ACID NEUTRALIZATION CAPACITY AND CHARACTERISTICS OF ANTACID PRODUCTS

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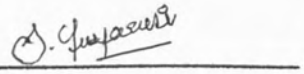

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ABSTRACT

Six brands of antacids, including three for tablet and three for liquid samples were analyzed for their acid neutralization capacity (ANC) and acid neutralization rate. The acid neutralization capacity was determined according to back titration method. Excess amount of HCl was reacted with an antacid sample and the HCl remaining after the antacid neutralization reaction occurs was titrated by standardized NaOH solution to a phenolphthalein endpoint. Results obtained showed the ANC of the tablet and liquid samples ranged 0.72 – 1.66 moles/tablet and 0.66 – 1.65 moles/mL, respectively. Results obtained for the potentiometric titration showed Povil can neutralize more of HCl acid where the magnitude in pH decrease for Povil is less than Maalox-Plus and Actal. For liquid antacids, Mixture Magnesium Trisilicate (MMT) can neutralize more of HCl acid followed by Alucid and Dhalumag. Maalox-Plus showed the highest neutralization rate followed by Actal and Povil, both in the tablet and powder form. For liquid antacids, MMT showed the fastest rate followed by Alucid and Dhalumag. Comparatively, antacids in the form of liquid showed higher rate of neutralization compared to powder and tablet antacids.

KAPASITI PENEUTRALAN ASID DAN CIRI-CIRI
PRODUK ANTASID

ABSTRAK

Enam jenis antasid, tiga dalam bentuk pepejal dan juga tiga dalam bentuk cecair telah dianalisis untuk menentukan kapasiti peneutralan asid dan kadar tindak balas peneutralan setiap satunya. Teknik yang digunakan adalah titratan berbalik. Asid hidroklorik berlebihan yang diketahui isipadunya ditindakbalas dengan suatu antasid dan larutan itu dititrat dengan NaOH dan penunjuk fenolftalein sehingga mencapai takat akhir. Keputusan diperolehi menunjukkan kapasiti peneutralan untuk antasid pepejal adalah dalam julat 0.72mol/tablet hingga 1.66 mol/tablet manakala bagi antasid cecair adalah dalam julat 0.66 mol/mL hingga 1.65 mol/mL. Keputusan yang diperolehi daripada titratan potentiometrik menunjukkan Povil boleh meneutralkan asid yang lebih banyak di mana magnitud penurunan pH bagi Povil adalah lebih rendah berbanding Maalox-Pluc dan Actal. Bagi antacid cecair, MMT mempunyai kapasiti peneutralan asid yang paling tinggi diikuti oleh Alucid dan Dhalumag. Maalox-Plus menunjukkan kadar tindak balas peneutralan paling tinggi diikuti oleh Actal dan Povil, dalam kedua-dua bentuk tablet dan juga serbuk. Bagi antasid cecair, MMT menunjukkan kadar yang paling tinggi diikuti oleh Alucid dan Dhalumag. Secara perbandingan, antasid dalam bentuk cecair mempunyai kadar peneutralan yang lebih tinggi berbanding antasid dalam bentuk pepejal yang dianalisis.

CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF UNITS, SYMBOLS AND ABBREVIATIONS

ANC	Acid Neutralization Capacity
USP	United States Pharmacopeia
MMT	Mixture Magnesium Trisilicate
M	Molarity ($molL^{-1}$)
mEq	milli-Equivalent
K_{sp}	Solubility Product
g	gram
mL	milli Litre
mg	milli gram
V	volume
^{o}C	degree Celsius
n	number of moles
NaOH	Sodium Hydroxide
HCl	Hydrochloric acid
MW	Molecular Weight
Wo	weight
%	percent
w/w	weight per weight
RM	Ringgit Malaysia

CHAPTER 1

INTRODUCTION

1.1 Antacid and its application

The parietal cells in the stomach secrete hydrochloric acid at a concentration of about 0.155 M HCl to begin the chemical breakdown of the food that we eat. The flow of HCl increases when food enters the stomach. When eat or drink too much, the digestive system may generate too much acid. Excessive secretion of this acid can lead to many stomach problems such as heartburn or indigestion, gastritis, gastric ulcers and peptic acid disease.

