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ORIGINAL ARTICLE

Assessment of the Acid Neutralizing Capacity and Other Properties of Antacid Formulations Marketed in the Gaza Strip

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ABSTRACT:

Background: Antacids are frequently used as over-the-counter (OTC) medications to reduce symptoms of dyspepsia and to neutralize stomach acidity. Evaluation of antacids efficacy depends on in vitro testing like acid neutralizing capacity (ANC) and acid neutralization potential (ANP). The purpose of this study was to examine ANC, ANP, and other characteristics of commercially available antacid formulations (both liquid and solid formulations) in the Gaza Strip.

Methods: Both liquid (n=2) and solid (n=4) antacid formulations were acquired from the Gaza Strip's central community pharmacies. Preliminary antacid test (PAT) was carried out to determine if the tested formulation is classified as antacid. The general monograph <301> in USP34/NF29 was used for the estimation of ANC, while ANP was investigated using Rossett Rice procedure. Both tests were conducted to evaluate the efficacy of antacid. In addition, cost effectiveness per formulation and statistical analysis test of data were calculated.

Results: All formulations were classified as antacids because they all passed the PAT test (pH of antacid-HCl over 3.5). The ANC of antacids (n=6) varied from 8.74±0.37 to 29.14±0.84 mEq per minimum labeled dose (MLD). The ANC/MLD ratios for solid formulations were higher than those of liquid formulations. No statistically significant difference in ANC/MLD between the two groups was estimated (P>.0.05). ANP test - the time duration during which an antacid formulation maintains pH above 3.5 - ranged from 43 to 90 minutes. According to this study liquids were inefficient in acid neutralization and expensive as a result.

Conclusions: The ANC and ANP results indicated the better neutralizing efficacy and duration of solid antacids in comparison to liquids**.** A1 and A2 formulations– calcium and magnesium salt based solid antacids had the most appropriate properties in terms of efficacy, onset and duration of neutralizing activity. Antacids in the form of chewable tablets were the most cost-effective formulations. It is recommended to examine more batches of the same antacids and to add ANC data on the label of antacids.

KEYWORDS: Antacid; Acid neutralizing capacity (ANC); Acid neutralization potential (ANP); Preliminary antacid test (PAT); Minimum labeled dose (MLD).

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INTRODUCTION:

Hydrochloric acid is one of the main ingredients of the gastric juice which is secreted at the rate of 1.2 to 1.5 liters per day from the parietal cells (Wolfe, and Soll, 1988). The gastric juice is quite acidic due to the high concentration of hydrogen ion (Steingoetter et al., 2015). On the pH scale, its pH value can be close to 1.5. This acidic solution is essential for the function of digestive enzymes and digestion process (Katz et al., 2013, Garg et al., 2022). Excess acid produced by the gastric glands, mainly hydrochloric acid (HCl), can cause hyperacidity or dyspepsia, a medical condition that affects the majority of people (Madisch et al., 2018, Holle, 2010). It results from an unbalanced acid – secreting process and shielding system. Numerous factors can cause hyperacidity, including irregular meal times, eating spicy and fried meals, excessive caffeine consumption, smoking, alcohol abuse, and being under stress and anxiety (Burton Murray & Kuo, 2020, Harer & Hasler, 2020). Heartburn, Gastroesophageal Reflex Disease (GERD), peptic ulcer and other conditions have all been linked to hyperacidity (Yadlapati et al., 2022, Parakh and Patil, 2018, Badillo & Francis, 2014). With a prevalence of 20%, GERD is one of the most often diagnosed digestive illnesses in the US. It has a negative impact on the quality of life and imposes a major economic burden in direct and indirect costs. The global pooled prevalence of GERD was reported 13.98% in a meta-analysis of 96 studies from 37 countries with considerable regional and national variations. Compared to 19.55% in North America and 14.12% in Europe, the estimated rate was 12.92% in Asia (El-Serag et al., 2014, Nirwan et al., 2020).

