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Original Research Article

Comparative evaluation of Polygel Dual and commonly used alginate-antacid formulations (ACIDUAL Study)

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Abstract

Purpose: *To compare Polygel Dual (PD) and four marketed alginate-antacid combination products, with respect to raft formation and antacid properties.*
Methods: *The pharmacopeial tests used were selected based on demonstrable performance of raft-forming potential, including speed and thickness, for all selected products. Evidence-based methods were used to determine the antacid effects in terms of acid-neutralizing capacity and increase in pH.*
Results: *Raft-forming ability was demonstrated by three products, with AF-4 and PD outperforming in speed and thickness. PD, AF-1 and AF-2 exhibited superior antacid properties. However, PD was the only product that demonstrated superior performance with respect to raft-formation and antacid potential. Raft-forming capacity was exhibited by 3 out of 5 products, viz, PD, AF-1 and AF-4. Raft formation was faster in AF-4 (15 s), followed by in PD (25 s). Similarly, raft thickness (14.79 mm) was highest in AF-4, followed by (4.39 mm) in PD. Preliminary antacid test results showed that AF-4 failed to raise pH above 3.5, but PD raised pH to 5.86, while AF-1 raised pH to 5.88. Similarly, periodic test analysis revealed that PD maintained pH above 7 for the entire test duration of 210 min, whereas AF-4 failed to raise pH to 7 during the test period.*
Conclusion: *Polygel dual (PD) demonstrates desirable raft-forming potential and antacid properties. Moreover, it effectively raises pH and maintains it for longer duration than any of the other antacid products. Thus, PD may be considered a potentially effective treatment for acid-reflux problems. However, this claim should be validated in suitable clinical trials.*

Keywords: *Acid reflux, Heartburn, Antacid, Alginate, Alginic acid, Polygel Dual, Acid neutralizing capacity*

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INTRODUCTION

Gastro-esophageal reflux disease (GERD), a common and usually chronic ailment of the upper digestive tract, has prevalence of 10 – 20 % [1,2]. The prevalence of GERD is on the rise in Africa due to epidemic of obesity, advancing age, changes in diet, and sedentary lifestyle. A study

has reported a 26.34 % prevalence of GERD in Nigeria [3]. The common symptoms of GERD are heart burn and acid reflux. These symptoms reduce the quality of life of millions of GERD patients, majority of whom engage in self-treatment. Thus, physicians are consulted only when the condition becomes chronic or intractable [4]. Mild GERD affects millions of people, and the prevalence of reflux is as high as 29 % in people aged 20 – 69 years [5].

Given the consistent effect of gastric acid in reflux symptoms and mucosal damage, inhibition of gastric acidity is the mainstay of treatment for GERD patients. The intermittent nature of reflux symptoms implies that medicines are prescribed only when necessary. However, this approach leads to partial relief of the symptoms. Therefore, in order to treat reflux symptoms completely, one option is to use alginate-based reflux suppressants which offer rapid symptom relief. Indeed, alginate-based reflux suppressants are considered the best option for on-demand treatment. Alginate-based products are of two types i.e. alginate-only and alginate-antacid combination [6].

Alginate-based reflux suppressants have a long history of clinical use, and are suitable for the symptomatic treatment of heartburn and esophagitis. Moreover, they appear to act through a unique mechanism which differs from that of traditional antacids [4]. The alginate-antacid combinations are more beneficial than alginate-only formulation since the former offer dual action in which alginate prevents reflux by forming a raft, while the antacid component neutralizes stomach acid [5]. The rafts formed by alginate-antacid combinations floats on the top of the ingested food in the region of the acid pocket, thereby offering more effective targeted therapy [7].

The raft also serves as a barrier that prevents penetration of stomach acid into the esophagus. Evidence has shown that the raft may be sustained for up to 4 h, leading to rapid and long-lasting relief from postprandial heartburn [8]. In addition, it has been demonstrated that alginate-antacid combinations provide longer-lasting symptom relief than antacids alone, which makes them more suitable as over-the-counter medications [9]. Alginate-antacid combinations are available in various forms such as suspensions, granules for suspension, or tablets. Liquid formulations are considered more effective than solid formulations because of availability of liquid formulations in dispersed forms [10].

There are several alginate-antacid combination products available in African markets. However, their raft-forming capacity and antacid efficacy vary to a great extent. Therefore, this study was aimed at comparing a new formulation (*polygel dual*) with four alginate-antacid combinations available in African markets, with respect to raft-forming potential and antacid effect, using *in vitro* methods.

EXPERIMENTAL

Sampling and composition of samples

Samples of four marketed products from different African countries, and *Polygel Dual* (Shalina Healthcare) were transported to Research and Development Department of Shalina Healthcare, India. The four marketed products were assigned codes, i.e., AF-1 to AF-4. The name, code and composition of all selected products are shown in Table 1.