Antacid is a substance which is used by physicians to treat the excessive production of hydrochloric acid by the parietal cells lining the stomach. A little bit of NaOH might be as equally effective as antacid, but it is quite rough on the other digestive system, so antacids need to be formulated to reduce acidity while avoiding physiological side-effects. Many antacids use $CaCO_3$ for this purpose (Littman and Pine, 1975).

Commonly used antacid preparations can contain any one or combination of the following alkaline active ingredients: aluminium hydroxide, calcium carbonate

(commonly known as chalk), various magnesium compounds such as magnesium hydroxide and sodium bicarbonate. These active ingredients are used because they are weak bases since strong bases would lead to the risk of damaging the stomach if too much were taken.

Antacids are over-the-counter medication where anyone can get them readily in local pharmacies or medical shops. Antacids are available in two different formulations such as tablet form as well as liquid or slurry form. There are many different brands of antacid available in market and contain a diverse range of active ingredients. Due to the differences in the active ingredients, the effectiveness or the acid neutralization capacity of antacid products is variable. An example of tablet antacid and liquid antacid is illustrated in Figure 1.1 and Figure 1.2.

Figure 1.1 Tablet Antacid

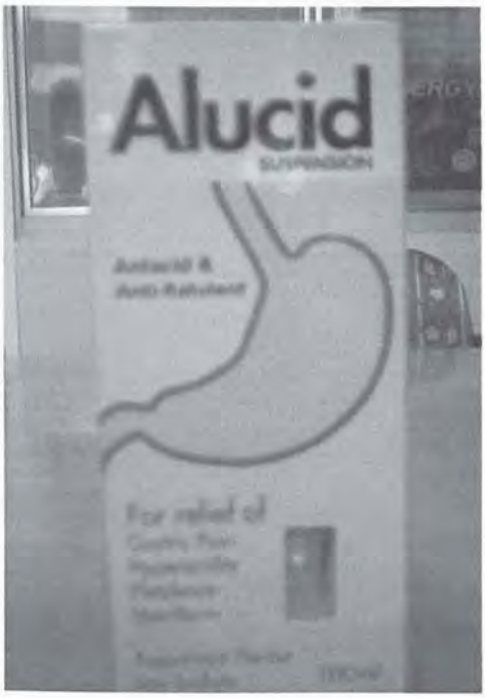

Figure 1.2 Liquid Antacid

1.2 Objectives of Study

The objectives of this study are:

a) To determine and compare the acid neutralization capacity of selected commercial antacid products.

b) To determine the rate of acid neutralization of the antacid products

1.3 Scope of Study

In this study, different brands and formulations of antacids purchased from the local pharmacies will be analyzed to determine their acid neutralization capacity (ANC) and acid neutralization rate.

CHAPTER 2

LITERATURE REVIEW

2.1 Antacid

2.1.1 Definition

An antacid is any substance, generally a weak base, which can neutralize the stomach acids by reacting with them chemically. Antacids are swallowed to neutralize this excess acid and "relieve" but not eliminate the condition (Littman and Pine, 1975). The United States Pharmacopeia (USP) defines an antacid in terms of its ability to neutralize acid. To be called an antacid, the lowest dose of the substance when added to 10 mL of 0.5 N HCl (5 mEq) must produce a pH of 3.5 or greater after 10 minutes of stirring. This is a somewhat arbitrary choice that is not related to efficacy, and manufacturers can simply increase the minimum dosage to qualify as an antacid (Rockville, 1990).

