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Evaluation of acid neutralizing and buffering capacities of selected antacids in Ghana

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ABSTRACT

This study has evaluated the acid neutralizing and buffering capacities (BC) of nine selected antacid brands ("L_1-L_9") in Ghana. The active acid neutralizing ingredients were recorded and the preliminary antacid test (PAT) determined with 0.5 N HCl after 10 min. The acid neutralizing capacity (ANC) was evaluated with 1 N HCl by neutralizing the excess with 0.5 N NaOH after 15 min stirring. Buffering capacity (BC) was estimated with 0.1 N HCl and titrated with 0.1 N NaOH at 5 min interval up to 50 min. All determination were at 37±3 °C using a pH meter. All brands had as part of their active ingredients dried aluminum hydroxide and magnesium hydroxide, with 67% containing simethicone as antifoam. The PAT declared all brands to be antacids with pH range of 4.38 ± 0.21–6.43 ± 0.06. The ANC of all brands were in the range 13.16 ± 0.55–20.70 ± 0.18 mEq/g with "L_4" and "L_9" having the lowest and highest values respectively. "L_9" further demonstrated a considerably higher BC up to 40 min whiles "L_6" had the least BC up to 15 min. The ability of an antacid to have a high ANC and to resist significant changes in pH (longer BC) is crucial in assuring quality and efficacy of the brand.

1. Introduction

Gastric juice is made up of water, electrolytes, hydrochloric acid (HCl), enzymes, mucus, and intrinsic factor. HCl is secreted by the parietal cells. On the average, an adult stomach produces 1.5–2.5 litres of gastric juice per day [1]. Measuring a pH of 1.5 on a pH scale (0–14), the gastric juice is a strongly acidic solution expressing a high concentration of hydrogen ions (H^+) [2]. The acidic stomach content is essential for food digestion and activation of digestive enzymes. The stomach however sheds the mucous lining every three days. Stimulation of H^+secretion occurs during feeding [3]. In the event of excess acid content, H^+ions retract to the blood, leading to muscular contraction, inflammation, bleeding, pain and ulceration due to the stomach lining break down with subsequent acid attack on the stomach wall [4]. It must however be mentioned

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that via a natural mechanism, the stomach protects itself from acid degradation by the production of bicarbonate-rich mucus and the provision of rich blood supply.

An antacid is an antidote for reducing the H^+in the stomach through neutralization reaction with the excess HCl in gastric juice and inhibition of the proteolytic enzyme, pepsin [5]. Antacids are a major class of over the counter pharmaceuticals sold globally. Importantly, a significant number of consumers or patients in Ghana self-medicate with antacids. In addition, a large part of the worldwide population is affected by acid indigestion and heartburn with consumers spending billions of dollars on antacids in search of relief globally [6]. Antacid specialties are prescribed to relieve the symptoms of peptic ulcers/ hyperacidity (acid indigestion) or Heartburn/Gastroesophageal reflux disease (GERD) and stomach upset [7]. GERD has emerged as an important and common acid related disorder affecting nearly 35–40% of adults in the western world with 36% of them reporting symptoms at the hospital once a month [7]. Furthermore, antacids also help relieve any pain usually associated with stomach ulcer and help prevent irritation of the stomach [8]. Most antacids are basic in nature with a net pH above 7 and may exist as buffer systems (substances that are capable of minimizing changes in the concentrations of hydrogen (H^+) and hydroxyl (OH^-) ions) to offer pH stability in the stomach [9]. A few studies have reported on the use of antacids to promote healing in duodenal ulcer [10].

Different brands of antacids are available to relieve heartburn and peptic ulcer pain in Ghana. These commercial brands of antacids come in various dosage forms, as either liquids or solids. Magnesium and aluminum as hydroxides alone or in combination form the principal composition of most antacids. Some also contain salts of calcium, sodium, carbon or bismuth in their formulations [11]. Liquid preparations of antacids are usually considered to be more effective than the solid ones (tablets) due to their already dispersed form [12]. Antacids are generally classified as being systemic (absorbable antacids – which are soluble, readily absorbable and capable of producing systemic electrolytic alterations and alkalosis e.g. sodium bicarbonate) and non-systemic (non-absorbable antacids – which are not absorbed to a significant extent). This group includes – (i) Aluminum containing antacids – aluminum hydroxide, aluminum phosphate (ii) calcium containing antacids – calcium carbonate, tribasic calcium phosphate (iii) magnesium containing antacids – magnesium carbonate, magnesium hydroxide (iv) combination antacid preparations – simethicone (defoaming agent) [13-14].