Antacids are the most common therapy for neutralizing stomach acidity and alleviating dyspepsia symptoms (Jagadesh&Chidananda, 2015). Additionally, it was noted that antacids were the primary line of treatment for heartburn, particularly during the COVID-19 epidemic, which has seen an upsurge in the use of self-medication (Garg et al., 2022). They are alkaline compounds made up of various cationic salts, which react with excess HCl in gastric juice to produce water and salt and stabilize the pH (Maton & Burton, 1999). Two categories of antacids were established based on its absorbability. Aluminum hydroxide, aluminum phosphate, and magnesium hydroxide are examples of non-systemic antacids. Sodium bicarbonate, calcium carbonate and magnesium carbonate are examples of systemic antacids. They are usually marketed in combinations of two or three components (Shetty & Vishwanath, 2022). Sodium alginate may be combined with the antacid salts which forms a low density gel (raft) that floats and protects the mucosa. In addition, some

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formulations may include dimethicone or simethicone as anti-flatulent agents(Mandel et al., 2000, Bhardwaj et al., 2011, Pawar et al., 2011). Antacids are sold in a variety of pharmaceutical forms including chewable tablet, effervescent tablet, effervescent powder, and oral suspension. For a better customer experience, producers are continuously improve and develop the formulations in terms of their palatability and organoleptic characteristics (Waller and Sampson, 2018).

Antacids are distinguished from other medications by raising gastric pH above 3.5. This can be examined by the preliminary antacid test (PAT). Importnant factors of antacid activity are the onset and the duration of action, which are varied according to formulation factors and administration conditions (Chao et al., 2016, Johnson& Suralik, 2009, Katakam et al., 2010). Acid neutralization potential (ANP) and acid neutralizing capacity (ANC), which are measured in vitro, are key factors in indicating antacid effectiveness. Acid neutralizing capacity (ANC) is defined as antacid's ability to neutralize gastric acid at temperature 37^{o}C ± 2^{o}C and is measured in milli-equivalents (mEq). ANC is not stated on products labels, thus the selection of an antacid may depend only on the price aspect. Another in vitro test is the acid neutralization potential (ANP), which simulates the gastric conditions and examines the pH profile of acid neutralization reaction. ANP is based on Rossett Rice procedure (USP, 2016, Dinbandhu et al., 2017, Washington, 1991, Voropaiev & Nock,2021).

The preferential antacid should be effective and inexpensive with a long lasting impact, a pleasing taste, and convenienceof use. Literature review showed that antacid formulations examined in many countries had a significant variation in terms of efficacy (Orman et al., 2021, Ayensu et al., 2020, Mahmood et al., 2020, Jacob et al., 2016, Al-Mudhafar et al., 2016, Jagadesh & Chidananda, 2015).

For the first time in the Gaza Strip, this study aimed to examine acid neutralizing capacity and acid neutralization potential of antacids as well as their cost effectiveness.

Materials and methods

Equipments

PH meter (HI22019, Hanna, USA) was calibrated using standard buffer solutions (HI54710, Hanna, USA). Other instruments are analytical balance (NJ07054, USA, Model PA224), and hotplate stirrer (Thermo Scientific, Portugal). The experiments were performed using class A glassware.

Samples

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The commercially available antacid formulations of different brands were purchased from central community pharmacies of Gaza strip in June 2022. Four samples (A1 – A4) were solids and two samples (A5-A6) were liquids.

Chemicals and reagents

HCl (37% w/w, Merck, Germany) and NaOH (Pellets, Sigma-Aldrich, Germany) for analysis were used to prepare the reagents.

0.5 N NaOH solution: 21 grams of sodium hydroxide were accurately weighed and dissolved in distilled water to produce one liter (USP, 2016).

1.0 N HCl solution: It was prepared by transferring 85 mL of HCl into one liter volumetric flask and diluted by distilled water.

0.5 N HCl: It was prepared by transferring 42.5 mL of HCl into one liter volumetric flask and diluted by distilled water.

0.1 N HCl solution: It was prepared by transferring 8.5 mL of HCl into one liter volumetric flask and diluted by distilled water (USP, 2016).