2.1.2 Active Ingredients in Antacid

Antacids contain various kinds and amounts of active ingredients (base) as well as inactive binders, flavors, sweeteners, binders, filters, antifoam agents, pain relievers (aspirin) and other commercial goodies (Drake and Horlander, 1981). The active

ingredients neutralize acid through a variety of reactions while the inactive ingredients provide bulk and flavor. To decrease the possibility of the stomach becoming too basic from the antacid, buffers are added as part of the formulation of some antacids (Rhodes, 1982). Some preparations contain substances such as magnesium trisilicate that reduce the formation of gas.

a. Calcium carbonate

Calcium carbonate is a fast-acting and potent antacid. The base present in this antacid is ion carbonate (CO_3^{2-}). Compared to other active ingredients, its actions are more prolonged and its side effects less severe. Even though calcium carbonate can be used safely in small doses (0.5 g) for occasional gastric upset, it should not be used chronically for long-term treatments. Calcium carbonate is only very slightly soluble n water (Knodel, 1998).

b. Magnesium salts (hydroxide, oxide, carbonate and trisilicate)

Magnesium salts have less antacid potency than sodium bicarbonate and calcium carbonate. Even so, the magnesium salts are effective acid neutralizers. The actions of these salts are somewhat slow to develop, but are long-lasting. Use of the magnesium compounds is relatively safe even if continued for long periods of time. These agents do not cause the same severe adverse effects associated with sodium bicarbonate or calcium carbonate use. Because of these factors, magnesium salts are the most commonly used of the antacid ingredients. Magnesium hydroxide is the active ingredient found in most

aqueous suspension antacid. $Mg(OH)_2$ is rather insoluble compound (Littman and Pine, 1975).

c. Aluminum salts (hydroxide, carbonate, phosphate)

Aluminium salts possess the least amount of neutralizing capability of the antacid ingredients, particularly the aluminum phosphate salt, and are almost always combined with a magnesium salt. They are also slower to act than sodium bicarbonate and calcium carbonate (Gadad et al., 2006).

d. Sodium Bicarbonate

It is the active ingredient found in ordinary *baking soda* and is a potent, effective, and fast-acting antacid. It quickly reacts with the hydrochloric acid of the stomach to form water, sodium chloride, and the gas, carbon dioxide. Although occasional, short-term use is well tolerated; chronic, continual use of this agent can be dangerous and should be avoided. Because of the potential problems with this antacid, its use is rarely recommended by physicians (Gadad *et al.*, 2006).

e. Dihydroxyaluminium Sodium Carbonate ($NaAl(OH)_2CO_3$)

The dihydroxyaluminium compound contains two ions that can serve as bases: carbonate and hydroxide.

There are other forms of antacid that work in less direct means. There are two types of pharmaceutical drugs that act indirectly to reduce the amount of stomach acid. They are called histamine H_2 antagonists (such as Pepcid, Zantac and Tagamet) and proton pump inhibitors (such as Prilosec and Prevacid). Both of these types' drugs act to suppress the formation of stomach acids. Essentially, they turn off the biochemical machinery that produces the stomach acid. These drugs are slower acting than the bases mentioned above, but they provide relief for a much longer time. They are usually taken by people with chronic stomach problems (Gaisford *et* al., 2004).

2.1.3 Formulation of Antacid Products

Antacid products are either in the form of chewable tablets or suspensions. Chewable tablets should be masticated and swallowed at once, with a drink of water. According to Temple and Nahata (2000), chewable tablets can have unpleasant taste and grittiness mouth feel, leading to poor patient compliance. Hence, to circumvent these disadvantages, the non-chewable antacid tablets (disintegrating tablets) were formulated.

2.1.4 Disadvantages of Active Ingredients

Although the active ingredients in antacids are effective, each one has certain disadvantages. For example, sodium bicarbonate loses its effectiveness quickly, and many people must limit their intake of sodium. Magnesium compounds can cause constipation, aluminium hydroxide can act as a laxative, and calcium carbonate has an unpleasant taste (Littman and Pine, 1998).

