted in triplicates. Upon using KHPh for determining the normality of NaOH and HCl, the values were substituted in the formula and ANC was calculated.[6,17]

Acid neutralizing potential

Rossett Rice Test is an acid neutralizing dynamic test. The procedure attempts to stimulate gastric conditions and record pH profile towards acid neutralization of the antacid under test.[18]

In order to determine the ANP of antacid effervescent formulations, one packet each of the products was added in a 100ml conical flask containing 10ml of distilled water and the solution was stirred at 300±30 RPM till the reaction subsided. The volume was then made up to 30 ml with distilled water while stirring at 300±30 RPM on a magnetic stirrer. The stirring was followed for another one minute.

The acid reactivity of the antacids was determined using Rossett-Rice procedure. To the water-antacid solution, 70 ml of 0.1 N HCl was added and the contents were stirred for 10 min at 300±30 RPM on a magnetic stirrer. The pH meter and a pump calibrated to deliver a constant volume 2.0 ml of 0.1 N HCl per min were activated. The pH time profile was recorded throughout the test until the pH of the solution fell below 3.0 and it was constant for a minute.[6, 19]

Onset of action

For the onset of action, one packet of each product was added in a 100 ml conical flask containing 10 ml of distilled water and the solution was stirred at 300±30 RPM till the reaction subsided. The volume was then made up to 30 ml with distilled water while stirring at 300±30 RPM on a magnetic stirrer. The stirring was followed for another one minute.

The prepared solution of 0.1 N HCl was kept on a magnetic stirrer at 300±30 RPM with a pH electrode dipped in the flask. The sample solution was added to the flask containing 0.1 N HCl and time taken for pH to rise above 3.5 was recorded.[6]

Statistical analysis

For the obtained data two samples independent t test analysis was conducted using PAWS statistics 18.

RESULTS

Standardization of NaOH and HCl

The average volume of NaOH required to neutralize 0.26 g of KHPh was 2.2 ml. Upon substituting in the formula, the calculated normality of NaOH was found to be 0.559 N. This 0.559 N NaOH was used to neutralize 10 ml of 1.0 $N_{(theoretical)}$ HCl and the average volume of NaOH required was 18.3 ml. The calculated normality was 1.022 $N_{(calculated)}$ for HCl.

Preliminary antacid test

The preliminary antacid test (PAT) results are given as average±standard deviation in Table 1. Both formulations can be classified as antacids as their pH is >3.5.

Table 1: PAT results of the marketed effervescent formulations.

Sample	Average	SD
Digene ultra fizz F1	8.20*	0.026458
F2	6.53*	0.017321

***Indicates the difference in the mean is statistically significant ($p<0.001$)

Acid neutralizing capacity

The volume of NaOH is added to the antacid-HCl solution to determine unutilized or un-neutralized HCl. More the amount of NaOH required, lesser is the ANC of the given antacid under given experimental conditions. Table 2 gives the ANC of F1 and F2.

From the results, it is evident that F1 showed higher ANC as compared to F2.

Acid neutralizing potential and onset of action

Both the samples could raise pH above 3.5 for more than 90 min. F1 raised the pH above 3.5 and maintained it there with constant acid influx for 245 minutes. While conducting the experiment it was evident that with even 2 ml of 0.1 N HCl added per min to the antacid solution, F1 could raise the pH, however, with F2 there was an alteration in pH once it was lowered. This shows that F1 could demonstrate buffering capacity, while F2 could simply raise the pH of the solution. Table 3 represents the ANP and onset of the action of F1 and F2.

Table 2: ANC results of the marketed effervescent formulations.

Sample	ANC			Average	SD
Digene ultra fizz F1	46.944	47.543	46.211	46.89933*	0.667122
F2	29.65	32.252	30.123	30.675*	1.386048

*Indicates the difference in the mean is statistically significant (p=0.008)

Table 3: ANP results of the marketed effervescent formulations.

Sample	Initial pH	Time Taken to reach (in mins)				Final pH
		Onset of action	Above pH 3.5	Max pH	To maintain pH above 3.5	
Digene ultra fizz F1	6.04	<2 seconds	<2 seconds	1 min	245 min*	2.74
F2	5.87	<2 seconds	<2 seconds	2 min	90 min*	2.82

*Indicates the difference in the mean is statistically significant (p=0.001), N=3

DISCUSSION

There is a need to study marketed antacid formulations on a regular basis to determine their dosage, efficacy, safety along with economic considerations. The market is flooded with antacids and physicians are baffled with the existing choices available in market. The decision to choose proper antacid must be done on the basis of high ANC and the ability to maintain pH above 3.5 for a longer period with buffering capacity. This buffering capacity shall reduce the changes of acid rebound. Thus, hospital settings should have information of antacids with regards to their ANC, ANP and BC for proper patient care and management of gastric acidity associated disorders.[20] F2, a well-established non-prescription-based OTC drug, was used as a standard while determining the PAT, ANC, and ANP of Digene Ultra Fizz. According to food and drug administration, HHS, part 331, Antacid products for over-the-counter (OTC) human use, if the PAT values are less than 3.5, the antacid under study shall not be labeled as an antacid. Also, if pH is greater than 3.5, only then ANC can be determined. The PAT values of both F1 and F2 were greater than 3.5. The ANC of Digene Ultra fizz was 1.53 times more than F2. Similarly, a higher ANP was noted with Digene Ultra Fizz F1 also, Digene Ultra Fizz (F1) showed buffering capacity in comparison to F2, a marketed formulation. In the case of F2, it was noted that the pH rose initially when HCl was added due to the ANC of F2 formulation. However, with the subsequent addition of HCl to examine the effect of acid-reflux, the pH only decreased by unit proportional to amount of HCl added without any buffering effect. However, with Digene Ultra Fizz F1, it was noted that the pH decreased with the addition of HCl and was subsequently increasing due to the antacid to rise above the existing decrease in pH by a few units. This explains the buffering capacity of F1 and this may be the reason that F1 could maintain pH above 3.5 for longer time duration of 245 mins as compared to 90 minutes with F2. Buffering capacity along with high ANC indicates higher efficiency of F1 as compared to F2.[21]

Limitations

The study findings are limited by the fact that antacid effectiveness may alter due to many parameters such as interaction of with other drugs, food or gastric emptying.[22,23] Since this study focuses on determination of *in vitro* antacid effectiveness, further research is warranted to study their efficiencies on actual human volunteers.

CONCLUSION

Considering the widespread use of antacids, antacids are proven to be safe and effective agents. However, it is important for the better understanding of the consumers that the products display efficacy and buffering capacity of the antacid. This helps explain medical rationale, efficacy and cost comparison between antacid products. Digene Ultra Fizz F1 was found to exhibit higher PAT, ANC, buffering capacity and ANP than the antacid formulation

F2when tested *in vitro*. Both Ultra Fizz and F2 can be used by patients with hyperacidity owing to the fact that both products showed high ANC. However, more data from clinical studies is required to better understand dosage, efficacy, and safety profile of both the products in human volunteers.

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