EVALUATION OF ACID NEUTRALIZING CAPACITY OF SELECTED ANTACID SUSPENSION IN BENIN CITY USING BROMOPHENOL BLUE INDICATOR

BY

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BEING A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF DOCTOR OF PHARMACY (PHARM D) DEGREE OF THE UNIVERSITY OF BENIN, BENIN CITY.

JANUARY, 2023

CERTIFICATION

This is to certify that this work was carried out by Irechukwu Augustine Obumneme in the Department of Pharmaceutical chemistry, Faculty of Pharmacy, University of Benin, Benin city In partial fulfilment for the award of the Pharm.D degree of the University

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Date

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Date

Head of Department

DEDICATION

This project is dedicated to the Almighty God and to my family and friends for their immense support throughout the course of this pursuit

ACKNOWLEDGEMENTS

My profound and sincere gratitude goes to God Almighty, the Sole of my existence and the main reason for the success of this project work. He made this possible even when things seem to fall apart.

I wholeheartedly appreciate my highly esteemed supervisor Dr. Aghayere for his unrelenting efforts, commitment and assiduity to make sure this work is well carried out and presented in a way its essence would be best communicated. He challenged me to do better when I was ready to setle for the little I had done. He was indeed the pivot to this epic research.

I am particularly grateful to my Head of Department Dr. Imeje Vincent and our diligent lecturers of the Faculty of Pharmacy.

My heartfelt appreciation goes to my ever loving and caring parents, Mr and Mrs Irechukwu, for all you have put in to make me who I am today. Your every bit of prayer, advice,instruction and finance amounts so much. To all my siblings, thank you so much for your belief in me to deliver our common goals. You will be in the bone of my heart forever. You are one of a kind.

To my friends,Sunday,Godspower,I just want to tell you that I appreciate aIl your efforts and contributions to the completion of my work.

Thank you all so much.

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ABSTRACT

Background: Antacids are usually alkaline substances that are used to neutralize excess acid in the stomach and they are common over the counter (OTC) medications used by patients to obtain fast symptomatic relief from dyspepsia, heartburn, peptic ulcer, etc. Some antacid products may neutralize more acid in the stomach than others, the ability of an antacid to neutralize acid is expressed as its acid neutralizing capacity (ANC). High technology equipment like standard pH meter which is needed in the determination of acid neutralizing capacity (ANC) are not readily available in developing countries like Nigeria and there is also the issue of epileptic power supply which makes it essential to determine a suitable indicator that can be used in titrimetric method of determining ANC which is inexpensive, simple and could be used in routine monitoring of the quality of antacid suspensions.Also,the Buffering capacity of the antacids are investigated to understand the duration of action of their acid neutralizing action

Method: The United States Pharmacopeia (USP) method of analysis of antacids was adopted,using acid-base titration (back/indirect titration), the use of an indicator (Bromophenol Blue) was used to determine the pH change in place of a pH meter. The samples were coded A-T to avoid any bias in the study. All the sampled brands has at least 1 year to expiry as indicated on the label.

Results: A pH greater than 3.5 was recorded for all the antacid brands analyzed in the preliminary antacid test (PAT), this proved that they are all antacids. All the brands of antacids analyzed for their ANC were found to meet the specification of 5mEq/dose. However, a wide variation in the ANC results was observed among the brands where sample I was found to have the highest ANC value (25.50mEq/dose), while sample A has the lowest ANC value (8.50mEq/dose). Sample B has the highest buffering capacity which was maintained for 25minutes while sample A and G also has the lowest buffering capacity of just 5minutes.

Conclusion: The titrimetric procedure used in this study is simple, inexpensive, and easy to use and could be used in routine monitoring or periodic evaluation of the quality of Antacid suspensions and this could help prescribers to make informed choices for their patients.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

The stomach is an organ of the digestive tract, which has the special task of processing food and preparing it for absorption into the intestines. The secretion of gastric juice is one of the important functions of the stomach. (Wolfe and Sol,1988)

The composition of gastric juice are water, electrolytes,hydrochloric acid (HCI), enzymes,mucus,and intrinsic factor.HCI is secreted by the parietal cells. On the average, an adult stomach produces1.5-2.5 litres of gastric juice per day.(Pohl et al., 2008)

There is a very high concentration of hydrogen ions (H+) in the gastric juice which makes it a strong acidic solution, it has a PH of 1.5 on a PH scale (0-14). (Steingoetter et al., 2015)

The acidic environment of the stomach plays an important role in the digestion of food anddigestive enzymes activation.

When the concentration of H+ gets too high, it retracts to the blood which in turn leads to muscular contraction, inflammation, bleeding, pain and ulceration due to the breaking down of the stomach lining and subsequent acid attack on the stomach wall.(Dixon,1991)

An antacid is a substance which neutralizes the acid in the stomach and is administered to relieve heartburn, indigestion or a stomach upset. (Internal Clinical Guidelines Team,UK 2014)

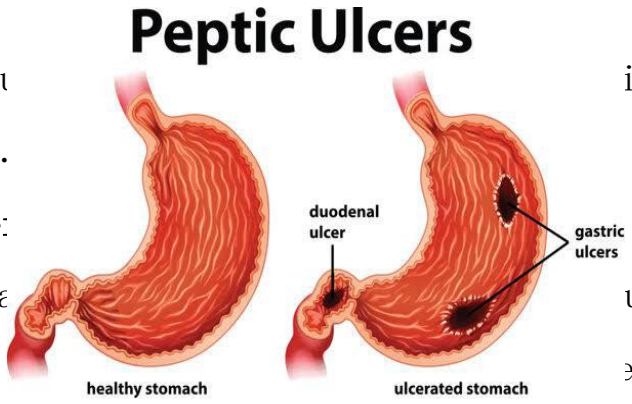
Antacids are pharmaceutical drugs which are bases or basic in nature and are capable of neutralizing the acid of the gastric content (such as stomach) and thus lower the acidity of the content (Van Riet-Nales et al., 2002).

Antacids are known to be effective in gastric and duodenal ulcer and GERD for several decades.

Although they have not been proven to directly act on the erosive lesions, they are able to neutralize the excess of HCI in the gastric juice and therefore, reduce the activity of pepsin, enhance the healing process, and offer rapid relief of heartburn and acid reflux. (Patrick, 2011)

Some antacid products may neutralize more acid in the stomach than others.The way to express the ability of an antacid to neutralize acid is by determining the antacid's neutralizing capacity(ANC).ANC measures the ability of the antacid to neutralize acids (pH of 3.5 to 4). The US FDA requirement is that an antacid must have a neutralizing capacity of ⩾5 mEq per dose. The most effective antacids should have a high acid neutralization capacity and rapid gastric acid neutralization qualities. Most antacids contain magnesium hydroxide, aluminium

hydroxide, calciu ion of these. (Ngwuluka et al.



1.2 Peptic Ulce:

Peptic ulcers a used by stomach acid tat cause e submucosa. The stomach or proximal duodenum are the typical sites for peptic ulcers, however they can also develop in the oesophagus or Meckel's diverticulum, the term peptic ulcer disease refers to peptic ulcers located in the stomach or duodenum. (Del, 2015)

Fig1.1 Peptic ulcer

The majority of peptic ulcer diseases were previously believed to be brought on by a hypersecretory acidic environment, along with dietary factors or stress, but the identification Of helicobacter pylori infection and the widespread use of nonsteroidal anti-inflammatory drugs(NSAIDs) in the latter half of the 20th century have altered this belief. (Lance, 2017)

1.2.1 Epidemiology of Peptic Ulcer Disease

The estimated lifetime prevalence of peptic ulcer disease in the general population is 5-10%,with an annual incidence rate of 0-1-3%.(Del,2015)

However, epidemiological studies have revealed a sharp decreasing trend in the incidence, rates of hospital admissions, and mortality associated with the disease in the past 20-30 years,suggesting that the prevalence and incidence of peptic ulcer disease are now probably lower than these estimates globally, especially in high-income countries.(Sonnenberg,2013)

These numbers may be falling as a result of new treatments being made available or they may reflect a cohort trend that cannot be fully explained by recognized factors (such as H-pylori infection and NSAID use).

ince the prevalence of many gastrointestinal disorders fluctuates, it is possible that peptic ulcerisease is affected by an underlying birth-cohort trend.

eptic ulcer disease-related mortality peaked in the last quarter of the 19th century and declined ine first half of the 20th. The overall pattern corresponds to the declining prevalence of H pylor infection in the population, with a birth-cohort effect also being observed in nations with low prevalence of the infection, despite the fact that the decrease noted includes all types of ulcers (H-pylori-associated, NSAID-associated, and idiopathic).

1.2.2 Mechanism of Gastric Acid Secretion

Gastric acid breaks down solid foods to more easily absorbed portions which makes it very essential for food digestion. The formation of acid by the stomach is a finely regulated physiological process that involves numerous different types of epithelial cells,as well as neurological and hormonal systems. Protons and chloride are the gastric acid's active ingredients. These species-which are often crudely referred to as hydrochloric acid-are created by parietal cells in the gastric glands of the stomach. The secretion process is intricate and relatively energy-intensive. The vast secretory network found in parietal cells, known as canaliculi, is where "hydrochloric acid" is secreted into the stomach lumen.The proton pump H+/K+ATPase regulates the pH of gastric acid in the human stomach lumen, which ranges from 1.5 to 3.5. (Marieb et al, 2008)

There is a transient elevation in the blood PH which is caused by the release of bicarbonate in the bloodstream by the parietal cells. An average adult human stomach produces 1.5 liters of gastric acid every day. Gastric acid secretion is produced in many steps. From the cytoplasm of parietal cells, chloride and hydrogen ions are released independently and combined in the canaliculi. After then, gastric acid is secreted into the gastric gland lumen and moves progressively toward the stomach lumen.(Dworken,2016)

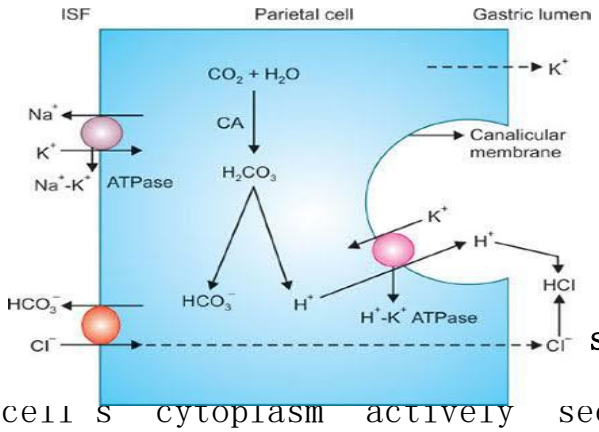


Fig secretion

The parietal cell's cytoplasm actively secretes sodium and chloride ions into the canaliculus lumen. As a result, the parietal cell membrane develops a negative potential of between -40 and-70 mV, which causes some sodium and potassium ions to permeate into the parietal cell canaliculi from the cytoplasm.

The reaction between carbon dioxide and water to create carbonic acid is catalyzed by the enzyme carbonic anhydrase. This acid splits into hydrogen and bicarbonate ions right away. Through H+/K+ATPase anti porter pumps, the hydrogen ions escape the cell.