All antacids have side effects, the most serious of which are metabolic. In clinical terms, the harmful sustemicside effects of calcium carbonate and sodium bicarbonate outweigh their benefit as neutralizing agents; they should rarely be employed in the treatment of acid-peptic disease. The more common antacid side effects of diarrhea (magnesium hydroxide) and constipation (aluminum hydroxide) are best managed by appropriately alternating the agents or by using one of the various antacid mixtures (Green *et* al., 1975).

2.2 Acid Neutralization Reactions of Antacids

Since the active ingredients in antacids are weak bases, the reaction that takes place is an acid/base reaction. Bases in antacids neutralize acids by reacting with them to produce a salt and water. This chemical reaction of a weak base with stomach acid can be written in general form:

Weak base + hydrochloric acid → salt + water Eq. 1

Example of common neutralization reactions are shown in Table 2.1. It can be summarized that the neutralization reactions are dependent on the type of base present in the antacids. One mole of base can react with one to four moles of H^+. For example, one mole of $Al(OH)_3$ reacts with three moles H^+ whereas one mole of $NaHCO_3$ reacts with only one mole of H^+. Some antacids such as calcium carbonate or sodium bicarbonate are inorganic bases that react stoichiometrically with acid; each mole of the base neutralizes one mole of acid (MacCara *et al.*, 1985).

Table 2.1 Active Ingredients in Common Commercial Antacids

Compound	Chemical Formula	Chemical Reaction
Aluminium hydroxide	$Al(OH)_3$	$Al(OH)_{3\,(s)} + 3HCl_{\,(aq)} \rightarrow AlCl_{3\,(aq)} + 3H_2O_{\,(l)}$
Calcium carbonate	$CaCO_3$	$CaCO_{3\,(s)} + 2HCl_{\,(aq)} \rightarrow CaCl_{2\,(aq)} + H_2O_{\,(l)} + CO_{2\,(g)}$
Magnesium carbonate	$MgCO_3$	$MgCO_{3\,(s)} + 2HCl_{\,(aq)} \rightarrow MgCl_{2\,(aq)} + H_2O_{\,(l)} + CO_{2\,(g)}$
Magnesium hydroxide	$Mg(OH)_2$	$Mg(OH)_{2\,(s)} + 2HCl_{\,(aq)} \rightarrow MgCl_{2\,(aq)} + 2H_2O_{\,(l)}$
Sodium bicarbonate	$NaHCO_3$	$NaHCO_{3\,(s)} + HCl_{\,(aq)} \rightarrow NaCl_{\,(aq)} + H_2O_{\,(l)} + CO_{2\,(g)}$
Dihydroxyaluminum Sodium Carbonate	$NaAl(OH)_2CO_3$	$NaAl(OH)_2CO_{3\,(s)} + 4H^+_{\,(aq)} \rightarrow Na^+_{\,(aq)} + Al^{3+}_{\,(aq)} + 3H_2O_{\,(l)} + CO_{2(g)}$

The dissociation of calcium carbonate is given by:

$$CaCO_{3\,(S)} \leftrightarrow Ca^{2+}_{\,(aq)} + CO_3^{2-}{}_{(aq)} \qquad \text{(Rxn. 1)}$$

The concentration of the base, CO_3^{2-}, is present in low concentrations. As predicted by Le Chatelier's Principle, as the CO_3^{2-} ion of Rxn. 1 is removed by the formation of HCO_3^- in Rxn. 2, the equilibrium of Rxn. 1 will shift to the right, to compensate for the loss of $CaCO_3$ dissolves. The equations for the removal of the carbonate ion, bicarbonate ion and carbonic acid are:

$$H^+_{\,(aq)} + CO_3^{2-}{}_{(aq)} \leftrightarrow HCO_3^-{}_{(aq)} \qquad \text{(Rxn. 2)}$$

$$H^+_{\,(aq)} + HCO_3^-{}_{(aq)} \leftrightarrow H_2CO_{3\,(aq)} \qquad \text{(Rxn. 3)}$$

$$H_2CO_{3\,(aq)} \leftrightarrow CO_{2\,(g)} + H_2O_{\,(l)} \qquad \text{(Rxn. 4)}$$