The effectiveness of each antacid depends on its neutralizing capacity and the transit time in the stomach (buffering capacity). Manufacturers of over the counter medicines including antacids often reformulate some products in order to improve on palatability and organoleptic properties of products to attract clients. The Ghanaian market is thus flooded with several antacids products that are advertised on the print, electronic and the airwaves purporting their relative advantages over one another. The public and the physician are therefore baffled with choices that are not underpinned with predetermined quality and efficacy of the products. However the decision to select a particular antacid must be informed ideally by it having a relatively high acid neutralizing capacity (ANC) stated in milliequivalents and the demonstration of a buffering capacity (BC) to maintain gastric pH above 3.5 for a considerable amount of time. Marketed antacid products may be differentiated with reference to their ANC determined at 37 $^{\circ}C \pm 3$ °C to neutralize stomach acid. The ANC unfortunately is not stated on product labels but differs significantly among competing brands [15]

This study thus aimed at evaluating the acid neutralizing and buffer capacity of nine (9) different commercial brands of antacid oral liquid products, commonly marketed in Ghana. To the best of our knowledge, this is the first report on antacid neutralization and buffering capacities of antacids marketed in Ghana.

2. Materials and methods

2.1. Sampling and composition of samples

Nine different brands of commonly marketed antacids ($n = 9$) found in Pharmacies, OTC medical stores and some supermarkets in Accra and Kumasi (Ghana) were purposively sampled and transported to the centre for Drug Analysis and Quality Control Laboratory of the Department of Pharmaceutical Chemistry, KNUST, Kumasi, for analysis. The samples were coded "L_1-L_9". Four of the brands are locally manufactured, 4 imported from India and 1 from England. For the primary packaging, 4 were found in plastic amber bottles, 4 in glass amber bottle and 1 in plastic plain bottle. Seven out of nine had stated volumes of 200 mL with "L_1" and "L_7" having 180 mL and 125 mL respectively. The cost per bottle of antacid ranged from GH₵ 6.00 to GH₵ 14.00 (approximately US$ 1–3). All vital information such as volumes, cost, batch numbers, the primary packaging and the source of manufacture captured are displayed in Table 1. Three different batches were generally analysed for all sampled brands. The active pharmaceutical ingredients were recorded. Table 2 shows the compositions of the various brands of antacids. All the nine brands of antacids sampled had as part of their active ingredients dried aluminum hydroxide and magnesium hydroxide. Six (6) out of the 9 contained simethicone. Two (2) brands also had magnesium trisilicate as ingredient. Other ingredients such as sodium alginate, alginic acid, simethicone and dimethicone were also found. Only sample "L_1" had Deglycyrrhizinated liquorice as an active.

2.2. Preliminary antacid test (PAT)

An accurate amount of a well-mixed antacid product equivalent to the minimum labeled dosage; (5 mL) was weighed into a 100 ml beaker. For brand "L_5", 15 mL was the minimum labelled dosage. Sufficient carbon dioxide free distilled water was added to obtain a total volume of about 40 ml and mixed on a Hotplate magnetic stirrer (IKA C-MAG HS7) at

Table 1
Volumes and batch numbers of sampled brands of antacid suspensions .

Sample	Volume (mL)	Cost (GH₵)	Batch Number		
##L_1*	180	9.00	10,161,779	10,160,998	10,180,058
#L_2**	200	7.00	0103T	0403T	0505T
##L_3***	200	9.00	BI094	ALI014	BL067
#L_4**	200	6	RO279	RO272	RO295
##L_5**	200	15	BO(10)NUS7027	BO(10)NUS7017	BO(10)NUS7021
#L_6**	200	8	16,029	16,018	16,022
#L_7*	125	5	1,200,176	1,200,046	1,200,067
##L_8*	200	14.00	EL-397	EL-356	EL-394
##L_9*	200	8.00	G6026	G6012	G6027

_Locally manufactured
_Imported, *Plastic amber, **Glass amber, *** Plastic plain