To enhance the rate at which gastric acid is secreted in order to digest food, there are three steps. (Dworken, 2016)

The cephalic phase: Thirty percent of the total gastric acid secretions to be produced is stimulated by anticipation of eating and the smell or taste of food. This signaling occurs from higher centresin the brain through the vagus nerve (Cranial Nerve X). It activates parietal cells to release acid and ECL cells to release

histamine. The vagus nerve (CN X) also releases gastrin releasing peptide onto G cells. Finally, it also inhibits somatostatin release from D cells.

The gastric phase: About sixty percent of the total acid for a meal is secreted in this phase. Acid secretion is stimulated by distension of the stomach and by amino acids present in the food.

The intestinal phase:The remaining 10% of acid is secreted when chyme enters the small intestine,and is stimulated by small intestine distension and by amino acids. The duodenal cells release entero-oxyntin which acts on parietal cells without affecting gastrin.

1.2.3 Causes of Peptic Ulcer

Infection with H. pylori and usage of nonsteroidal anti-inflammatory medicines (NSAIDs) account for 48 and 24% of cases of peptic ulcer disease respectively in the United States. (Kurata and Nogawa,1997)

A variety of other infections and co-morbidities are associated with a greater risk of peptic ulcer disease (e.g.,cytomegalovirus, tuberculosis, Crohn's disease, hepatic cirrhosis, chronic renal failure,sarcoidosis, myeloproliferative disorder). Critical illness, surgery, or hypovolemia leading to splanchnic hypoperfusion may result in gastroduodenal erosions or ulcers (stress ulcers);these may be silent or manifest with bleeding or perforation. (Ziegler,2005)

Smoking increases the risk of ulcer recurrence and slows healing.

Helicobacter Pylori

Only a small number of people with H. pylori infection develop peptic ulcer disease (10 to 15 percent of patients), despite the fact that H. pylori is typically found in the gastroduodenal mucosa patients with duodenal ulcers.There is an increase in virulence and likely the ulcerogenic potential due to the presence of an outer inflammatory protein and a functional cytoxin-associated gene island in the bacteria chromosome.(Nilsson er al.,2003)

Patients with H.pylori infection have higher levels of gastrin at rest and after meals, as well as lower levels of gastric mucus and duodenal mucosal bicarbonate secretion,both of which are favorable to the development of ulcers. The rate of ulcer recurrence is drastically decreased when H. pylori is eradicated,dropping from 67 to 6 percent in patients with duodenal ulcers to 59 to 4 percent in patients with stomach ulcers.(Hopkins et al, 1996)

Non-Steroidal Anti-inflammatory Drugs (NSAIDS)

In people without H. pylori infection, NSAIDs are the most frequently cited cause of peptic ulcerdisease.Submucosal erosions are brought on by NSAID topical action. Additionally, NSAIDs prevent the production of prostaglandins and their protective cyclooxygennse-2-mediated actions by inhibiting cyclooxygenase (i.e., enhancing gastric mucosal protection by stimulating mucus

and bicarbonate secretion and epithelial cell proliferation and increasing mucosal blood flow). The frequency and severity of NSAID-induced damage are both increased when H.pylori infection exists. (Huang et al,2002)

patients who use NSAIDs for a prolonged period of time run a 1-4% annual risk of developing life-threatening ulcer-related complication, with elderly patients running the largest risk. The majority of perforated ulcers, which most frequently affect elderly individuals taking aspirin other NSAIDs for cardiovascular disease or arthropathy, are caused by the use of NSAIDs.(Lanas et al,1997)

Stress:

Stress due to serious health problems, such as those requiring treatment in an intensive care unit, is well described as a cause of peptic ulcers, which are also known as stress ulcers.(Steinberg,2002).While chronic life stress was once believed to be the main cause of ulcers, this is no longer the case. It is, however,still occasionally believed to play a role (Fink, 2011).This may be due to the well-documented effects of stress on gastric physiology, increasing the risk in those with other causes, such as H. pylori or NSAID use (Yeomans,2011).

Diet

Dietary factors, such as spice consumption, were hypothesized to cause ulcers until the late 20th century,but have been shown to be

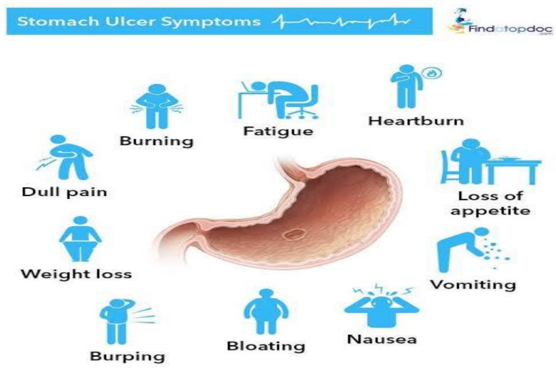
of relatively minor importance (National Digestive Disease information,2006). Caffeine and coffee, also commonly thought to cause or exacerbate ulcers,appear to have little effect (Rubin et al,2011 and Ryan-Harshman, 2004)

Similarly,while studies have found that alcohol consumption increases risk when associated with H.pylori infection, it does not seem to independently increase risk. Even when coupled with H.pylori infection,the increase is modest in comparison to the primary risk factor (Salih et al,2007).Other causes of peptic ulcer disease include gastric ischaemia, drugs,metabolic disturbances,cytomegalovirus), upper abdominal radiotherapy, vasculitis. Gastrinomas (Zollinger-ellison syndrome), or rare gastrin-secreting tumors, also cause multiple and difficult-to-heal ulcers(Feliberti et al., 2013)

1.2.4 Signs and Symptoms of PUD

Signs and symptoms of a peptic ulcer can include one or more of the following:

1. Abdominal pain, classically epigastric, strongly correlated with mealtimes. In case of duodenal ulcers, the pain appears about three hours after taking a meal and wakes the person from sleep.
2. Bloating and abdominal fullness.



3. Waterbrash (a rus … regurgitation to dilute the acid i … re associated with gastroesophagea …

4. Nausea and copiou …

5. Loss of appetite … r.

6. Weight gain, in d … lieved by eating.

7. Hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer or from damage to the esophagus from severe/continuing vomiting.

8. Melena (tarry, foul -smelling feces due to presence of oxidized iron from hemoglobin).

9. Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis and extreme, stabbing pain, and requires immediate surgery (Bhat, 2013).

Fig 1.3: Symptoms of Peptic Ulcer

A history of heartburn or gastroesophageal reflux disease (GERD) and use of certain medications can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAIDs(non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase and most glucocorticoids (e.g.,dexamethasone and prednisolone).
In people over the age of 45 with more than two weeks of the above symptoms, the odds for peptic ulceration are high enough to warrant rapid investigation by esophagogastroduodenoscopy.The timing of symptoms in relation to the meal may differentiate between gastric and duodenal ulcers. A gastric ulcer would give epigastric pain during the meal, associated with nausea and vomiting, as gastric acid production is increased as food enters the stomach. Pain in duodenal ulcers would be aggravated by hunger and relieved by a meal and is associated with night pain.Also,the symptoms of peptic ulcers may vary with the location of the ulcer and the person's age.urthermore, typical ulcers tend to heal and recur, and as a result the pain may occur for few days and weeks

and then wane or disappear.Usually,children and the elderly do not develop any symptoms unless complications have arisen.

A burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours commonly accompanies ulcers. This pain can be misinterpreted as hunger, indigestion,orheartburn.Pain is usually caused by the ulcer, but it may be aggravated by the stomach aid when it comes into contact with the ulcerated area. The pain caused by peptic ulcers can be felt anywhere from the navel up to the sternum, it may last from few minutes to several hours,and it may be worse when the stomach is empty. Also, sometimes the pain may flare at night, and it can commonly be temporarily relieved by eating foods that buffer stomach acid or by taking anti-acid medication. However, peptic ulcer disease symptoms may be different for every sufferer.

1.2.5 Complications of PUD

1. The more frequent complication of peptic ulcer disease (PUD) is the bleeding(hemorrhage),followed by perforation and obstruction (Wang et al,2010)

2.Bleeding: The occurrence of hemorrhage complication is clearly higher than perforation,bleeding problems can arise and range in severity. Nearly half of all occurrences of upper gastrointestinal bleeding are brought on by peptic ulcers. The most dangerous

bleeding incidents are typically brought on by chronic duodenal ulcers. (Eisner et al,2017)

3. Perforation: Between 2 and 10% of people worldwide experience perforation as their peptic ulcer condition progresses. Duodenal ulcers are the most common site for perforation, occurring 60% of the time; antral and stomach body sites experience 20%perforations.(Behrman,2005)

4.Pyloric obstruction: The stenosis is the less frequent complication of the peptic ulcer disease, based on the evolution of the disease due to inflammation, edema, muscular spasm,followed by repair process with scaring. The detected frequency ranges between 5 and 8%.In detail,the development of this complication comprises various factors, some functional,other pathological. Most patients with gastric outlet obstruction symptoms have a history of peptic ulcer illness. The clinical symptoms of anorexia, nausea, early satiety, epigastric discomfort, and vomiting are present. Weight loss and a decline in general health follow this long-untreated clinical condition. (Behrman, 2005)

1.2.6 Diagnosis and Evaluation

In order to evaluate the patient, a complete history and physical examination are required. In each time,we should check for alarm features such as; (Ramakrisnan & Salinas, 2007)

1. Evidence of overt or occult gastrointestinal bleeding: hematemesis, melena, anemia, heme-positive stool
2. Iron deficiency anemia
3. Dysphagia
4. Left supraclavicular lymphadenopathy (Virchow's nodes)
5. Palpable abdominal mass
6. Symptom of impending perforation: severe persistent epigastric pain
7. Symptom of obstruction: persistent vomiting
8. Malignancy: anorexia, unintended weight loss.

Diagnostic tests should include complete blood count, and tests for detection of H. pylori infection. EGD is preferred over UGI series as it has much higher diagnostic yield and mucosal biopsy can be taken. During endoscopy, the location, size, depth, and any sign or stigmata Gastroenterology (CAG) suggest tha patients ≥60 years of age presenting with dyspepsia should undergo upper endoscopy to exclude any organic cause.

1.2.7 Management of peptic ulcer disease

Most peptic ulcers heal if gastric acid production is adequately suppressed. The rationale behind the treatment of peptic ulcer disease is twofold. The reduction of hostile factors is

essential,as is augmentation of protective factors. Antacids, histamine H2-receptor antagonists,proton pump inhibitors (e.g., omeprazole, lansoprazole), and surgery succeed by neutralization or reduction of gastric acid. Sucralfate and prostaglandin agents boost mucosal protection. The eradication of H.pylori infection restores normal mucosal resistance, but unlike other treatment options, does not require maintenance therapy to prevent ulcer recurrence. Patients should avoid factors known to contribute to peptic ulcer disease, such as NSAIDs and smoking. The choice of medication must be made empirically based on regional bacterial resistance patterns,local recommendations, and drug availability because pretreatment susceptibility is rarely known to the primary care physician.(Ford,2006)

The goal of therapy for peptic ulcer disease is to relieve symptoms, heal craters, prevent recurrences, and prevent complications. Medical therapy should include treatment with drugs, and attempt to accomplish the following:

1.Reduce gastric acidity by mechanisms that inhibit or neutralize acid secretion.