Rxn. 2 shows the carbonate ion acting as a base to neutralize H^+. Rxn. 3 and Rxn. 4 show that during the neutralization process, there are significant quantities of HCO_3^- and

H_2CO_3 present. (Actually, the H_2CO_3 is present largely in the dissociated form of CO_2 and H_2O). Since a mixture of a weak acid and its conjugate base is a buffer, this system will contain both of the HCO_3^-/CO_3^{2-} and H_2CO_3/HCO_3^- buffers during various stages of the neutralization (Mihaljovic *et al.*, 2006).

If HCl is added to the H_2CO_3/HCO_3^- buffer, the acid is neutralized as HCO_3^- (bicarbonate ion) accepts the proton of the acid and converts into H_2CO_3 (carbonic acid). The pH will change very little during this process. This is good for stabilizing our stomach, but leads to difficulties when we try to determine the strength of an antacid by titration using an acid. A distinct indicator "endpoint", or color change, requires a rapid change of pH near the equivalence point of the titration, and this does not occur in a buffered solution.

Magnesium hydroxide is insoluble and its dissociation is as seen in Rxn. 5. The low concentration of hydroxide ion in solution for a $Mg(OH)_2$ slurry greatly lessens the effects of the strong OH^- base on tissue.

$$Mg(OH)_{2\,(S)} \leftrightarrow Mg^{2+}{}_{(aq)} + 2OH^-{}_{(aq)} \qquad \text{(Rxn. 5)}$$

$$K_{sp} \text{ of } Mg(OH)_2 = 1.2 \times 10^{-11} \text{ (at 18°C)}$$

The concentration of hydroxide ion is never high enough to damage body tissue. As the hydroxide ion in solution reacts with stomach (as given in Rxn. 7), more $Mg(OH)_2$ dissolves, as described in Rxn. 5. This provides additional OH^- until the $Mg(OH)_2$ is all dissolved. Similar reaction occurs for antacids which have aluminium hydroxide as the active ingredient. Since this compound is insoluble, one way to write equation for the reaction with acid is:

$$Al(OH)_{3\,(S)} + 3H^+{}_{(aq)} \leftrightarrow 3H_2O_{\,(l)} + Al^{3+}{}_{(aq)} \qquad \text{(Rxn. 6)}$$

The hydroxide ions found in dihydroxyaluminium sodium carbonate, magnesium hydroxide and aluminium hydroxide compounds neutralize acid by Rxn. 7:

$$OH^-_{(aq)} + H^+_{(aq)} \rightarrow H_2O_{(l)} \qquad \text{(Rxn. 7)}$$

2.3 Acid Neutralization Capacity

According to Drake and Horlander (1981), acid neutralizing capacity is the capacity to neutralize strong acids and is due to any dissolved species (usually weak acid anions) that can accept and neutralize protons. In the case of antacid, the acid neutralizing capacity is the amount of hydrochloric acid an antacid can neutralize. It is the quantity which is referred to in some advertisements when it is stated that the antacid "neutralizes X times its weight in stomach acid" (Gilman *et al.*, 1975).

The potency of antacids is expressed in terms of milli-equivalents (mEq) of Acid-Neutralizing Capacity (ANC), which means the amount of stomach acid neutralized by the antacid per dose over a specified period of time (Miederer *et al.*, 2003). According to Temple and Nahata (2000) the ANC of antacid products vary considerably, depending on the product's ingredient(s) amounts, formulation, and manufacturer (brand).