Table 1: Composition of *Polygel Dual* (PD) and alginate-antacid combination products studied

Product name/code	Volume (mL)	Composition
Polygel Dual (PD)	5	Dried aluminum hydroxide gel (254 mg) + magnesium carbonate (237.5 mg) + sodium alginate (250 mg) + simethicone (50 mg)
AF-1	15	Dried aluminum hydroxide gel (250 mg) + magnesium hydroxide (250 mg) + magnesium trisilicate (250 mg) + alginic acid (200 mg) + simethicone (125 mg)
AF-2	5	Dried aluminum hydroxide gel (200 mg) + magnesium hydroxide (100 mg) + magnesium trisilicate (200 mg) + sodium alginate (100 mg) + simethicone (25 mg)
AF-3	15	Dried aluminum hydroxide gel (250 mg) + magnesium hydroxide (250 mg) + magnesium trisilicate (250 mg) + alginic acid (200 mg) + dimethicone (125 mg)
AF-4	5	Sodium alginate (250 mg) + sodium bicarbonate (133.5 mg) + calcium carbonate (80 mg)

The raft-formation and antacid properties of all selected products were determined using the following tests.

Raft-formation capacity and raft-formation speed

The time required for raft formation was measured as per the British Pharmacopoeia method [11]. In this measurement, 150 mL of 0.1 M hydrochloric acid (HCl) was added to a 250-mL beaker and placed in a water bath in such a way that the volume of water in the bath was level with the top of the acid in the beaker. The setup was allowed to equilibrate at temperature range of 36.5 - 37.5 °C. Using a syringe (without needle), an equivalent of 5 mL of suspension was removed from each antacid bottle which was previously shaken. The outer side of the syringe was wiped clean with a cotton wool, after which the 5-mL suspension was evenly dispensed into the central part of the beaker (the time taken to add the entire dose was approximately 5 sec). After 30 min, the beaker was removed from the water bath and dried on the outside. Then, the content of the beaker was examined for raft formation [11].

Raft thickness

The thickness of the raft from the upper and lower marked positions from four sides of the beaker was measured using a calibrated Vernier caliper, and the value was recorded in millimeters (mm) for each of the products studied [11]. Raft thickness is a marker of good physical barrier against gastric reflux, and the thicker the raft, the better the quality of the product [12].

Antacid effects

Antacid properties were measured using preliminary antacid test (PAT) [10], periodic pH [13] and acid neutralizing capacity (ANC) [14,15].

Preliminary antacid test

Preliminary antacid test (PAT) was carried out as per the method described by Ayensu *et al* [10]. An accurate amount of a well-mixed antacid product (5 mL) was put into a 100-mL beaker. Sufficient carbon dioxide-free distilled water was added to the antacid to obtain a total volume of 40 mL which was mixed by placing the beaker on a magnetic stirrer. Then, 10 mL of 0.5 N HCl was added to the test solution, after which stirring on the magnetic stirrer was done for exactly 10 min. The pH of the resultant solution was measured with a standardized pH meter to see if the value was 3.5 or higher, in order to ascertain the claim of antacid on the product label [10].

Periodic pH

The objective of periodic pH is to measure the time taken by antacid product to raise the pH of 0.1 N HCl above 7. The shorter the time, the faster the rate of acid neutralization by the product. In the determination of periodic pH, an accurate volume of a well-mixed antacid product equivalent to 10 mL was transferred into a 100-mL beaker. Fifty milliliters (50 mL) of 0.1 N HCl was added to the test solution and mixed on the magnetic stirrer. Using a standardized pH meter, the pH of the resultant solution was recorded immediately, and also at different time intervals thereafter i.e. 15, 30, 60, 120 and 210 min [13].

Acid-neutralizing capacity

The acid-neutralizing capacity (ANC) test was performed as per the procedure described in United States Pharmacopoeia (USP) [14]. In essence, 5 mL of an antacid suspension was measured into a 25-mL beaker and weighed. The suspension was transferred into a 250-mL beaker and made up to 70 mL with carbon dioxide-free distilled water, followed by stirring for 60 sec. Then, 30 mL of 1.0 N HCl was pipetted into the suspension while stirring for 15 min. The excess HCl was titrated against 0.5 N NaOH to a threshold pH of 3.5 [14]. The number of milliequivalents (mEq) of acid consumed per gram of antacid was calculated using Eqs 1 and 2.

$$\text{Total mEq} = (V_{HCl} \times N_{HCl}) - (V_{NaOH} \times N_{NaOH}) \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where V_{HCl}, and V_{NaOH} represent the volume of 1 N HCl, and volume of 0.5 N NaOH, respectively, while N_{HCl}, and N_{NaOH} represent the normality of HCl, and NaOH, respectively.

$$\text{ANC (per gram of antacid)} = \text{Total mEq/Density of antacid} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

The higher the neutralizing effect of the antacid, the more effective the antacid [15].