2. Coat ulcer craters to prevent acid and pepsin from penetrating to the ulcer base.

3. Provide a prostaglandin analog.

4. Remove environmental factors such as NSAIDs and smoking.

5. Reduce emotional stress (in a subset of patients).

The following are standard treatment options used in the management of peptic ulcer disease;

1. Standard Triple Therapy: A seven-to 10-day triple drug regimen consisting of a PPI,amoxicillin 1 g,and clarithromycin 500 mg (Biaxin) twice daily has long been the first-line therapy to eradicate H. pylori. However, increasing resistance to clarithromycin is associated with declining eradication rates, now well below 80%.(Houben et al,1999)Therefore,this regimen is not recommended where the prevalence of clarithromycin-resistant strains of H. pylori exceeds 15% to 20%. An alternative triple drug regimen substitutes metronidazole 500 mg twice daily for amoxicillin. Adding probiotics to triple therapy, specifically Saccharomyces boulardii and Lactobacillus, has been shown to increase eradication rates (absolute increase of 9% and 5%, respectively) and decrease adverse effects of treatment, particularly diarrhea (absolute decrease of 14% and 7%,respectively).(Zou,et al.,2009)

2. Sequential Therapy: Sequential therapy consists of a five-day course of a PPI and amoxicillin 1 g taken twice daily, followed by a five-day course of a PPI, clarithromycin500 mg,and metronidazole 500 mg (Flagyl) or tinidazole 500 mg (Tindamax) taken twice daily. The overall eradication rate is 84%, with an eradication rate of 73% for clarithromycin-resistant strains. A recent meta-analysis of available global data revealed that

sequential therapy is superior to seven-day triple therapy, but it is not superior to 14-day triple therapy, bismuth-based quadruple therapy, or non-bismuth-based quadruple therapy.(Gisbert et al.,2010)

3. Non-Bismuth-Based Quadruple Therapy (Concomitant Therapy): This approach involves the addition of metronidazole 500 mg or tinidazole 500 mg twice daily to the standard triple regimen. It is less complex than sequential therapy with similar eradication rates.(Gisbert & Calvet, 2011) Additionally, non-bismuth-based quadruple therapy may be more effective than sequential therapy in patients with dual antibiotic resistance to clarithromycin and metronidazole.(Molina-Infante,et al, 2011)It has the highest eradication rate, about 90%, even in areas with high clarithromycin and metronidazole resistance,but would presumably cost more than sequential therapy because clarithromycin is taken for 10 days.

4. Bismuth-Based Quadruple Therapy: Taking a bismuth salt (subsalicylate 525 mg or subcitrate potassium 420 mg), metronidazole 250 mg, tetracycline 375 to 500 mg, all four times day, together with a PPI twice a day, makes up the classic quadruple regimen.Quadruple therapy based on bismuth is frequently used as salvage therapy when first-line therapy fails, but it may also be used as first-line therapy in regions with significant resistance or when cost is a key factor.

(Malfertheiner, et al, 2012) Although a three-in-one combination capsule comprising bismuth subcitrate potassium,metronidazole,and tetracycline has been created to help patients take fewer pills, they still need to take three capsules four times daily in addition to a PPI. The treatment is typically administered for 10 to 14 days.

5. Levofloxacin-Based Triple Therapy: A PPI, 1 g of amoxicillin twice a day,and 500 mg of levofloxacin (Levaquin) once a day make up this 10-day treatment plan. According to the ACG,this regimen needs to be approved in the US. It is more tolerable than quadruple therapy based on bismuth and should only be used as second-line therapy. (Berning, et al.,2011)

1.3 Gastroesphageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD), as generally defined, is a common condition that results from the reflux of gastric material through the lower oesophageal sphincter (LES) into the esophagus or oropharynx, causing symptoms and/or injury to esophageal tissue. (Spechler,1992)After bouts of gastroesophageal reflux, the distal esophagus is exposed to acidic stomach contents,which results in symptoms and pathophysiologic alterations to the esophageal mucosa. Numerous symptoms and esophageal pathologic alterations that are indicative of GERD are brought on by pathologic gastroesophageal

reflux. Pathologic reflux episodes can happen during the day or at night, and they are more frequent and last longer than normal physiologic reflux.(Szarka,1999).

Usually,they result in esophageal mucosal injury, inflammation, or persistent discomfort.Therefore, gastroesophageal reflux disease (GERD) is a clinical illness in which the symptoms of GERD or its effects on esophageal tissue are severe enough to interfere with a patient's life or harm oesophageal tissue.

1.3.1 Clinical Overview of GERD

GERD pathogenesis involves several factors. Pathologic reflux is hypothesized to happen when typical esophageal protective anti-reflux barriers, such as esophageal acid clearance and mucosal resistance, are overcome by the harmful qualities of refluxed stomach acid, bile, pepsin, and duodenal contents.

A malfunctioning LES appears to be the main underlying mechanism producing pathologic reflux,increasing the amount of acidic stomach contents that reflux into the esophagus. This increase inacid volume tips the scales in favor of pathologic reflux by exceeding the esophagus mucosa's normal tolerance to acid. (Orlando, 1999)

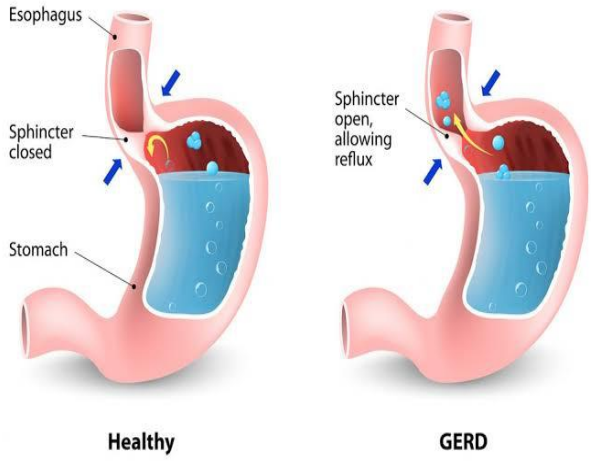


Fig1.4:Gastroesophageal Reflux Disease

Heartburn and acid regurgitation are the two GERD symptom that are most frequently reported,however they are not the only ones. A wide range of GERD clinical manifestations, including dysphagia/odynophagia and noncardiac chest discomfort, can be brought on by pathologic acidreflux.Laryngitis,pharyngitis, chronic sinusitis, dental erosions, asthma, and persistent cough are significant extraesophageal symptoms.

Laryngitis, hoarseness, noncardiac chest discomfort, or asthma are a few laryngeal or pulmonary symptoms that can come from stomach acid reflux into the throat and vocal cords or down into the lungs. Inflammation at the back of the throat brought on by stomach acid reflux can lead to pharyngitis. Teeth might deteriorate owing to acid reflux brought on by GERD.

While GERD is usually non progressive, in a minority of cases disease progression is associated with the development of complications. The range of GERD complications includes esophagitis,bleeding, esophageal erosions and ulcerations, stricture formation, Barrett's esophagus,and adenocarcinoma of the esophagus.

Esophageal erosions or ulcerations may form as a result of damage to esophageal tissue brought on by reflux.(Spechler,2000) Esophageal stricture can result from esophageal scarring, which is the deposition of fibrous tissue as a protective reaction to ulceration. Barrett's esophagus develops when the ulcerated squamous epithelium is replaced by a metaplastic intestinal-type epithelium.A considerable rise in the incidence of esophageal cancer has been associated with Barret's esophagus, a devastating sideeffect of reflux esophagitis in severe, protracted GERD.

1.3.2 Diagnosis

The diagnostic guidelines for GERD depend on whether the symptoms are complicated or uncomplicated. An uncomplicated presentation (heartburn, regurgitation,or both, often occurring after meals and aggravated by lying down or bending over, with relief obtained from antacids) is treated empirically with single daily-dose PPI.(DeVault and Castell,2005)

The dosage is doubled if relief is not experienced. Further diagnostic testing (upper Gl endoscopy,esophageal biopsy, ambulatory esophageal pH monitoring, impedance monitoring, and esophageal Bilitec for bile detection) is required if a PPI does not function.

In patients with chronic symptoms or alarm signs, endoscopy is utilized to detect Barrett's esophagus and esophagitis. Even though the majority of GERD patients have negative endoscopy findings,a negative endoscopy does not necessarily rule out GERD. Barrett's esophagus (which occurs in only 0.25-3.9 percent of all cases of GERD but in 6-12 percent of alI GERD patients referred for endoscopy), hemorrhagic esophageal stricture,and oesophageal adenocarcinoma are also often asymptomatic.

1.3.3 GERD and Acidity

The mechanisms by which people experience reflux episodes are intricate.They include the amount of reflux,how long it stays in the esophagus,whether the esophagus can neutralize the reflux with salivary bicarbonate, and how acidic the reflux fluid is.(Miwa et al.,2010)

A consensus definition of differing levels of acidity in reflux contents has been established:"Acidreflux"(pH<4),“weakly aci reflux" (pH 4-7),and "weakly alkaline reflux" (pH≥7)..(Sifrim etal.,2004). An estimated 50% of all reflux episodes in GERD

patients who are not using PPIs havea slightly acidic pH over 4.(Smout,2007)

Both mildly acidic and acidic reflux were able to cause heartburn symptoms in a study examining the acidity of reflux and its symptom-provoking effects.Weakly acidic reflux may account for 30-40% of symptoms in GERD patients who do not react to PPIs.(Zerbib et al., 2005)

The gas in weakly acidic reflux may cause distension of the proximal esophagus,which results in dilation of the intercellular spaces (DIS), a known mechanism in esophagitis that increases mucosal permeability and causes heartburn, according to one theory put forth to explain why weakly acidic reflux can cause esophageal damage. People who are exposed to mildly acidic bile-containing liquids have been proven to experience increased esophageal DIS that causes heartburn.(Siddiqui,2005)

1.3.4 Treatment: Lifestyle, Drug Therapy & Surgery

Lifestyle modifications:

Lifestyle modifications are the first option for most patients and they include;

1. Weight loss: This can lessen and even get rid of GERD symptoms. According to a prospective cohort research, symptoms decreased in 81% and disappeared entirely in 65%of obese

individuals who completed a systematic weight loss program. (Singh et al,2013)

2.Diet,smoking cessation, alcohol moderation: The goal of several research has heen to identify foods that make GERD symptoms worse. In the past, doctors have encouraged patients to stay away from things like alcohol, chocolate,fizzy drinks,spicy food,fatty food,and smoking. There haven't been any studies done yet that link quitting drinking or smoking to a reduction in GERD symptoms.No food has been definitively related with worsened GERD symptoms in terms of intake.

3. Sleep position: Other studies have encouraged raising the head of the bed,sleeping in the left decubitus position, and avoiding meals two to three hours before night in those with nocturnal GERD symptoms.

