Asian Journal of Chemistry Vol. 18, No. 4 (2006), 2742–2746

Assaying Antacids for Neutralizing Capacity with Different Indicators

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Antacids have been assayed titrimetrically for their neutralizing capacity using copper sulfate, methyl orange and methyl red as indicators of equivalence points. End-point with copper sulfate is marked with the appearance of a stable bluish-white turbidity. Estimated values (mL 1 N acid consumed per 100 mg antacid base) with copper sulfate did not differ from those obtained with methyl orange ($P > 0.1$). The values obtained with methyl red were significantly lower than those obtained with either copper sulfate or with methyl orange for those preparations containing aluminum as common cationic species ($P < 0.05$) and for others were not significantly different ($P > 0.1$). Investigations reveal that choice of indicators affects estimated values and copper sulfate is a valuable substitute to methyl orange for assaying antacids for neutralizing capacity. Copper sulfate offers obvious advantages, provides stable end-point and is suitable for measuring titratable acidity of coloured solutions.

Key Words: Neutralizing capacity, Antacids, Copper sulfate, Indicators.

INTRODUCTION

Antacids are weak bases containing one or more of the main ingredients including aluminium hydroxide, magnesium hydroxide, magaldrate and light magnesium carbonate. Pharmaceutical assays focus on assaying antacids for their cationic species using laborious complexiметric techniques[1, 2] whereas therapeutic considerations emphasize determination of their neutralizing capacity[3]. Indian Pharmacopeia (1996)[1] outlines only a potentiometric technique for determining the neutralizing capacity of one antacid, magaldrate. A simple titrimetric assay for tablets containing mainly carbonates and hydroxides of aluminium and magnesium has been outlined using methyl orange as indicator[4]. Copper sulfate has been identified as a valuable indicator in neutralizing titrimety[5, 6]. In view of these considerations, the present investigations were carried out to standardize a uniform protocol for assaying antacid tablets and suspensions and to evaluate efficiency of copper sulfate as indicator for assaying antacids for neutralizing capacity in comparison to organic indicators including methyl orange and methyl red.

EXPERIMENTAL

The experiments were carried out at 25 ± 1°C. Double distilled water was used wherever required. The chemicals used were of standard quality. The drug formulations were procured from the local market. These formulations include Aryacid-M suspension (Aryan Pharmaceutical Ltd., Thane), each 5 mL suspension containing magaldrate 400 mg, simethicone 60 mg, liquorice base and excipients. Exocid suspension (Ex-Laboratories, Gujarat) each 5 mL, provides dried $Al(OH)_3$ gel 300 mg, $Mg(OH)_2$ 125 mg, simethicone 25 mg with flavoured base and excipients. Milk of magnesia (Dey's Medical Stores Ltd., Kolkata) each 5 g provides 400 mg $Mg(OH)_2$. Dioval tablets (Wallace Pharmaceuticals Ltd., Mumbai), each tablet of 1006 ± 1 mg weight, provides $Al(OH)_3$ 240 mg, $Mg(OH)_2$ 100 mg, light magnesium carbonate 60 mg, simethicone 24 mg and other excipients. pH 4 tablets (Biological E., Hyderabad), each tablet of 596 ± 1 mg weight, contains magaldrate 400 mg, simethicone 20 mg, chocolate flavoured with permitted colours and excipients. Chemical grade antacids used were hydrated aluminium hydroxide dried gel, light magnesium carbonate (labelled $3MgCO_3 \cdot Mg(OH)_2 \cdot 3H_2O$) and magnesium oxide GR (all from Loba Chemie, Mumbai).