300 ± 30 r.p.m for a minute. 10.0 mL of 0.5 N HCl (VS) was added to the test solution while stirring on the magnetic stirrer at 300 ± 30 r.p.m for exactly 10 min after addition of acid. The pH was read and recorded with a standardized Eutech instruments pH meter (ION 2700) to ascertain label claim as an antacid if pH is 3.5 or greater [16]

2.3. Acid neutralizing capacity (ANC)

The ANC was determined for all the brands since each had a pH of 3.5 or greater from the PAT. An accurate volume (5 mL) of the antacid suspension was measured into a 25 ml beaker and weighed. The suspension was then transferred into a 250 ml beaker and made up to 70 ml with carbon dioxide-free distilled water and stirred for one minute. An accurate volume of 30 ml of 1.0 N HCl was pipetted into the suspension whiles stirring for 15 mins. The excess HCl was titrated with 0.5 N NaOH (VS) to attain a threshold pH of 3.5. The experiment was carried out for the different brands and their respective batches at a temperature of 37 °*C* ± 3 °C on a magnetic stirrer. The number of milliequivalent (mEq) of acid consumed per gram of antacid was calculated [17].

The acid neutralizing capacity (ANC) was calculated using Equation 1

Total mEq = (30 x N_{HCl}) – (V_{NaOH} x N_{NaOH}).....Equation 1

Where N_{HCl} and N_{NaOH} are the normalities of HCl and NaOH, respectively, and V_{NaOH} is the volume of NaOH used for the back titration.

2.4. Buffering capacity (BC)

An accurate volume of 5 mL each of the antacid samples were measured and transferred into a 250 mL beaker and 50 mL of distilled water added and heated to 37 °*C* ± 3 °C. The suspension was stirred for one minute and the initial pH recorded with standardized pH meter. An accurate volume of 100 mL of 0.1 N HCl previously heated to 37 °*C* ± 3 °C was added to the suspension with continuous stirring. The rate of pH change of the resulting solution was measured 10 times at an interval of 5 mins, at ambient temperature.

During this process, a quantity of 20 mL of the suspension was removed by means of a pipette and replaced with 20 mL of fresh 0.1 N HCl. This process was repeated at 5.0 min interval until a pH below 2.75 was observed for the different brands in triplicates [18].

3. Results and discussion

3.1. Sampling and composition of samples

The use of antacids through self-medication is a common practice in Ghana since antacids are available as Over-the-counter (OTC) medications. The dispensing of antacids is thus not only restricted to nationally regulated pharmacies. Three (3) bottles of each batch were sampled and analysed for ANC and BC by titration with pH recording. Chidananda et al., [19] have evaluated various antacid products for their ANC by both the titrimetric and the potentiometric methods.

Dried aluminum hydroxide, magnesium hydroxide and magnesium trisilicate are active ingredients responsible for the acid neutralizing capacity of antacids. Aluminum hydroxide ($Al(OH)_3$) as a typical antacid active was used in combination with magnesium hydroxide to obtain the desired acid neutralizing capacity (ANC) in 100% of the brands analysed. Aluminum hydroxide as gels contain carbonate in the gel structure and are amorphous in nature which improves the reactivity of the aluminum, permitting for its acid neutralizing capacity and resulting in a more effective antacid. Some brands had the gel form of aluminum hydroxide in the label claim. In addition, the combination of aluminum hydroxide and magnesium hydroxide offers a good pH buffering effect and further compensates for their side effects. The bloating, pain and discomfort resulting from excess gas in the stomach and intestinal tract aggravates the hyperacidity condition. However, these are ameliorated by throwing in the formulation, an antifoaming agent such as simethicone (a suspension of polydimethylsiloxane

Table 2
Composition of different brands of antacid suspensions.

Brand	Composition (mg/5 mL) Dried Aluminum Hydroxide	Magnesium Hydroxide	Dimethicone	Simethicone	Deglycyrrhizinated liquorice	Sodium alginate	Magnesium Trisilicate	Alginic acid
L_1	365	80		100	400			
L_2	250	250		50				
L_3	125	250		50		100		
L_4	250	250	50 (activated)					
***L_5**	250	250	125				250	200
L_6	200	200		25				
L_7	300	100					200	
L_8	250	250		50				
L_9	250	250		50				

*Label claim for "L_5" is 15 mL per dose.

Table 3
PAT and ANC for brands of antacids.