2.3.1 Effect of Product Type

The acid neutralization test provides a basis for rational substitution of one antacid for another. According to Knodel (1998), most antacid products will effectively relieve mild gastroesophageal reflux disease (GERD) symptoms if taken in the appropriate doses. However, potency differs between antacid products. This means that one teaspoonful of

REFERENCES

Covington, T.R. 1996. *Handbook of Nonprescription Drugs*. Acid-Peptic Products. 11th Edition. American Pharmaceutical Association, Washington DC, pp193-224.

Drake, D. and Horlander, D., 1981. Neutralizing capacity and cost effectiveness of antacids. *Journal of Ann Intern Med* **94**, 215-217.

Gadad, A.P., Dandagi, P.M., Mastiholimath, V.S., Patil, M.B., Rasal, V.P. and Dasankoppa, F.S., 2006. Non-chewable antacid formulations: Effects of different disintegrating agents on their acid neutralization properties. *Indian Journal of Pharmaceutical Sciences* **68** (2), 269-273.

Gaisford, S., Royall, P.G. and Greig, D.G.T., 2004. Solution calorimetry as a tool to study the neutralizing capacity of magnesium trisilicate mixture BP and its components. *Journal of Thermochimica Acta* **417** (2), 217-221.

Gilman, A.R., Goodman, L.S., Rall T.W. and Murad F. (eds.). 1975. *The Pharmacological Basis of Therapeutics*. 5th Edition. MacMillan Publishing Company, New York, pp935-960.

Graham, D.Y. and Patterson, D.J., 1983. Double-blind comparison liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. *Journal of Digestive Diseases Science* **28**, 559-563.

Green, F.W., Norton, R.A. and Kaplan, M.M., 1975. Pharmacology and clinical use of antacids. *American Journal of Hospital Pharmaceutical* **32** (4), 425-429.

Knodel, L.C. 1998. *Nonprescription Products: formulations and Features '98-99*. Acid-Peptic Products. American Pharmaceutical Association, Washington DC, pp162.

Koujout, S. and Brown, D.R., 2005. Calorimetric basic absorption and neutralization studies of supported sulfonic acids. *Journal of Thermochimica Acta* **434** (2), 158-164.

Lin, M.S., Sun, P. and Yu, H.Y., 1998. Evaluation of buffering capacity and acid neutralizing-pH time profile of antacids. *Journal of Formos Medical Association* **97** (10), 704-710.

Littman, A. and Pine, B.H., 1975. Antacids and anticholinergic drugs. *Journal of Ann Intern Med* **82**, 544-551.

MacCara, M.E., Nugent, F.J. and Garner, J.B., 1985. Acid neutralization capacity of Canadian antacid formulations. *Journal of Canadian Medical Association* **132**, 523-527.

Miederer, S.E., Wirtz, M. and Flapung, B., 2003. Acid neutralization and bile acid binding of hydrotalcite compared with other antacids. *Chinese Journal of Digestive Diseases* **4** (3), 140-146.

Mihajlovic, R.P., Jaksic, L.N. and Dzudovic, R.M., 2006. Coulometric generation of acids and bases for acid-base titrations in non-aquoeus solvents. *Journal of Analytica Chimica Acta* **557** (2), 37-44.

Myriam, D., Fabien, G. and Fabien, T., 2005. Sensitivity of the acid-base properties of clays to the methods of preparation and measurement. *Journal of Colloid and Interface Science* **289** (1), 139-147.

Rhodes, J., 1982. Eshophagitis and the role of antacid therapy. *Scand Journal of Gastroenterol* **17**, 74-76.

Rockville, M.D., 1990. The United States Pharmacopoeia., USP 22. United States Pharmacopoeial Convention Inc., pp1528.

Rossett, N. E. and Rice, 1954. The neutralizing ability of antacid tablets. *Journal of Gastroenterology* **26**, 490-496.

Temple, R. and Nahata, F., 2000. Comparative palatability of 22 liquid antacids. *Journal of Alimentary Pharmacology and Therapeutics* **14** (4), 421-425.