Samples and sample processing

Sample size was equivalent to 400–425 mg antacid base. Tablets were individually weighed, pulverized to a fine powder and average tablet weight powder processed. To each sample was added standard sulfuric acid @ 6.5 mL 1 N per 100 mg antacid base. Sulfuric acid was standardized against standard sodium hydroxide that had been previously standardized against the primary standard 0.1 N succinic acid. The samples in mineral acid were heated on a sand bath to the point of boiling to facilitate rapid neutralization of antacid base. Preparations containing magnesium carbonate required additional boiling for 2–3 min to expel carbon dioxide from the reaction mixture. Chemical grade aluminium hydroxide required special treatment for obtaining a clear solution, sample size 100 mg, 25 mL of H_2SO_4 (1 N) and reflux boiling for 20–30 min. Heated solutions were cooled to room temperature and volume made to 100 mL with water. Formulations containing simethicone and insoluble excipients were centrifuged at 6000 rpm for 10 min and then filtered over Whatmann filter paper No. 1 to obtain a clear solution. All solutions were colourless except that obtained from pH 4 tablets which was intensely reddish.

Titrimetry

Sample solutions were assayed for their residual acidity by back-titration against 0.5 N NaOH using different indicators @ 0.5 mL/10–20 mL aliquot size. Copper sulfate pentahydrate as 5% (w/v) and methyl orange was prepared as 0.1% (w/v) in water while methyl red as 0.1% (w/v) in 0.0014% NaOH. Volumes of

standard alkali used to obtain end-points were recorded. End-point with copper sulfate was recorded when clear titrating solution turned turbid with bluish-white opalescence that did not dissolve. Each formulation/preparation was processed in triplicate and each sample solution subjected to two titrations for each of the indicators used.

The amount of acid consumed, reflecting neutralizing capacity of antacid, was calculated per 100 mg antacid base:

$$\text{Acid consumed (mL 1 N/100 mg antacid base)} = (X - Y) \times (100)/W$$

where X = the amount of acid (volume × normality) added to the sample for processing,

Y = the amount of alkali (volume × normality) used to obtain end-point as extrapolated to 100 mL sample solution,

W = the amount of antacid base (mg) present in the sample as per label claim that was used for processing.

Control studies were undertaken to evaluate the effect of heat, if any, on estimation of standard mineral acid following its exposure to heat on a sand bath for 30 min. Besides, the effect of varying amounts of aluminium sulfate (0.25–1.0 mL 1 N) on functioning of methyl red indicator was studied as a follow-up to the observation that aluminium containing antacids delayed end-points obtained with methyl red.

The data were analyzed by Student's t-test for any differences in means obtained with test indicators. Per cent decrease in estimated values with methyl red indicator, as compared to those obtained with copper sulfate and methyl orange and calculated aluminium content in test antacids, were subjected to correlation analysis.

RESULTS AND DISCUSSION

As evident from the results (Table-1), the values of neutralizing capacity of test antacids obtained with copper sulfate did not differ significantly from those obtained with methyl orange ($P > 0.1$). Methyl red provided comparable values except for antacids containing aluminium cation: (a) antacids containing aluminium hydroxide or magaldrate showed significantly lower values than those obtained with copper sulfate or methyl orange ($P < 0.05$), (b) decrease in estimated values was positively correlated to calculated Al content in the antacid ($r = 0.98$) with per cent decrease ranging from 36 ± 1 (pH 4 tablets), 40.3 ± 1.3 (Aryacid suspension), 44.3 ± 0.6 (Dioval tablets), 51.5 ± 1.1 (Exocid suspension) to 65.2 ± 1.3 ($Al(OH)_3 + H_2O$ gel) containing aluminium content (by calculation), respectively, as 12.3, 12.3, 20.8, 24.4 and 34.6 mg Al per 100 mg base, and (c) aluminium sulfate added to 20 mL 0.104 N sulfuric acid in varying amounts of 0.25, 0.50 and 1.0 mL 1 N, respectively, caused per cent deviation in end-point as 9.7 ± 0.3, 19.3 ± 0.8 and 37.2 ± 0.3 from control acidity ($P < 0.05$).