Medications Used to Treat GERD

1.Antacids: Over-the-counter (OTC) antacids provide quick, temporary relief from the symptoms of GERD. Antacids were frequently utilized in a trial with 1,009 GERD patients to treat breakthrough symptoms that were ineffectively controlled by regular PPI treatment. Antacids can alleviate symptoms, but they have not been proven to speedup the recovery from erosive esophagitis.(Pettit,2005)

2. Histamine H2-receptor Antagonists:Similar to antacids, histamine H2-receptor antagonists (ranitidine, famotidine,

cimetidine, nizatidine) offer momentary relief, a lit withonset of action. Because the body develops tolerance to these drugswithidrugs within and because they are less efficient than PPIs at treating erosiveesoerosive oesophagitisd use of these drugs for GERD is not advised.(Khan et al.,2005)

3.Prokinetics: The delayed esophageal clearance experienced by GERD patients isaddresseis addressedetic drugs (cisapride, metoclopramide), which stimulatesstimulate serotoninergicnergic receptors to increase gastric and esophageal peristalsis.(Tack, 2005)

About 70 percent of the gur's acid is suppressed by prokinetic medicine,but the symptom relief is slow to start and only lasts for a short time (4-8 hours).High-grade esophesophagitis has been demonstrated to respond well to these treatments.Prokinetics' usage for GERD is constrained by their adverse effect profile, which includes tremor,tardives dyskinesia and an increased risk for cardiac events. (Pettit, 2005)

4. Protein inhibitors: The gold standard of treatment for GERD is(pantoprazole, lansoprazole, esomeprazole, omeprazole, and rabeprazole). In the past tens, the amount of PPI prescriptions written each year has increased.(Shaheen,2006)

PPIs work by inhibiting the parietal cells' ability to produce gastric acid, according to their mechanism of action. The final

step required for the release of hydrochloric acidfacid from parietal cell into the stomach lumen is this pump, also known as hydrogen potassium ATPase (H+/K+-ATPase). (Vesper et al., 2008)

PPIs offer speedier relief than prokinetics or H2-blockingcations, and there is strong evidence that they can cure esophageal erosion (including Barrett's esophagus)over the long run. The list of side effects includes anaphylaxis, nausea, headaches,diarrhea and insomnia.

Failure to respond, rebound gastritis, atrophic gastritis, Helicobacter pylori or clostridium difficile infection as well as other drug-induced adverse effects, are issues with therapy for GERD.

While the standard of care with PPI involves doubling the dose if an initial single dose is ineffective, only 20-25 percent of patients who fail initial treatment respond to doubling the dose.Evidence suggests that patients who stop using PPIs after receiving long-term treatment eventually relapse.(Pohle and Domschke,2000)

Surgical Intervention for GERD

Laparoscopic fundoplication,a surgery where the fundus of the stomach is wrapped around the esophagus to produce a new heart valve-equivalent at the gastroesophageal junction, is the main surgical intervention for the treatment of GERD.

Patients with erosive GERD, Barrett's esophagus, cardiac conduction deficits, postmenopausal women with osteoporosis, patients with poor medication compliance, and patients with severe respiratory or oral GERD signs frequently receive this recommendation.

The Agency for Healthcare Research and Quality found that 10-65% of patients undergoing surgical intervention still require medication after examining the data on the comparison of medication versus surgical intervention. PPIs seem to be as beneficial as surgery at alleviating symptoms and reducing exposure to esophageal acid, according to the analysis.

1.4 Acid Neutralizing Agents (ANTACIDS)

In its simplest form, antacids are drugs that are usually alkaline substances that are used to neutralise excess acid in the stomach. Excess secretion of acid into stomach or impaired resistance by the lining of the stomach or reflux into the oesophagus may produce symptoms and the treatment of these symptoms is by reducing the acidity in the stomach.

Antacids have been used as the mainstay of treatment for peptic ulcers, gastritis, gastro oesophageal reflux disease (GERD), and functional dyspepsia(Maton et al,1999).Approximately 20% of the population in the United Kingdom visits their general practitioner each year with dyspeptic symptoms, while in Nigeria,

the prevalence rates range between 70% and 90%(Moayyedi et al,1999).

Marketed antacids contain salts of aluminium, calcium, magnesium, or sodium.(Salisbury et al,2020). Some preparations contain a combination of two salts, such as magnesium carbonate and aluminum hydroxide. They are available over the counter and are taken by mouth to quickly relieve occasional heartburn, symptoms of gastroesophageal reflux disease and indigestion.Treatmentwith antacids alone is symptomatic and only justified for minor symptoms (U.S. Department of Health and Human services,2011)

1.4.1 Criteria of an ideal antacid preparation:

• The antacid should not be absorbable or cause systemic alkalosis.

.The antacid should not be a laxative or causes constipation.

.The antacid should exert its effect rapidly and over a long period of time.

.The antacid should buffer in the pH 4-6 range.

.The reaction of the antacid with gastric HCI acid should not cause a large evolution of gas.

• The antacid should probably inhibit pepsin.

1.4.2 Classification of antacids

Antacids can be classified into two main category:

Table 1.1: Classification based on chemical nature

Absorbable Antacids	Non-absorbable Antacids
They show the most rapid onset of action	They show slower onset of action
They may cause "rebound effect"	They are less likely to cause "rebound effect"
Examples are sodium bicarbonate, magnesium oxide, magnesium carbonate,and calcium carbonate	Examples are magnesium hydroxide, Aluminium hydroxide, Aluminium phosphate, Magnesium silicate
They are inappropriate for patients with hypertension and kidney failure	They can be used to prevent significant stress ulcer bleeding in post-operative patients or those with severe burns

Table 1.2:Classification based on pharmacological properties of Antacid.

Non-Systemic Antacids	Systemic Antacids
Non-systemic antacids are compounds that are not absorbed into the systemic circulation.	Systemic antacids are absorbed into the systemic circulation.
Their anionic group neutralizes the H+ions in gastric acid. This releases their cationic group which combines with HCO3- from the pancreas to form an insoluble basic compound that is excreted in faeces.Thus these agents do not produce metabolic alkalosis	They have a cationic group that does not form insoluble basic compound with HCO3-, thus the HCO3-can be absorbed producing a metabolic alkalosis.
Examples are Aluminium Hydroxide and Magnesium Hydroxide	Example is Sodium bicarbonate

Non-absorbable antacids have many others favorable properties:

- Absorb pepsin, resulting in reduced proteolytic activity of gastric acid.

• Connect lysolecithin and bile acid, which havea damaging effect on the gastric mucosa.

Possess cytoprotective function through the activation of prostaglandin synthesis, which stimulate a secretion of mucin and bicarbonates, improve microcirculation.

Possess ambient function, forming a protective film on the gastric mucosal surface.

Able to bind epithelial growth factor and fix it in the ulcerous defect region effectively stimulating cell proliferation, angenesis and angiogenesis.

1.4.3 Mechanism of antacid:

Antacids were developed based on the hydroxides and carbonates of the group II and III metals,as well as the bicarbonates of the alkali metals. All antacids contain at least one of the following metals: aluminum, calcium, magnesium, sodium, potassium, or bismuth. Antacids help neutralise excess acid produced in the stomach, i.e. the hydrogen ion concentration is reduced.

Each antacid has a specific active ingredient. This ingredient whether metallic or nonmetallic hasa different effect on the gastric acid. They act similar to when an acid reacts with a hydroxide; asalt and water are produced as in the following equation:

HCI(aq)+NaOH(aq)→NaCl(aq)+H2O

Sodium Bicarbonate: HCI(aq)+NaHCO3(aq)→NaCl(aq)+H2O+CO2.

Calcium Carbonate: HCI(aq)+CaCO3(aq)→NaCl(aq)+H2O+CO2.

Magnesium Compounds:MgO+H2O→Mg (OH)2;HC1(aq)→MgCl2+H2O

Aluminum Compounds:Al(OH)3+HC1→AlCl3+H2O

1.4.4 Indications and Principles of Clinical Use

Antacids therapeutic indications:

Proton pump inhibitors (PPIs), H2 antagonists (H2 blockers), and Helicobacter pylori eradication therapy have all proven effective in the treatment of acid problems. Antacids are mostly considered in this context as an adjunctive treatment. High security antacids are the medicine of choice for self-treatment due to their immediate symptomatic impact, simple presentation (suspensions,chewable pills), and appealing organoleptic qualities.

1. Gastroesophageal reflux disease (GERD): Antacids neutralize hydrochloric acid,inactivate pepsin, absorb bile acids, stimulate the synthesis of bicarbonates,raise the tone of the lower esophageal sphincter, thus affecting on the majority of units in the GERD pathogenesis.Antacids can be used as a standalone treatment for GERD that is not erosive.Antacids are recommended as a co-drug to the PPIs main course in cases of

monotherapy failure (heartburn saving) and in the erosive type of GERD.(Zhang,2014).It is preferable to use nonabsorbable combined antacids in liquid form, such as those that contain aluminum phosphate,pectin gel,and agar,aluminum-magnesium antacids,and aluminum-magnesium antacids with alginic acid (is derived from seaweeds).

2. Gastric and duodenal ulcers: Antacids are useful for managing severe pain in gastric and duodenal ulcers during the screening phase and on the first day after using PPIs,before the acid production blocking (after 1-3 days). Antacids are ued in conjunction with PPIs when an ulcer is not linked to Helicobacter pylori (to increase the cytoprotective impact when ulcers are not healing). When an ulcer is linked to Helicobacter pylori, antacids (in conjunction with PPIs) are advised if the ulcer is difficult to cicatrize (the phenomenon of growth factors fixation) following eradication therapy or if dyspeptic symptoms are persistent. Antacid usage is not recommended during eradication therapy due to possible self-tapering effects. (Holle, 2010).

3. Acute gastritis/gastroduodenitis: Antacids are used in addition to PPI therapy, H2-blockers in the treatment of acute gastritis, gastroduodenitis, especially with severe pain and dyspeptic syndromes. (Holle,2010).

4. Chronic gastritis/gastroduodenitis: Antacids are used either alone or in combination with antisecretory medicines to stop recurrences. As bile acids and lysolecithin are the major aggravating factors in reflux gastritis, these medications are the ones of choice for both treating and preventing the condition.

5. Gastropathy caused by nonsteroidal anti-inflammatory drugs (NSAIDs-gastropathy): Antacids can be taken alone or in addition to antisecretory drugs in order to prevent gastro-and duodenopathies affected by the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

6. Pain and dyspeptic syndromes: For healthy individuals with discomfort or epigastric pain, dyspeptic symptoms (heartburn, belching, meteorism), antacids are advised.Heartburn during pregnancy, which occurs in around (50-80%)% of cases,is treated with non-absorbable antacids as the primary medication. (Uenishi,2010)

7. Cholecystitis, biliary dyskinesia: Antacids are included in the treatment regimen for patients with acalculous and calculus cholecystitis, biliary dyskinesia's to eliminate the symptoms of bail and mixed refluxes. The effectiveness of antacids is related to their capacity to absorb bile acids and lysolecithin, which enter the esophagus and stomach incases of gastroesophageal and duodenogastric refluxes.

8. Chronic pancreatitis in the exacerbation phase: PPIs, H2-blockers, and antacids are essential parts of the therapy due to the function that stomach acid plays in stimulating pancreatic output during the aggravation of chronic pancreatitis. Antacids work to normalize the evacuation process, lower intragastric and intraduodenal pressure, and raise stomach pH, all of which negate the flatulent distention.