Brands	Density (g/ml)	PAT (pH) 0.5 N HCl		ANC (pH) 1.0 N HCl		ANC mEq/g
		0 min	10 min	0 min	15 min	
L_1	0.96	8.02	4.38±0.21	8.6	1.25	19.53±0.37
L_2	1.06	8.18	4.49±0.16	8.79	1.31	18.37±0.10
L_3	0.98	8.84	6.43±0.06	8.81	1.12	13.88±0.58
L_4	1.03	8.48	6.24±0.04	8.62	1.10	13.16±0.55
L_5	0.85	7.82	4.85±0.26	8.06	1.20	19.59±0.17
L_6	1.03	8.40	5.43±0.00	8.85	1.12	14.32±0.21
L_7	0.96	8.70	5.15±0.02	9.02	1.17	17.19±0.37
L_8	0.96	8.60	5.64±0.01	9.09	1.31	20.49±0.18
L_9	0.96	8.47	4.51±0.14	8.88	1.27	20.70±0.18

Sample calculation using product L_1.
Total mEq = (30 x N_{HCl}) – (V_{NaOH} x N_{NaOH}).
N_{HCl} = 1.0 M N_{NaOH} = 0.5 M V_{NaOH} = 22.5 mL.
Total mEq = (30×1.0) – (22.5 × 0.5) = 18.75 mEq.
ANC per gram of antacid $= \frac{\text{total mEq}}{\text{density of antacid}} = \frac{18.75}{0.96} = 19.53$ mEq/g of antacid

and silica gel). Simethicone was commonly used in six of the brands analysed but dimethicone, with similar activity was used in brands "L_4" and "L_5" at 50 mg (activated) and 125 mg dose of antacid respectively (Table 2). The difference between simethicone and dimethicone lies in the absence of silica in dimethicone. Only brand "L_3"employed sodium alginate which is a very reactive antacid active that combined with magnesium hydroxide and others. In addition to dried aluminum, magnesium hydroxide and simethicone, brand "L_5" had magnesium trisilicate and alginic acid. The presence of magnesium is significant for laxative effect through relaxation of stomach muscles.

3.2. Preliminary antacid test

A pH greater than 3.5 was recorded for all the antacid brands analysed, a demonstration that products are antacids. The Preliminary Antacid Test (PAT) is however not an efficacy or quality indicating test. Brand "L_3"rcorded the highest PAT pH with "L_1" recording the least value (Table 3), the difference of which however is considered very statistically significant (p value = 0.004) for unpaired *t*-test (graphpad.com). The closest PAT value to "L_3" is that of "L_4" where the difference was not statistically significant. Having passed the PAT, all the sampled brands were deemed qualified as 'antacids' and therefore were subjected to the ANC and buffering capacity tests that distinguishes one product from the other with respect to efficacy.

3.3. Acid neutralizing capacity

Official methods for measuring the acid neutralizing capacity of antacid in vitro at 37 °C include a United States Pharmacopoeia (USP) test, British Pharmacopoeia (BP) Test (European Pharmacopoeia [pH Eur] Test), pH Stat or Sjogren Test, Acid Consuming Capacity (ACC) and Rossett Rice Test. These tests in addition measure the speed of neutralization. Antacid active ingredients may reach the same neutralization capacity but at different speeds. In this work, the USP method was employed in determining the ANC of the sampled antacid brands.

The ANC for the antacids analysed (n = 9) were determined and expressed as milliequivalent (mEq) of the antacid as specified by the USP 32 NF 27 (Table 3). The ANC of all the brands were determined to be in a range of 13.16 ± 0.55 to 20.70 ± 0.18 of antacid per dose. Brand "L_4" had the lowest ANC of 13.16 ± 0.55 mEq/g whiles brand "L_9" had the highest ANC of 20.70 ± 0.18 mEq/g. However other brands such as "L_1", "L_2", "L_5" and "L_8" had very good ANC values above 18. The USA-FDA [20] specifies that the ANC for an antacid should not be less than 5 mEq per dose of the antacid. Based on this criterion, all brands of antacids sampled passed. It is worth noting grounded on data from the product labels that brands "L_1", "L_6", "L_8" and "L_9", had the dried aluminum hydroxide in gel form. The acid neutralizing capacities of brands "L_1", "L_8" and "L_9" were amongst the highest of the brands analysed. The high ANC values observed for these brands could have been influenced by the gel nature of the aluminum hydroxide though same cannot be said for brand "L_6".