Preliminary antacid test (PAT)

Twenty tablets were ground and powdered using mortar and pestle to determine PAT. The minimal labeled dosage (MLD) of powder was accurately weighed and put in a 100 mL conical flask then mixed with 10 mL of distilled water. On a hotplate magnetic stirrer, the solution was blended at a speed of 300±30 rpm for a minute. Then, using distilled water, the volume was increased to 40 mL and was stirred for a minute.

For oral suspensions, the bottles were shaken well and a volume of MLD was put in a 100 mL conical flask. Distilled water was then added to provide a final volume of 40 mL. The solution was stirred on a hotplate magnetic stirrer at 300±30 rpm for one minute.

While the above solution of antacids were stirred 10 mL of 0.5 N HCl were added. Stirring was continued for exactly 10 minutes at 300±30 rpm. The pH of the solution was measured. An antacid is identified when the recorded pH is 3.5 or higher (Richa et al., 1997).The process was performed in triplicate.

2.5 Acid neutralizing capacity (ANC)

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For chewable tablets, the average weight of twenty tablets was calculated and the tablets were then ground into a fine powder using mortar and pestle. A precise weight that matched the minimum labeled dose was put into 250 mL conical flask. Then, the powder was mixed adequately with 70 mL water for 1 minute using a magnetic stir. While the mixture under stirring 30 ml of 1.0 N HCl solution were added and stirred for further 15 minutes. After that, back titration of excess HCl was done using 0.5 M NaOH until a stable pH value of 3.5 for 10 -15 seconds was recorded. Titration should be completed within 5 minutes.

For oral suspension, the density was measured and an accurate weight equivalent to minimum labeled dose was transferred into 250 mL volumetric flask. After that, distilled water was added to a final volume of 70 mL. The solution was then mixed on the magnetic stirrer for one minute. The procedure was continued as mentioned above in chewable tablets. The process was performed in triplicate.The ANC was carried out at temperature of 37 ± 2°C (USP, 2016).

The ANC was calculated using equation 1.

$$ANC\ (mEq) = (Volume\ HCl\ (mL) \times Normality\ HCl)\ - (Volume\ NaOH\ (mL) \times Normality\ NaOH)$$

Equation 1

To express the ANC as mEq per weight equation 2 is used.

$$ANC\ \left(\frac{mEq}{g}\right) = \frac{ANC\ (mEq)}{Weight\ of\ antacid\ (g)}$$

Equation 2

Acid neutralization potential (ANP)

To evaluate ANP, twenty tablets were ground and powdered using motor and pestle. The minimum labeled dose (MLD) of powder was accurately weighed and put in 100 mL conical flask containing 10mL of distilled water. On a hotplate magnetic stirrer the solution was blended at a speed of 300±30 rpm. Distilled water was then added to produce a final volume of 30 ml and the mixture was stirred at the same speed for a minute.

For oral suspension, the bottles were thoroughly shaken and the MLD was put in 100 mL conical flask. Distilled water was then added to produce a final volume of 30 ml. The mixture was stirred at 300±30 rpm for one minute.

After that 70 mL of HCl (0.1 N) was added to the solution and the content stirred for 10 minutes on a

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hotplate magnetic stirrer at the same speed. PH meter and a pump delivering 2.0 mL 0.1 N HCl/minute were supplied. The pH time profile was recorded every 10 minutes until the pH value was below 3.0 and remained constant for a minute (Washington, 1991). The process was performed in duplicate.The ANP was carried out at temperature of 37 ± 2^{o}C.

Cost effectiveness test

The cost-effective antacid was evaluated by calculating the ratio of acid neutralized (mEq) for the price of minimum labeled dose (PMLD, $) (Jacob et al., 2016). The economically favorable antacid would have a high ratio of mEq per PMLD.

2.8 Statistical analysis

The data of ANC/MLD were analysed using Microsof Excel (2010). The t-test was applied to examine the difference between the means of antacids for both groups (Solid - and liquid formulations) at 0.05 level of signifigance.