9.Prevention of stress ulcers: Antacids are used in the intensive care units to prevent so-called «stress» ulcers (in patients after a major operation, with craniocerebral traumas - Cushing's ulcers or with severe burns - Curling's ulcers,etc.).

1.4.5 Administration principles

Antacids are used in the form of tablets and suspensions. These presentations differ significantly in their Acid Neutralizing Capacity (ANC). Since antacids only interact with hydrogen ions in their solute state,solubility has an impact on the ANC.In compared to tablets, suspensions contain smaller particle sizes, a bigger surface area, and dissolve more quickly in the stomach's acidic environment. As a result, antacids in suspension form are more effective.(Belousov,2010)An antacid's typical therapeutic dose is 10-15 ml (1 teaspoon or 1 package content) of liquid or 1-

2 tablets three to four times per day.

Before consuming, tablets should be chewed or thoroughly dissolved. It is advised to take antacids before meals in several patient information leaflets.

Antacids, however, are quickly discharged into the duodenum when taken on an empty stomach,and they also have no effect since food acts as a buffer for antacids. Antacids should be taken 1-1.5 hours after meals or right before bed (to lessen the acidic effects of hydrochloric acid on the stomach mucosa at night). In exceptional circumstances, such as when there are lengthy stretches between meals, it may be advised to take more antacids 3-4 hours after a meal.

Antacids can be used singly as a symptomatic treatment in case of complaints («on-demand therapy») or on a regular basis as a course. Course duration may range from 1 to 3-4 weeks.

1.4.6 Antacids side effects

1.After a brief period of acid neutralization caused by the administration of absorbable antacids (sodium hydrogen bicarbonate, less frequently calcium carbonate), a secondary acid hypersecretion (the "rebound" syndrome) develops as a result of pH increases up to 7 and/or as a direct result of calcium ions. Antacids can result in systemic metabolic alkalosis (together with a headache,sicchasia, and vomiting) when used long-term and at large dosages.

2. The water-salt metabolism may be negatively impacted by sodium bicarbonate since 1.5 gof sodium chloride and 2 g of sodium both retain liquids when consumed. In senior individuals with cardiovascular system disease,blood pressure may raise, edema may occur or worsen, and cardiovascular failure symptoms may worsen.

3.When hydrochloric acid and antacids containing carbonates-sodium hydrogen carbonate,,and magnesium carbonate-react, carbon dioxide gas is created. This results in belching meteorism, and gastric distension, all of which are particularly unfavorable incases of GERD.

4. Sodium hydrogen bicarbonate and magnesium drugs (oxide,hydroxide, and carbonate)cause urinary alkalization, which may cause phosphates to settle and form phosphate stones

k and calcium antacids shouldn't be combined since doing so encourages the "milk-alkali syndrome"(sicchasia, mental problems, polyuria, and vomiting).

6.In contrast to absorbable antacids, non-absorbable ones have fewer side effects,and these effects are more usually brought on by prolonged and unregulated medication usage.Aluminum hydroxide can reduce intestinal phosphate absorption over time, which can occasionally in hypophosphatemia.

7. Constipation is the most frequent adverse event to aluminum hydroxide medication,but magnesium hydroxide has a laxative

effect and may result in diarrhea.The effect of the medication on gastrointestinal tract motility in combination aluminum/magnesium antacids relies on the raio of aluminum/magnesium. The medicine has no impact on motility or, in rare instances, may have a laxative effect if this ratio is 1 or a little bit higher(as a rule, at a dose increase).

1.4.7 Contraindications

Currently, the administration of absorbable antacids is undesirable.Contraindications for non-absorbable antacids are severe kidney failure, Alzheimer's disease.Aluminum phosphate is contraindicated in pregnancy.(Zhang,2014)

Antacids interaction with other drugs

Antacids that contain calcium, magnesium and aluminum ions are chelators. They bind a great number of drugs such as digitoxin, tetracycline, bishydroxycoumarin, indomethacin, aspirin,cimetidine, ranitidine, famotidine, theophylline etc. Antacids administration reduces the bioavailability of weak acids: barbiturates, sulfonamides, penicillins and others. The absorption of weak bases increases (atropine, chlorpromazine, propranolol etc.(Veber, 2009) It is advisable to combine antacids with M-anticholinergics (to prolong the effect of antacids) and with PPIs (to reduce their destruction in the stomach). Because of pharmacodynamic drg

incompatibility,antacids cannot be combined with bismuth, subcitrate and sucralfate. To avoid undesirable interactions, antacids are usually used 2 hours before or after taking any medication.

1.5. Acid Neutralizing Capacity (ANC) of an Antacid

Stomach acid contains-hydrochloric acid, which aids in food digestion. Excess stomach acid produces a condition known as acid indigestion or acid reflux. Commercial antacids containing one or more bases are available to treat this conditions by neutralizing the excess acid in the stomach. The ANC of an antacid is the amount of acid that it can neutralize. It is expressed as the ability of an antacidd to neutralize acid. The potency of the antacids depends mainly on theiracid neutralizingng capacity (ANC) and this can vary from one brand of antacid to another.

According to the US Food and Drug Administration (FDA),although in vitro test caapproximate in in vivo conditions with respect to acid-consuming capacity, the speed of action, duration action andand maximum buffering capacity of antacid, it cannot account for variations in antacid actividue toeto gastric

emptying,changes in acid secretion rate in fasted and non-fasted state,interactiof antacidsids with glycoprotein and mucoproteins of gastric juice, coating of gastric mucoby antacidsids, and the effects of antacid on the endogenous control of acid secretion (Katakam etal.,2010).

An important features of antacid preparation are rapid onset of action and effectineutralization ofnof acid (Katakam etal.,2010). The US FDA requirement is that an antacid must have a neutralizicapacity ofyof≥5mEq per dose(U.S. FDA Code of Federal Regulation, 2020). The most effective antacids should havehigh acidcid neutralization capacity and rapid gastric acid neutralization qualities. Most antacicontain magnesiumium hydroxide, aluminium hydroxide, calcium carbonate, or a combination of these.

Most market surveillance or monitoring involves all activities undertaken to obtain more daand informationion about a product after it had been granted marketing authorization and maavailable foreor public use. It is imperative to conduct post market surveillance monitoringing approved medicinesnes in order to adequately assess the quality of therapeutic effectiveness and safeof medicineine. Routine laboratory testing of drug in the market is crucial to protect the publespecially inlyn developing countries where counterfeit and substandard drug have become a major challento healthlth care services. In Nigeria

several attempt have been made to combat counterfeit afake drugsugs (Ochekpe et al., 2006 and Raufu, 2003). Counterfeit and fake drugs are a major cause of morbidity, mortality and loss of public confidence in drugs and health system (Cockburn et al.2005).

1.6 Overview of Pharmaceutical Analysis

Pharmaceutical analysis is a broader term which can be defined in many ways.It is the series of processes that are used for identification, determination, separation,purification,and structure elucidation of the given compound used in the formulation of pharmaceutical products.Thecomponents, to which the pharmaceutical analysis is done, are normally active pharmaceutical ingredients, pharmaceutical excipients, contaminants present in pharmaceutical products,or drug metabolites. In pharmaceutical analysis,the samples are typically finished pharmaceutical products, biological samples, impurities,contaminants, and pharmaceutical raw materials.Pharmaceutical analysis can be done using various analytical techniques.

Based upon the determination type, there are mainly two types of analytical methods.

1. Qualitative analysis (identification).
2. Quantitative analysis (estimation).

1. Qualitative analysis: Qualitative analysis is performed to establish composition of natural/synthetic substances. These tests are performed to indicate whether the substance or compound is present in the sample or not. Various qualitative tests are detection of evolved gas, formation of precipitates, limit tests, colour change reactions, melting point and boiling point test etc.

2. Quantitative analysis: Quantitative analytical techniques are mainly used to quantify any compound or substance in the sample. These techniques are based in (a) The quantitative performance of suitable chemical reaction and cither measuring the amount of reagent added to complete the reaction or measuring the amount of reaction product obtained,(b)The characteristic movement of a substance through a defined medium under controlled conditions, (c) Electrical measurement, (d) Measurement of some spectroscopic properties of the compound.

Various types of Quantitative analysis:

1. Physico-Chemical methods of analysis: These include:

a) Chemical method of analysis such as:

i. Titrimetric or Volumetric method of analysis.

ii. gravimetric methods.

b) Electrical methods such as: Potentiometry, Conductimetry, Amperometry,Voltammetry,Polarography etc.

c) Instrumental methods such as: Atomic Absorption Spectrophotometry(AAS), Flame photometry,(AES), UV/Visible spectrophotometry, Infrared spectroscopy,Mass spectroscopy, Fluorimetry,Refractometer,Polarimetry etc.

d) Chromatography: Column chromatography, Thin layer chromatography (TLC), Gas liquid chromatography (GLC),Gas liquid performance liquid chromatography (HPLC) etc.

2. Biological and microbiological methods of analysis: These includes bioassays, minimum inhibitory concentration minimum inhibitory concentrations(MIC),radioimmunoassay, pyrogen testing, sterility testing etc.

3. Biopharmaceutical methods of analysis: These includes particle size analysis,disintegration test, dissolution test, friability test,bioavailability testing etc.(Pharmatutor,2013).

1.6.1 Criteria for the Choice of Analytical Method

1. Cost

2.Availability of instrument and accessibility.

3. Selectivity: The method should be capable of discriminating between ingredients and impurities/excipients c.g UV/Visible spectrophotometry is selective for compounds having chromophores.

4. Specificity; c.g Spectrofluorimetry is specific for drugs that fluoresce.

5. Sensitivity; c.g HPLC is a highly sensitive method.

6. Reliability:The method should provide accurate and reproducible results.

7.Convenience:The method should be simple and fast to carry out.

1.6.2 Application of Pharmaceutical Analysis

Manufacturing industries require both qualitative and quantitative analysis to ensure that their raw materials meet certain specifications, and to check the quality of final product. Raw materials areto be checked to ensure that the essential components are present within the predetermined range of composition and there are not any unusual substances present which might upset the manufacturing process or it may appear as a harmful impurity in the final product.

In the development of new products which contains mixtures other than the pure material,it is necessary to ascertain composition of mixture which shows the optimum characteristics for which the material has been developed (pharmtutor,2013)

1.7 Titrimetric Methods of Analysis

This is also known as Volumetric Analysis and the basic procedure is called Titration.

Titration (also known as titrimetry) is a common laboratory method of quantitative chemical analysis to determine the concentration of an identified analyte (a substance to be

analyzed).A reagent, termed the titrant, is prepared as a standard solution of known concentration andvolume.The titrant reacts with a solution of analyte to determine the analyte's concentration.

The volume of titrant that reacted with the analyte is termed the titration volume.

The titrant is added to the sample until the amount of titrant added is chemically equivalent to neutralize the entire analyte present. The point at which this equivalence occurs is known as the equivalence point and the volume of the titrant read out from the burette is known as the titration end point. From the volume of the titrant(end point) and the concentration of the titrant, the amount of analyte can be calculated using the stoichiometry of the titration.