The antacid worked on are deflocculated suspensions having a range of particle sizes. No clear boundaries are formed but in a few situations like products "L_1", "L_5" and "L_8", the supernatant remains turbid for a considerable period of time. This confirms the deflocculated nature of the antacids analysed.

3.4. Buffering capacity

The rate of pH change with time representing the Buffering capacity for each antacid was determined and compared as shown in Table 4. All the brands had their initial pH ranging from 7.91 – 8.91. Based on the data from the buffering capacity of the antacids analysed, it is observed that brand "L_8" had buffering capacity being maintained for 35minutes whilst product "L_9", had buffering capacity maintained for 40 min. Product "L_9" had the highest initial pH of 8.91 and

Table 4
Buffering Capacity (Rate of pH change of antacid suspension with time).

Sample	0 min	pH								
		5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	50 min
L_1	8.48	3.63	3.96	4.10	3.31	2.52	ND	ND	ND	ND
L_2	8.45	3.58	3.86	4.29	3.76	3.00	2.54	ND	ND	ND
L_3	8.09	4.01	4.53	5.74	4.07	3.25	2.60	ND	ND	ND
L_4	8.62	5.51	6.19	5.40	3.48	2.36	ND	ND	ND	ND
L_5	7.91	4.23	3.27	3.46	2.58	ND	ND	ND	ND	ND
L_6	8.85	4.17	2.92	2.21	ND	ND	ND	ND	ND	ND
L_7	8.85	3.28	3.29	3.15	2.97	2.78	2.25	ND	ND	ND
L_8	8.85	4.09	4.15	4.22	3.39	3.36	3.06	2.52	ND	ND
L_9	8.91	6.12	6.17	6.24	5.48	5.30	4.27	2.79	2.47	ND

ND- Not Determined after the threshold pH *value of 2.*

showed a consistently resilient change to pH with time followed by brand "L_8". The consistent data obtained indicates the superior stability of brand "L_9", followed by brands "L_2", "L_3", "L_7" and "L_8". A demonstration of a high ANC and a longer buffering capacity by an antacid indicates its efficacy and quality.

The stability of the active ingredients in the antacid suspensions provide an indication of how stable the formulations are and how resilient these formulations could withstand environmental stress such as temperature and humidity. In addition, the viscosities of the acid neutralizing components and that of simethicone used in the formulation have a significant effect on the stability of the product upon storage. Although the viscosity grade of the samples containing simethicone in addition to aluminum hydroxide and magnesium hydroxide were not quoted by the manufacturers, variations in their values could account for the differences observed in the ANC and buffering capacities reported. It must however be added that deactivation of the antifoaming agents in combination with other inorganic salts such as aluminum hydroxide and magnesium hydroxide have been reported [21-22]

Deductions from the *in-vitro* data obtained indicate that antacid efficacy cannot be established based solely on ANC. A demonstration of a good buffering capacity in addition to a high ANC by an antacid is requisite in estimating the efficacy as observed with brand "L_9". Further, the current work has indicated that the cost of an antacid does not reflect in the quality or efficacy of the product as was similarly observed by Rao et al., [23]. For these reasons, this research recommends the quoting of ANC and buffering capacity values in the product leaflet of antacids marketed in Ghana to aid prescribers and consumers make informed decision and get value for money.

4. Conclusion

The study has shown that all the antacid brands analysed ($n = 9$) had dried aluminum hydroxide and magnesium hydroxide as active acid neutralizing agents, with 67% containing simethicone as antifoam. All the brands qualified as antacids with each having PAT pH greater than 3.5. In addition, they all recorded ANC values above the acceptable limit of 5 mEq/g. The buffering capacities observed were however not consistent with the ANC except for brands "L_2", "L_7", "L_8" and "L_9" that demonstrated consistent ANC and buffering capacity to assure quality and efficacy in vitro. Brand "L_9", with dried aluminum hydroxide gel showed superior ANC and Buffering capacity values. The current work has further shown that cost does not translate to quality as both expensive and low cost brands were found within the acceptable limits of antacid action. Antacids exert their effects by the combined action of their acid neutralization and buffering capacities. Therefore to improve human welfare with respect to the use of antacids, it is highly recommended for manufacturers to state ANC and BC values on labels or in drug information leaflets to assure medicine quality, efficacy and value for money.

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Declaration of Competing Interest

The authors report of no conflict of interest for the research presented.

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