3. Results and discussion

3.1 Characteristics of antacids

Antacids available in the Gaza Strip pharmacies at the time of study were purposively collected. Effervescent tablets and effervescent powder as pharmaceutical formulations were not available in the Gaza Strip. In addition, non of the antacids were locally manufactured. Calcium carbonate as acid neutralizing salt was the main component of most formulations as given in Table 1**.**

In samples aluminum hydroxide as antacid was in combination with magnesium hydroxide. This combination enhances the antacid efficacy of formulations and compensates their side effects (Garg et al., 2022). Calcium and aluminium containing antacids are known to cause constipation. Magnesium antacids are accompanied by diarrhea. On the other hand, aluminium hydroxide containing antacids are known to prevent mucosal necrosis and hemorrhage in stomach caused by noxious agents like aspirin (Tarnawski et al., 2013). A combination of famotidine-antacid tablet (A2) was identified among formulations, which contained 10 mg of famotidine -a potent H2 receptor antagonist- with standard calcium and magnesium containing antacids. This combination has been reported to have the benefit of more rapid relief of symptoms than famotidine alone, and a longer duration of relief than antacid alone (Ohning et al., 2000, Garg et al., 2022).

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Dimethicone and simethicone are anti-flatulent agents were found in two antacids. Antifoaming properties of these agents reduce the stomach gases and discomfort, which exacerbate hyperacidity (Meier & Steuerwald, 2007). Sodium alginate in combination with buffering salts is available in oral suspension formulation. The pharmacological effect of alginate-based antacid depends on a raft forming system which floats on the stomach content and protects it (Bhardwaj et al., 2011, Pawar et al., 2011). Sodium bicarbonate is responsible for production of carbon dioxide upon reacting with gastric juice, which becomes entrapped in the alginate gel. As a result, a foam floating over the gastric content is formed. Alginate-based rafts can trap antacid ingredients like calcium or aluminium salts present in some formulations, providing a comparatively pH-neutral barrier (Mandel et al., 2000).

Table 1: Characters of sampled antacids.

Sample	Content	Strength of MLD (mg)	Package	Country of origin	Batch No.	Expiry date
Chewable tablet						
A1	$CaCO_3$ $MgCO_3$	680 80	96 Tablet	France	N02959	01/2024
A2	Famotidine $Mg(OH)_2$ $CaCO_3$	10 165 800	50 tablet	Palestine	082F21	05/2023
A3	Simethicone $Mg(OH)_2$ $Al(OH)_3$	25 200 200	40 tablet	Italy	1U0011	03/2024
A4	$CaCO_3$	600	60 tablet	Israel	338707	03/2025
Oral suspension						
A5	Alginate Sod. $CaCO_3$ $NaHCO_3$	500 160 267	300 mL	UK	ACW646	05/2023
A6	$Al(OH)_3$ $Mg(OH)_2$ Simethicone	175 200 25	355 mL	Italy	1I006	01/2023
MLD: Minimum labelled dose.						

Preliminary antacid test (PAT)

All samples passed the PAT test since the pH values were above 3.5 (Table 2). PAT demonstrated the samples as antacids (USP, 2016), but it is not an indicator of the efficacy or the quality (Richa et al., 1997, Lirazan et al., 2018, Dhawal and Brave, 2020). To examine efficacy, ANC and ANP were further investigated. PAT of A1 and A2 antacids showed pH above 5. These formulations may provoke acid

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rebound resulting in adverse effects like bloating, meteorism, and eructation (Miederer et al., 2003).

Table 2: Results of Preliminary antacid test (PAT).

Sample	PH (0 min) Mean ± SD	pH (10 min) Mean ± SD
A1	8.64±0.34	5.81±1.02
A2	8.87±0.16	5.31±0.41
A3	7.92±0.22	4.50±0.33
A4	8.21±0.31	4.25±0.47
A5	8.54±0.18	4.38±0.30
A6	8.61±0.50	4.61±0.22
SD: Standard deviation of triplicate.		

Antacid neutralizing capacity (ANC)

In this study the official USP monograph was applied. All antacid formulations that were tested meet the acceptable limit of ANC, which is 5 mEq per MLD (Table 3) (USP, 2016). ANC ranged from 8.74±0.37 to 29.14±0.84 mEq/MLD. In general, the ANC values of tablets were higher than those of oral suspensions in tested samples.