TABLE-1
NEUTRALIZING CAPACITY OF ANTACIDS WITH DIFFERENT INDICATORS

Antacid formulation/preparation (Source)	Neutralizing capacity (mL 1 N acid consumed/100 mg antacid base)		
	Copper sulfate	Methyl orange	Methyl red
Pharmaceutical Grade:			
Aryacid-M Suspension (Aryans, Thane)	2.60 ± 0.01	2.59 ± 0.01	1.55* ± 0.03
Exocid Suspension (Ex-Lab., Gujarat)	3.31 ± 0.02	3.26 ± 0.03	1.59* ± 0.04
Milk of Magnesia (Dey's, Kolkata)	3.83 ± 0.01	3.81 ± 0.02	3.77 ± 0.02
Dioval Tablet (Wallace, Mumbai)	2.90 ± 0.04	2.86 ± 0.02	1.61* ± 0.02
pH 4 Tablets (Biological E., Hyderabad)	2.85 ± 0.01	2.83 ± 0.01	1.82* ± 0.02
Chemical Grade:			
Light magnesium carbonate (Loba Chemie, Mumbai)	2.08 ± 0.02	2.09 ± 0.01	2.09 ± 0.01
Magnesium oxide (Loba Chemie, Mumbai)	4.57 ± 0.01	4.57 ± 0.01	4.54 ± 0.02
Aluminium hydroxide gel powder (Loba Chemie, Mumbai)	2.93 ± 0.03	2.93 ± 0.03	1.02* ± 0.04

The values are mean ± S.E. of six observations.
*The values are significantly lower than the corresponding values ($P < 0.05$).

The studies indicate that choice of an indicator is critical for determining neutralizing capacity of antacids and copper sulfate is a valuable substitute to methyl orange for such determinations. Methyl red is not suitable indicator for antacids containing aluminium either as $Al(OH)_3$ or as magaldrate. Overall neutralizing capacity values of antacids available in the Indian market ranged from 2.59–3.83 (average 3.03 ± 0.14) meq per 100 mg base. The values are comparable to those reported from international market ranging from 2.62–3.13 (average 2.3 ± 0.2) meq per 100 mg antacid base[3]. Heat exposure during processing did not contribute to estimated values, mean acidity on exposing 30 mL of sulfuric acid (1.168 N) to 30 min heat on sand bath was 0.347 ± 0.001 N compared to control acidity of 0.35 ± 0.001 N ($P < 0.1$, $n = 6$).

Quality control assurance for drugs ought to be use-oriented. Since antacids are advocated for their neutralizing capacity, it is mandatory to assay such drugs for their anionic functions rather than on their cationic components[1, 2]. The present investigation outlines a uniform standardized protocol for assaying antacids for their neutralizing capacity and also provides information about choice of different indicators to be used to accomplish this objective.

Till date only methyl orange has been identified as an indicator for assaying antacids for their neutralizing capaciity[4]. Methyl red is being used while processing aluminium based antacids for complexiметric assays as a monitoring agent[1]. The two indicators turn yellow in alkaline pH, methyl orange at *ca.* pH 4 and methyl red at *ca.* pH 6. Copper sulfate is known to form insoluble cupric

hydroxide at pH 6 and above[7]. Thus, three indicators were rationalized for investigation in view of the fact that strong acid-strong base titrations show sharp shift in pH from 4–10 units at equivalence point and the indicators with working range within these limits are quite satsfactory[8]. Copper sulfate has already proved a valuable indicator in such titrimetric studies[5, 6]. The present investigations further confirm its suitability in neutralization titrimetric studies. Copper sulfate has obvious advantages over organic indicators; it produces quite stable end-point and is suitable for measuring titratable acidity of coloured clear solutions. Present studies indicate that the practice of using methyl red while processing antacids containing aluminium for complexiметric studies[1] is not free from error, as aluminium interferes with its functioning.

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(*Received*: 4 August 2005; *Accepted*: 25 April 2006) AJC-4792