Titrimetry is the most frequently used method of analysis and is one of the first experiments to be encountered by students. It is simple, inexpensive and easy to carry out.

1.7.1 Endpoint and Equivalence point

Though the terms equivalence point and endpoint are often used interchangeably,they are differentterms.Equivalence point is the theoretical completion of the reaction: the volume of added titrant at which the number of moles of titrant is equal to the number of moles of analyte. Endpoint is what is actually

measured, a physical change in the solution as determined by an indicator or an instrument mentioned (Harris, 2003).

There is a slight difference between the endpoint and the equivalence point of the titration.

This error is referred to as an indicator error, and it is indeterminate. (Hannan, 2007).

1.7.2 Choice of Indicators

Colour Indicators that changes acidic or basic media are used in the detection of titration endpoints.

The colour change usually occurs at the endpoint.

An acid-base indicator is a weak acid or a weak base. The undissociated form of the indicator is a different colour than the iogenic form of the indicator. An indicator does not change colour from

pure acid to pure alkaline at specific hydrogen ion concentration, but rather,colour change occurs over a range of hydrogen ion concentration. This range is termed the colour change interval.It is expressed as a pH range and the useful range for any indicator is ±1pH it's pKa value.

A suitable pH indicator must be chosen in order to detect the end point of the titration. The colour change or other effect should occur close to the equivalence point of the reaction so that the experimenter can accurately determine when that point

is reached. The pH of the equivalence point can be estimated using the following rules:

1.A strong acid will react with a strong base to form a neutral(pH=7)solution.

2.A strong acid will react with a weak base to form an acidic(pH<7)solution.

3.A weak acid will react with a strong base to form a basic(pH>7)solution.

When a weak acid reacts with a weak base, the equivalence point solution will be basic if the baseis stronger and acidic if the acid is stronger. If both are of equal strength, then the equivalence pH will be neutral. However, weak acids are not often titrated against weak bases because the colour change shown with the indicator is often quick, and therefore very difficult for the observer to seethe change of colour.

The point at which the indicator changes colour is called the end point. A suitable indicator should be chosen, preferably one that will experience a change in colour (an end point) close to the equivalence point of the reaction.

Strong acid/Strong base

Phenolphthalein (PKa 9.4)

Methyl Orange (PKa 3.7)

Strong base/ Weak acid

Phenolphthalein

Strong acid/Weak base Methyl orange

Methyl Red(pKa 6.4)

Weak acid/Weak base Phenol Red (PKa 8.0)

Table 1.3: pH range of some Acid-Base indicator. (pH measurements with indicators,2005)

Indicator	pH Range	Colour In Acidic Medium	Colour in Basic Medium
Methyl violet	0.0-1.6	Yellow	Violet
Bromophenol blue	3.0-4.6	Yellow	Blue
Methyl orange	3.1-4.4	Red	Orange
Methyl red	4.4-6.3	Red	Yellow
Bromothymol blue	6.0-7.6	Yellow	Blue
Phenol red	6.4-8.0	Yellow	Red
Phenolphthalein	8.3-10.0	Colourless	Pink

1.7.3 Direct and Indirect (Back) Titration

1. Direct titration: Here, the acid or base is titrated directly against the base or acid in presence of an indicator. The titration of an acid against a base is known as Acidimetry,while the titration of a base against an acid is known as Alkalimetry.

2. Back or Indirect titration: This involves the addition of excess standard solution to a weighted amount of sample and then the determination of the excess standard solution not required by the sample. Quite often, a blank titration is performed, where the same volume of base or acid added to the sample is titrated with the standard acid or base. The difference between the volume of titrant used for the blank titration and the test sample is the volume of titrant equivalent to the sample.

Back titration is a titration done i reverse; instead of titrating the original sample, a known excess of standard reagent is added to the solution, and the excess is titrated. A back titration is useful if the endpoint of the reverse titration is easier to identify than the endpoint of the normal titration,as with precipitation reactions. Back titrations are also useful if the reaction between the analyte and the titrant is very slow, or when the analyte is ina non-soluble solid.(Kenkel,2003).

Back titration is used in the following situations:

1. For volatile substances e.g. Ammonia, volatile oils.

2. For insoluble substances that require a large volume of solution e.g Calcium Carbonate.

3. Substances that require the presence of the reagent for a quantitative reaction to proceede.g Acetic acid and Sodium hydroxide.

4. Substances requiring heating and cooling to ensure decomposition.

1.8 Justification/Background of study

The introduction of generic drug product from multiple sources into the health care delivery system of Nigeria was aimed at improving the overall health care delivery system in Nigeria.

However,this has been accompanied by a variety of problems of which the most critical is the widespread distribution of fake and substandard drug products, which are often more cheaper.Many brands of antacid suspensions are currently available in the Nigerian market and many more brands keeps entering the market. Thes various brands of antacids also vary in their costs, as majority of users always seek for a cheaper brand.

However,the efficacy of the antacid should be of utmost importance and this can be achieved by measuring the acid neutralizing capacity (ANC) of the antacid,which is considered

as the most desirable property of an antacid formulation. The food and drug administration (FDA) has introduced various in vitro tests uch as acid neutralizing capacity, buffering capacity, onset and duration of action to assess the activity of antacids (Vedavathi et al, 2013).

Measurement of acid neutralizing capacity is one of the widely used fests that evaluate the efficacy of antacids.There are several ways of assessing the acid neutralizing capacity of an antacid but one of simplest and most accurate method is acid-base titration the action.

Taking cognizance of the fact that in developing countries like Nigeria where high technology equipment are not readily available and there is also the issue of epileptic power supply, there is need to develop a simple, inexpensive and practical method to determine the acid neutralizing capacity of antacids, which will be easy to carry out by community pharmacists so as to make informed choices and recommendations to prescribers.

Antacids are available in different formulations like tablets, effervescent, powders, and suspensions. The suspension formulations are more preferred as they have the fastest onset of action(British Pharmacopeia Commission,2018). There is a high possibility of misuse and adulteration of these antacids due to the fact that they ane common on the market and can be purchased over the counter without any prescription. Thus,from health care

providers and patients'point of view,it is very essential to have information regarding the efficacy and cost effectiveness of various antacid preparations on the Nigerian market(Vedavathi et al,2013).

1.9 Aim of Study

The aim of the study is to develop a titrimetric assay that can be used to determine the acid neutralizing capacity of antacid suspensions by finding a suitable indicator that can be used in this assay.

CHAPTER TWO

MATERIALS AND METHOD

2.1 Antacid samples and Reagents

Twenty liquid antacids were randomly sampled and purchased from community pharmacies in the Benin Metropolis of Edo State, Nigeria. All the products were purchased on the same day and labeled A-T. Hydrochloric acid (Gunsgdong Guandgua Chemical Factory Co. Ltd. China), Sodium Hydroxide pellets (Central Drug House (P) Ltd. Corp, India), Bromophenol Blue (SD Fine Chemicals, India.) of analytical grade, were supplied by Pharmaceutical chemistry department, faculty of pharmacy, University of Benin. pH meter (Hanna Digital pH meter HI-98108) and all weighings were done using G & G Electronic weighing balance (G & G Electronic Scale JJ224BC), with sensitivity of 0.0001g. The room temperature over the study period was 29.6(1.2)℃.

2.2 Visual Inspection of the Samples

All the products were inspected using a modified checklist based on the inspection tools developed by the Department of Quality Assurance and Safety of Medicines of the World Health Organization, 2007 and Schiavetti et al., 2020. The checklist was modified to suit the products being investigated and avoid subjectivity. The evaluation was done to visually inspect the antacids as a quality check for improper packaging, labelling, and missing information about the strengths of active ingredients, dosage, and expiration date, amongst others.

Details of the antacids, including country of manufacture, colour, cost per bottle, batch number, dates of manufacture and expiry, bottle type and colour and indicated minimum dose, were recorded and are presented in **Table 3.1.** The active ingredients in the products have been presented in **Table 3.2.**

2.3 Evaluation of pH

The pH of each antacid was determined using a calibrated digital pH meter. Each antacid was well shaken, after which 10 mL of the suspension was transferred into a 25 mL beaker for pH measurement. Triplicate determinations were performed for each sample.

2.4 Determination of Relative density

Each antacid was well shaken, after which 10 mL of each suspension was weighed (weighing balance: G & G Electronic Scale JJ224BC) at room temperature. Triplicate weight determinations were performed for each sample and the mean weights were used to determine the densities for each sample. Water was used as the reference standard to determine the relative density for each sample.

2.5. Determination of Flow Rate

The time taken for 10 mL of each suspension to flow through a 10 mL pipette was determined. Triplicate determinations were performed for each sample at room temperature.

2.6. Determination of Acid Neutralizing Capacity (ANC) using Potentiometry

ANC was determined as described in the United States Pharmacopeia and National Formulary, 2008. First, a sample was well shaken until its contents were uniform. An accurately measured quantity of the uniform

suspension equivalent to the minimum dose indicated on the bottle label was then transferred into a 250 mL beaker. Water was added to the sample to obtain a 70 mL mixture, which was then stirred on a magnetic stirrer for 1minute. Next, an accurate volume of 30 mL of 1.0 N HCl was added to the suspension, followed by stirring of the mixture for 15 minutes. Excess HCI was titrated against 0.5N NaOH until a pH of 3.5 was obtained. Triplicate determinations were made.The number of milliequivalents (mEq) of acid consumed by each antacid was calculated using the
following equation:

Total mEq = (VHCI x NHCL) - (VNaOH x NNaOH)

Where NHcI and NNaoH are the normalities of HCI and NaOH, respectively, and VHCI and VNaoH are the volumes of HCI and NaOH, respectively.

2.7 Determination of Acid Neutralizing Capacity using Titrimetry

ANC was determined as described in the United States Pharmacopeia and National Formulary, 2008. First, a sample was well shaken until its contents were uniform. An accurately measured quantity of the uniform suspension equivalent to the minimum dose indicated on the bottle label was then transferred into a 250 mL beaker. Water was added to the sample to obtain a 70 mL mixture, which was then stirred on a magnetic stirrer for 1minute. Next, an accurate volume of 30 mL of 1.0 N HCl was added to the suspension, followed by stirring of the mixture for 15 minutes. 2 drops of Bromophenol Blue indicator was added to the mixture.Excess HCI was titrated against 0.5N NaOH until a colour change from yellow to blue was observed.Triplicate determinations were made.The number of milliequivalents (mEq) of acid consumed by each antacid was calculated using the following equation:

Total mEq = (VHCI x NHCL) - (VNaOH x NNaOH)

Where NHcI and NNaoH are the normalities of HCI and NaOH, respectively, and VHCI and VNaoH are the volumes of HCI and NaOH, respectively.

2.8 Determination of Buffering capacity (BC)

An accurate volume of 5mL of each of the antacid samples was transferred into a 250ml beaker, and 50 mL of distilled water was added to the suspension and heated to 37 ° C ± 3 ° C. The suspension was stirred for one minute and the initial pH was recorded with a standardized pH meter. An accurate volume of 100mL 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 ten times at an interval of 5 minutes, at ambient temperature. During this process, 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 minutes interval until a pH below 2.75 was observed for the different brands in triplicates.