Table 3: Results of ANC evaluation

Sample	ANC (mEq/MLD) Mean ± SD	ANC (mEq/g)
A1	20.56 ± 0.51	15.54
A2	29.44 ± 0.84	15.66
A3	12.64 ± 0.72	9.91
A4	16.29 ± 0.58	16.15
A5	8.74 ± 0.37	0.78
A6	10.31 ± 0.81	0.85
MLD: Minimum labelled dose, SD: Standard deviation of triplicate.		

The highest value of ANC was recorded for A2 (Magnesium hydroxide and calcium carbonate-based antacid) followed by A1, A4, and A3. Formulations containing calcium carbonate demonstrated better antacid neutralizing capacity. Moreover, a correlation between ANC and strength of MLD in calcium carbonate was observed in the tested samples. Since the highest ANC was recorded for A2 containing 800 mg calcium carbonate, the ANC is lower for a lower content (A1, and A4) or even absence as in A3. The lowest ANC was for the oral suspension (A5) of alginate-based formulation. Similar result was recorded in a study conducted in Morocco (Yafout et al., 2022). The activity of such formulation depends on formation of a raft coating the stomach and protecting it from gastric juice (Bhardwaj et al., 2011, Pawar et al., 2011). For alginate to form the foaming gel in the stomach, hydrogen carbonate

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must be added to the formulation. Therefore, the role of hydrogen carbonate is not to buffer gastric juice. This could explain the low ANC observed by alginate based antacid formulations. Studies showed that, the efficacy of alginate-antacid formulations to reduce heartburn symptoms does not appear to be totally dependent on the neutralization of bulk gastric contents (Lambert et al., 1990, Hampson et al., 2005, Tytgat & Simoneau, 2006).

Expression of ANC results in terms of mEq/MLD was related to the strength of antacid components. A difference in values of ANC was observed when expressed mEq per MLD or per g in oral suspension due to the high density.

Many studies were conducted in different countries showed variable dosage forms and composition of antacids, and showed significant differences in the neutralization capacity (Ayensu et al., 2020, Mahmood et al., 2020, Jacob et al., 2016, Al-Mudhafaret al., 2016, Jagadesh & Chidananda, 2015, Orman et al., 2021).

Acid neutralization potential (ANP)

ANP test is based on Rossett Rice assay which is a dynamic acid neutralizing assay used as a standard to evaluate or compare the *in vitro* efficacy of antacid formulations (Washington, 1991, Dinbandhu et al., 2017). All samples showed ability to bring pH above 3.5 and maintain the pH above 3.5 for 43 and up to 90 minutes (Table 4). All samples brought pH to 3.5 and more when mixed with HCl and stand for 10 minutes (Voropaiev & Nock, 2021).

Table 4: Results of ANP study.

Sample	Initial pH	Time taken to reach (min)		
		pH > 3.5*	Max pH	Maintenance of pH > 3.5
A1	10.01	1.2	3.0	90
A2	8.45	0	0.5	71
A3	9.11	2.9	3.7	50
A4	8.14	0	1.5	55
A5	8.93	1.1	2.0	43
A6	8.21	1.3	6.0	53
*: Values determined after 10 minutes of HCl addition to samples.				

Additional time was required for A1 and A3, which required more time for neutralization reaction onset. A3 chewable tablet formulation is aluminuim hydroxide and magnesium hydroxide-based antacid in combination with semithicone. Such salts are known to have a longer time for the antacid activity onset (Garg et al., 2022). Despite the expectation of a rapid onset of antacid activity for oral suspension in comparison to tablet a slow onset of action was recorded. A6 is an oral suspension

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based on aluminium- and magnesium salts in combination with semithicone, to which a delay in reaction onset was determined (Still shorter than the comparable tablet formulation A3). The longest time to reach the maximum pH was recorded for A6. Differences in ANP of antacids can be linked to the difference in buffering reactivity of raw materials used in the products or other formulation factors e.g. particle size, dissolution rate, type of dosage form, disintegrants and other excipients (Al-Lami, 2017).