2.9 Data Analysis

The data was fed into IBM SPSS 25 and the mean and the standard deviation for each brand was determined. Descriptive Statistics of the ANC values of the various brands were analyzed and the range, variance and standard error of mean was determined. Then a bar graph of the ANC values of the various brands was plotted in excel.

CHAPTER THREE

RESULTS

3.1 Details of the different Brands of Antacids.

Table 3.1 DETAILS OF THE DIFFERENT BRANDS OF ANTACIDS.

SAMPLE	MINIMUM ADULT DOSE	COLOUR	BATCH NUMBER	MANUFACTURE DATE	EXPIRY DATE	COST (NGN)	SOURCE (COUNTRY)	BOTTLE TYPE\COLOUR

A	10	White	AER730	07/2023	07/2025	5000	Britain	Glass/Amber
B	10	Pink	AD60423	07/2024	06/27	1200	Nigeria	Plastic/Amber
C	10	Pink	BY43E3001	03/2023	02/2025	1000	India	Plastic/White
D	10	White	L162D	04/2014	04/2027	1200	Nigeria	Glass/Amber
E	10	White	2M626001	12/2022	11/2025	900	Nigeria	Plastic/Pink
F	10	Pink	R12439	06/2024	06/2027	2000	Nigeria	Plastic/Amber
G	10	Pink	ULS6007	03/2024	07/2026	2000	India	Glass/Amber
H	10	Yellow	24277	06/2024	06/2027	2500	Nigeria	Plastic/Amber
I	10	White	B22A138	10/2022	10/2025	2500	Thailand	Plastic/White
J	10	White	MM750	07/2024	06/2026	1800	Nigeria	Plastic/White
K	10	White	L3024032	07/2024	06/2027	1500	Nigeria	Plastic/White
L	10	Pink	GT017C	12/2023	10/2026	3000	Nigeria	Plastic/Amber
M	10	Pink	AF67211	07/2022	06/2025	900	Nigeria	Glass/Amber
N	10	Pink	GCS204	07/2024	07/2026	3500	Nigeria	Plastic/Amber
O	10	Pink	AC2312	10/2023	09/2026	1000	Nigeria	Plastic/Amber
P	10	Off-white	10231698	06/2024	05/2027	2000	India	Plastic/Amber
Q	10	Pink	4033W	05/2024	04/2027	3500	Nigeria	Plastic/White
R	10	Pink	4130008	01/2024	12/2026	4000	India	Plastic/Amber
S	10	White	B32104	02/2024	02/2027	2100	Italy	Plastic/white
T	10	Pink	M19314	03/2024	03/2027	3400	Nigeria	Plastic/Amber

3.2 Active Ingredients/ Compositions and their strength in the products

Table 3.2 ACTIVE INGREDIENTS/ COMPOSITION AND THEIR STRENTH IN THE PRODUCTS.

SAMPLE	COMPOSITION AND STRENTH
A	Each 10ml contain Sodium Alginate BP 500mg Sodium Bicarbonate Ph Eur 267mg Calcium Carbonate Ph Eur 160mg in a suspension containing saccharine
B	Each 5ml contain Dried Aluminium Hydroxide Gel USP Equivalent to Aluminium Hydroxide 306mg Magnesium Hydroxide USP Simethicone Emulsion USP Equivalent to polymethylsiloxane 125mg
c	Each 5ml contains Dried Aluminium Hydroxide Gel USP 325mg Equivalent to Aluminium Hydroxide 248.62mg Magnesium Hydroxide USP 100mg Activated Polymethylsiloxane USP 125mg Excipients q.s
D	Each 5ml contains Aluminium magnesium silicate BP 30mg Magnesium Trisilicate BP 250mg Magnesium Carbonate BP 250mg Sodium Bicarbonate BP 250mg Simethicone BP 20mg

E	Each 5ml contain Oxethazine 10mg Magaldrate 540mg Simethicone 50mg
F	Each 5ml contains Activated methylpolysiloxane (simethicone) 125mg Magnesium Hydroxide 100mg Dried Aluminium Hydroxide Gel 468.1mg
G	Each 15ml contains Alginic Acid BP 200mg Dried Aluminium Hydroxide BP 250mg Magnesium Hydroxide BP 250mg Magnesium Trisilicate BP 250mg Simethicone 125mg
H	Each 5ml contains Magnesium Hydroxide BP 200mg Aluminium Hydroxide (Dry Gel) BP 225mg Simethicone BP 50mg
I	Each 15ml contains Aluminium Hydroxide Gel USP Equivalent to Aluminium Hydroxide 918mg Magnesium Hydroxide 300mg Simethicone USP 60mg
J	Each 5ml contains Sodium Bicarbonate 0.25g Magnesium Trisilicate 0.25g Light Mag Carbonate 0.25g
K	Each 5ml contains Magnesium Trisilicate 250mg Light Magnesium Carbonate 250mg Sodium Bicarbonate 250mg

L	Each 5ml contains Dried Aluminium Hydroxide Gel U.S.P Equivalent to Aluminium Hydroxide 380mg Magnesium Hydroxide 100mg Simethicone 125mg
M	Each 5ml contains Aluminium Hydroxide Gel USP (Equivalent to Aluminium Hydroxide 191.25mg) 250mg Magnesium Hydroxide USP 250mg Simethicone USP 50mg Excipients q.s Colour: Permitted colour Flavour Mint
N	Each 5ml contains Magnesium Trisilicate BP 250mg Light Magnesium Carbonate BP 250mg Sodium Bicarbonate BP 250mg
O	Each 10ml contains Alginic Acid BP 200mg Magnesium Hydroxide BP 250mg Dried Aluminium Hydroxide Gel BP 250mg Magnesium Trisilicate BP 250mg Activated Dimethicone BP 250mg Activated Dimethicone BP 125mg Colour: Erythrosine
P	Each 5ml contains Aluminium Hydroxide Gel USP Equivalent to Aluminium Hydroxide 365mg Magnesium Hydroxide 80mg Simethicone 100mg Deglycyrrhizinated Liquorice 400mg
Q	Each 10ml contains Dried Aluminium Hydroxide gel BP 600mg

		Magnesium Trisilicate BP 300mg Magnesium Hydroxide BP 200mg Dimethyl polysiloxane USP 50mg
	R	Each 5ml contains Simethicone USP 50mg Magnesium Hydroxide USP 250mg Dried Aluminium Hydroxide gel USP 250mg Colour: Erythrosine & Tartrazine Flavour: Mint
	S	Each 5ml contains Magaldrate USP 540mg Simethicone USP 100mg
	T	Each 5ml contains Dried Aluminium Hydroxide BP 475mg Magnesium Hydroxide BP 100mg Simethicone 125mg

3.3 Acid Neutralizing Capacity of Sampled Brands

Table 3.3: ACID NEUTRALIZING CAPACITY OF SAMPLED BRANDS USING TITRIMETRY AND POTENTIOMETRY

PARAMETERS TESTED FOR THE ANTACIDS

BRANDS/SAMPLES	DOSAGE FORM	VOLUME OF 1N HCL ADDED (ml)	VOLUME OF 0.5N NaOH THAT REACTED (ml)	ANC PER DOSE (mEq/10ml) USING TITRIMETRY	ANC PER DOSE (mEq/10ml) USING PH METER

A	Suspension	30	43.00	8.50	11.60±0.02
B	Suspension	30	14.00	23.00	20.70±0.04
C	Suspension	30	31.00	14.50	17.85±0.03
D	Suspension	30	18.00	21.00	24.15±0.02
E	Suspension	30	17.50	21.25	23.00±0.02
F	Suspension	30	31.50	14.25	16.30±0.02
G	Suspension	30	34.60	17.30	19.50±0.04
H	Suspension	30	18.60	20.70	24.80±0.03
I	Suspension	30	8.90	25.55	27.20±0.04
J	Suspension	30	9.00	25.50	26.70±0.03
K	Suspension	30	18.10	20.95	22.70±0.04
L	Suspension	30	18.50	20.75	22.50±0.03
M	Suspension	30	15.40	22.30	24.60±0.02
N	Suspension	30	17.30	21.35	22.25±0.03
O	Suspension	30	22.40	18.80	20.70±0.04
P	Suspension	30	27.00	16.50	19.75±0.02
Q	Suspension	30	18.20	20.90	18.75±0.03

R	Suspension	30	27.50	16.25	19.80± 0.03
S	Suspension	30	26.40	16.80	17.45± 0.04
T	Suspension	30	25.00	17.50	19.70± 0.02

3.4 pH, Flow Time (Minutes), Relative Density and ANC of the Different Antacid Brands.

Table 3.4 Ph, FLOW TIME (MINUTES), RELATIVE DENSITY AND ANC OF THE DIFFERENT ANTACID BRANDS.

Parameters tested, n=3 (±sd)

BRAND	pH (Mean±SD)	FLOW TIME±SD	RELATIVE DENSITY	ANC per dose Titrimetry (mEq/10ml)(Mean±SD)
A	8.49±0.04	1.12±0.03	1.03	8.50±0.04
B	7.96±0.06	9.20±0.06	1.05	23.00±0.02
C	8.56±0.07	1.36±0.04	1.17	14.50±0.03
D	7.98±0.02	79.23±0.25	1.11	21.00±0.04
E	8.30±0.03	9.36±0.03	1.05	21.25±0.02
F	8.14±0.01	5.31±0.04	1.05	14.25±0.03
G	8.45±0.05	1.25±0.05	0.96	17.30±0.04
H	8.64±0,04	1.14±0.02	1.09	20.70±0.02

I	8.90±010	9.38±0.02	1.05	25.55±0.04
J	8.81±0.03	1.03±0.06	1.08	25.50±0.05
K	8.16±0.01	0.41±0.015	1.06	20.95±0.02
L	8.59±0.04	0.30±0.015	1.04	20.75±0.03
M	8.75±0.03	1.30±0.01	1.05	22.30±0.03
N	8.45±0.03	40.26±0.25	1.11	21.35±0.02
O	8.23±0.01	1.17±0.15	1.10	18.80±0.03
P	7.97±0.02	0.43±0.03	1.08	16.50±0.04
Q	8.03±0.02	5.23±0.11	0.99	20.90±0.03
R	8.85±0.05	70.50±0.5	1.09	16.25±0.02
S	7.60±0.05	5.10±0.17	1.02	16.80±0.03
T	8.90±0.06	5.18±0.08	1.01	17.50±0.02

3.5 Descriptive Statistics of ANC values

Table 3.5 DESCRIPTIVE STATISTICS OF ANC VALUES

Max. ANC	Min. ANC	Range

25.55 (Brand I)	8.50 (Brand A)	17.05

The mean and standard deviation of the ANC of the antacids are 19.17 and 3.82 respectively with a standard error of the mean of 0.86

Brand I has the highest acid neutralizing capacity with an ANC of 25.50 mEq/10ml while Brand A has the least acid neutralizing capacity with an ANC of 8.50 mEq/10ml.