When the two oral suspensions A5 and A6 are compared, the delayed onset of action and the longer time to reach the maximum pH by A6 can be explained by the high viscosity of A6 due to component like semithicone (Garg et al., 2022). The present ANP results of liquid antacids are similar to those results recorded in India (Dhawal and Brave, 2020). In vivo studies showed that, the effect of alginate antacid may last approximately up to four hours (Deraman et al., 2020).

Oral suspension maintains the pH above 3.5 for a comparable time interval with solid formulations. A1 and A2 antacids should the highest duration of antacid activity. Calcium and magnesium buffering salts in A1 and A2 tablet formulations are characterized by a medium duration of buffering activity (Yafout et al., 2022, Garg et al., 2022).

Although in vitro studies can simulate the in vivo conditions, several factors such as gastric emptying rate, interactions between food and medications, and gastric juice secretion rate affect antacid function (Richa et al., 1997, Lirazan et al., 2018, Voropaiev& Nock, 2021). These findings strongly urge the examination of different batches of the same formulations.

Cost effectiveness

Antacid prices are a consideration while selecting the antacid (Jacob et al., 2016). The antacids marketed in Gaza Strip have a price for the minimum labeled dose (PMLD) in the range of 0.08 to 0.7 ($) (Table 5).

Oral suspensions have higher prices per MLD in comparison to tablets and the alginate based formulation is the most expensive in the local markets. To examine the cost effectiveness the ANC/PMLD ratio was calculated. The most favorable formulation should have a high ANC/PMLD ratio (Yafout et al., 2022). The highest value was for A4 followed by A2, which contain calcium carbonate buffering salts. A2 formulation showed also a rapid onset of action and long duration of buffering effect (Table 4). These results show that antacids containing calcium carbonate offer the economically favorable choice for customers. The lowest ratio of alginate-based formulation (A5) is expected, since

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the activity is not based on buffering of acid. The low ANC/PMLD ratio of alginate based oral suspension was recorded in other studies (Yafout et al., 2022, Mahmood et al., 2020).

These results are in line with earlier studies that have found a wide variation in antacid's cost effectiveness. This factor should be considered when selecting the economically appropriate product (Jacob et al., 2016, Yafout et al., 2022, Mahmood et al., 2020).

Table 5: Data of the minimum labelled dose and cost effectiveness.

Sample	Density Suspensions	MLD (mL) Suspension	Average weight of MLD(g) Tablets	PMLD ($)	Cost-effectiveness ANC/PMLD (mEq/$)
A1			1.323	0.15	137.07
A2			1.860	0.17	171.41
A3			1.274	0.17	74.35
A4			0.999	0.08	203.62
A5	1.16	10		0.7	12.48
A6	1.03	5		0.31	33.26
MLD: Minimum Labelled Dose, PMLD: Price of Minimum Labelled Dose					

Statistical analysis

The mean of ANC/MLD for solid formulations was higher than that of liquid antacid formulations. Statistical analysis showed insignificant difference between the means of the two tested groups (Table 6), since the p-value was greater than 0.05.

Table 6: Statistical analysis of ANC/MLD data for antacids

Groups	Mean	SD	df	t-test	P-value
Solid formulation	19.73	7.24	4	1.822	0.142
Liquid formulation	9.78	1.46			
ANC: Acid Neutralizing Capacity, MLD: Minimum labelled dose, SD: Standard deviation.					

Conclusion

All antacid samples marketed in the Gaza Strip met PAT and ANC criteria. While antacids with calcium carbonate buffering salt showed better ANC, sodium alginate-based suspension had lower ANC. Antacids A1 and A2 containing calcium and magnesium buffering salts showed high ANC values and a longer buffering duration in ANP study. In terms of cost-effectiveness the economically favorable choice for patients were chewable tablets. It is recommended to add ANC and ANP on the label of antacids or in the drug formulation leaflet. Further studies are recommended to evaluate ANC and ANP for different batches of the same antacids.

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