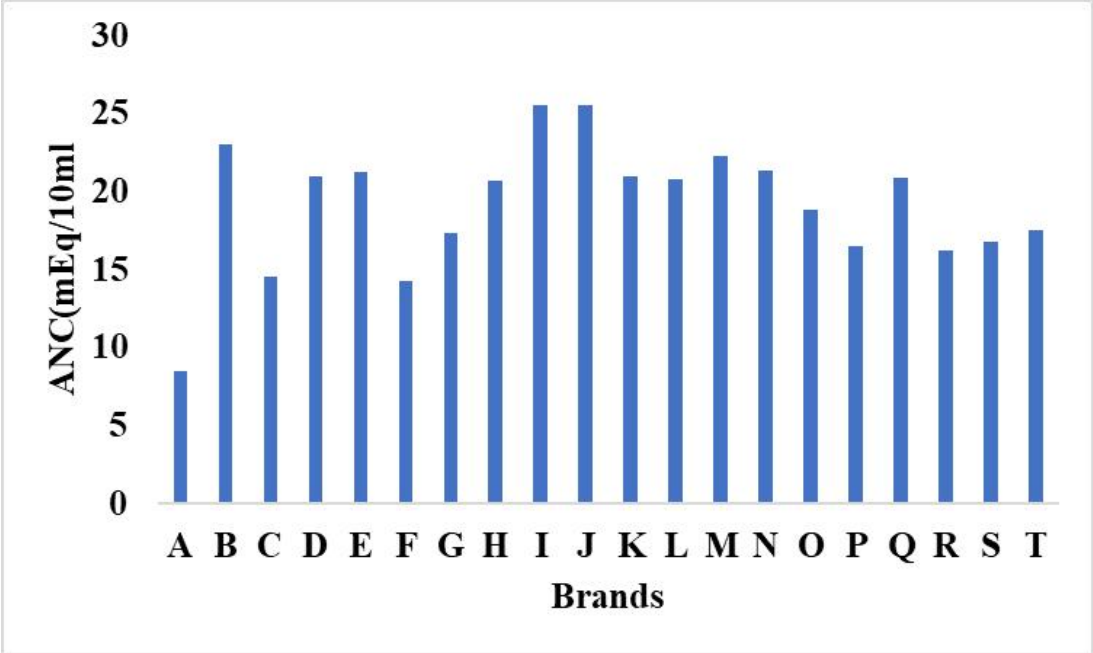


Figure 3.1 BAR CHART DISTRIBUTION OF ANC PER DOSE OF THE DIFFERENT BRANDS OF ANTACIDS.

3.6 Buffering capacity results

Table 3.5 Buffering capacity of the different brands of Antacids

Brand	0min	5min	10min	15min	20min	25min	30min	35min	40min	50min
A	8.46	2.01								
B	8.57	7.71	6.90	6.20	5.50	3.80	2.53			
C	7.30	3.01	2.20							
D	9.02	5.00	4.40	3.30	2.44					
E	8.41	3.05	3.01	2.56						
F	8.99	3.10	2.03							
G	7.47	2.10								
H	8.80	3.30	2.96	2.43						
I	8.42	5.33	3.55	3.24	2.80	2.32				
J	8.83	5.45	4.20	3.56	2.96	2.36				
K	8.56	4.20	3.33	2.68						
L	7.75	4.30	3.75	2.99	2.69					
M	8.50	3.99	3.92	3.76	2.51					
N	8.75	5.00	3.90	3.02	2.10					

O	7.82	3.70	2.45							
P	7.33	3.59	3.34	2.59						
Q	8.00	3.14	2.13							
R	7.80	3.58	3.25	2.30						
S	8.02	3.48	2.69							
T	8.27	3.10	2.33							

CHAPTER FOUR

4.1 DISCUSSION

Antacids are weak bases that can neutralize the acidity of the stomach. The efficacy of antacids is dependent on their acid-neutralizing capacity. Acid neutralizing capacity of an antacid is a parameter used to measure the effectiveness of an antacid in relieving ulcer pain.

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 ingredient was used in combination with magnesium hydroxide to obtain the desired acid neutralizing capacity (ANC) in most 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 aluminium,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 anti foaming agent such as simethicone (a suspension of polydimethylsiloxane and silica gel). Simethicone was used in virtually all the brands analysed but dimethicone, with similar activity was used in sample O.The difference between simethicone and dimethicone lies in the absence of silica in dimethicone. Only sample O employed sodium alginate which is a very reactive antacid active ingredient that combined with magnesium hydroxide and others. In addition to dried aluminum,magnesium hydroxide and dimethicone, sample G had magnesium trisilicate and alginic acid. The presence of magnesium is significant for laxative effect through relaxation of stomach muscles while Aluminium usually exerts a constipating effect.Hence,they are usually found in combination to annual their respective effects on the smooth muscles of the stomach

The study was conducted to develop a simple titrimetric method which can be used to determine the acid neutralizing capacity (ANC) of antacid suspensions. The challenge is to select a suitable indicator that will be sensitive within the pH range of 3.5 and the colour change will be visible enough so as to determine the end point.The Indicator selected for this experiment after considering the necessary criteria was Bromophenol Blue

Most antacid suspensions are coloured and this make it very difficult to observe the colour changeat the end point of the titration.This provides a great limitation to this experiment

The efficacy of antacids is dependent on their acid neutralizing capacity and buffering capacity.All specified antacids have been tested for their ANC and buffering capacity according to the procedure in United State Pharmacopoeia (USP).

All the brands of antacid suspensions used were within their shelf life as at the time of the study and all have NAFDAC (National agency for food drug administration and control) registration number.

In this study, preliminary antacid test, acid neutralizing capacity and buffering capacity was carried out on twenty brands of antacid suspensions which was brought around Benin metropolis. About Forty percent (40%) of the sampled antacids were imported brands, while sixty percent (60%) were locally manufactured brands. Ten (10) of the antacid suspensions were pink, nine (9) were white and one (1) was yellow (Table 3.1). The bottle type/colour of most of the antacids were plastic/amber (9),glass/amber (4),plastic/white (6) and Plastic/pink(1). (Table 3.1); this shows that the colour or bottle type does not have any influence on efficacy of antacids.

The pH of all the antacid suspensions were found to be in the range of 7.60 and 8.90 which is expected as antacids are alkaline substances.

In the preliminary antacid test, a pH greater than 3.5 was recorded for all the antacid brand analysed, a demonstration that products are antacids. The Preliminary Antacid Test (PAT) is however not an efficacy or quality indicaing test. Sample I recorded the highest PAT pH of 8.90 sample S recorded the lowest with a pH of 7.60. Having passed the PAT,all the sampled bands 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.

The acid neutralizing capacity which represents a vital pharmacological factor in antacid preparations and the rapid onset of drug action which is a worldwide admired quality of antacid formulations was determined in this study as well as the buffering capacity which signifies the duration of the acid neutralizing action of these antacids.

In developing countries like Nigeria where high technology equipment are not readily available and there is no stable power supply to power the equipment,there is need to develop an alternative method which will be easy, accurate and inexpensive that can be used to detemnine the ANC of antacid suspension.

Many indicators were considered but just few are sensitive in the range of a pH Of 3.5, Bromophenol Blue was selected for this study and titrimetric method of analysis was used to determine the ANC of the antacid suspensions.

A total of twenty (20) antacid suspension from twenty (20) different manufacturers were obtained for the study. These samples were analyzed by back titration for their acid neutralizing capacity.Acid neutralizing capacity (ANC) is an important quality assessment tool for evaluate effectiveness of antacid, as it gives information about the ability of the brand to react and neutralise gastric acid.

For an antacid to have adequate activity, it must have at least an ANC of five milliequivalents(5mEq) per dose (U.S. FDA code of Federal Regulation, 2020). From the result of the study (Table3.4), The ANC of all the antacid samples are adequate and were all above the United States Food and Drug Administration (FDA) requirement(≥ 5mEq/ dose) for an effective acid neutralizing capacity of an antacid formulation. Sample A had the lowest ANC of 8.50 mEq/dose while sample I had the highest ANC of 25.50 mEq/dose.. The USA-FDA 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.

From Table 3.3,It can be observed that there is closeness in result between the ANC values for the 20 different brands of Antacids when using Titrimetry and Potentiometry.This therefore indicates that Determination of ANC of Antacids using Titrimetry with a suitable indicator is an interchangeable method for Determination of ANC of Antacids when using Potentiometry

It is also imperative to state that determining the colour change while using Bromophenol Blue as an indicator was a bit difficult due to the colour of some of the antacids which is very similar to the colour of the indicator. However,it was easier to determine by carrying out the assay by using a blank and carrying out the experiment in triplicates.

Table 3.6 compares each antacid's buffering capacity as measured by the rate of pH change overtime for each one. The initial pH of each brand ranged from 7.8 to 8.90 Using information from the analysis of the antacids' buffering capacity, it is observed that sample B had buffering capacity being maintained for 30minutes..Sample I and T had the highest initial pH of 8.90 but showed a very low buffering capacity of 5min. A demonstration of a high ANC and a longer buffering capacity by an antacid indicates its efficacy

In comparison, a similar study was also conducted in Ghana, West Africa, to assess the acid neutralizing capacity of selected antacid suspensions, available in the Ghanaian market. From the results obtained from the study, it was inferred that the stability of the active components in the antacid suspensions gives a clue as to the formulations' stability and their capacity to survive environmental stressors including temperature and humidity. Although the makers did not specify the viscosity grade of the samples containing simethicone in addition to aluminum hydroxide and magnesium hydroxide, variances in their values may be responsible for the discrepancies in the ANC and buffering capacities noted.

Conclusions drawn from the in-vitro data show that antacid efficacy cannot be determined exclusively based on ANC. In order to estimate the effectiveness,an antacid must demonstrate both a high ANC and a good buffering capacity. In addition, recent research has shown that an antacid's price is unrelated to the product's effectiveness or quality.

4.2 Limitations of the Study

One of the study's shortcomings is that because only one geographic area was evaluated, the results may not be generalizable to other brands of antacid suspensions sold in the nation.

Another limitation of the study is that most of the antacids assessed were coloured,this made it difficult to determine the colour change at the end point, so careful observation of the colour change at end point of the titration was essential.

Another limitation is due to the fact that the antacids were bought from different premises,the storage conditions differ and this could affect the stability of the constituents which might affect the results obtained for the acid neutralizing capacity and buffering capacity

CHAPTER FIVE

5.1:Conclusion

The importance of an antacid preparation cannot be over emphasized in the health of an ulcer patient and those with heartburn. This study has revealed that different antacid preparations have different acid neutralizing capacities, 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 5mEq/dose. Sample I) had the highest ANC and had the highest buffering capacity (30minutes),while sample A had the lowest ANC and buffering capacity.Also, the closeness in result between the ANC obtained when using Titrimetry and when using Potentiometry indicates they can both be used interchangeably.

The Titrimetric procedure used in this study is simple, inexpensive, and easy to use and could be used in routine monitoring of the quality of Antacid

suspensions, especially in the absence of high technology equipment that are not easily available in most developing countries.

5.2: Recommendations:

Upon the completion of this study, the following recommendations could be made as observed;More research should be done on this study so as to determine a more suitable indicator than Bromophenol Blue because of the visibility issue encountered while carrying out this research for some antacids

It is also recommended that ANC values be included on labels of antacid products to assist physicians and patients to make more informed choices.

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APPENDIX