RESULTS

Raft-forming capacity

Raft formation potential was compared amongst the various brands. Raft formation occurred in only 3 of the 5 alginate-antacid products studied. These were *Polygel Dual* (PD), AF-1 and AF-4. In spite of the alginate in their formulations,

neither AF-2 nor AF-3 produced a raft. These results are shown in Figure 1.

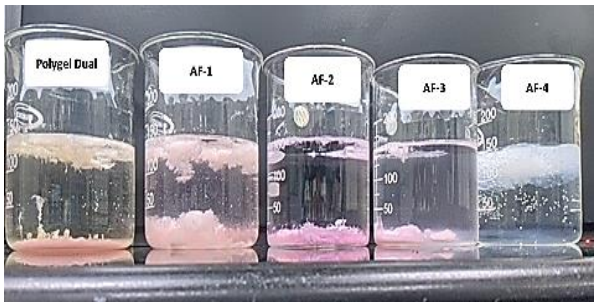

Figure 1: Raft-forming potential of the products studied

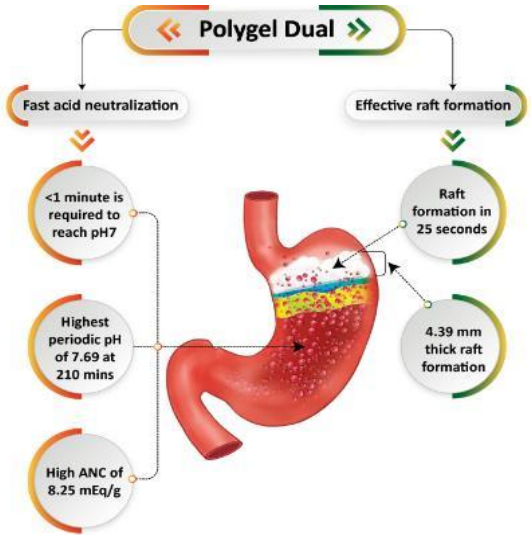

Figure 2: Schematic representation of *Polygel Dual* (PD) antacid efficacy and raft forming ability

Speed of raft formation

Results showed that AF-4 formed a raft in 15 sec. This was closely followed by *polygel dual* which required 25 s for raft formation, while raft formation was slowest in AF-1 (60 s). In contrast, raft formation did not occur in AF-2 and AF-3. The antacid efficacy and raft formation speed of PD are shown in Figure 2.

Raft thickness

Raft thickness values for AF-4, PD (Figure 2) and AF-1 were 14.79, 4.39, and 3.46 mm, respectively. Thus, raft thickness was highest in AF-4, and thinnest in AF-1.

Antacid efficacy

The results of preliminary antacid test revealed that all the products raised pH above 3.5, except AF-4, while AF-1 and PD (Figure 2) had higher values of pH rise i.e. 5.88 and 5.86, respectively. In contrast, AF-4 produced the lowest pH of 2.46.

Periodic pH

PD produced the fastest rise in pH (within 1 min), followed by AF-1, AF-2 and AF-3 which raised pH above 7 in 30, 60 and 120 min, respectively. All the products, except AF-4, raised and maintained pH above 7 for 210 min. These results are shown in Table 2 and Figure 2.

Acid-neutralizing capacity

All five products passed the ANC test as per USP, with AF-2 having the highest ANC of 11.44 mEq/g, followed by PD with ANC of 8.25 mEq/g. The lowest ANC value was seen in AF-4. These data are presented in Figure 2 and Figure 3.

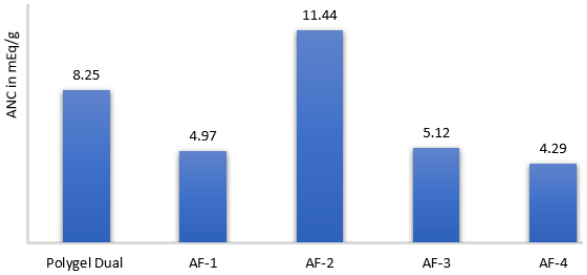

Figure 3: Acid-neutralizing capacity (ANC) of each of the products studied

DISCUSSION

The results of the study indicate that *polygel dual* produced the second best performance in raft-forming capacity, speed of raft formation, raft thickness and ANC. In addition, *polygel dual* raised pH faster, and maintained pH above 7 for longer duration than any of the other products studied.

Table 2: Antacid efficacy measured as change in pH

Product name	0 min	15 min	30 min	60 min	120 min	210 min
PD	**7.09**	7.26	7.42	7.44	7.74	7.69
AF-1	5.81	6.67	**7.14**	7.23	7.62	7.65
AF-2	5.93	6.68	7.07	**7.17**	7.3	7.32
AF-3	6.11	6.75	6.89	6.94	**7.11**	7.12
AF-4	6.03	6.17	6.44	6.39	6.51	6.66

This study also found that two alginate-antacid combinations did not form raft, despite having alginate in their compositions. The mechanism involved in raft formation may be explained thus: Alginate-antacid combination product contains carbonate-based compounds (e.g. calcium carbonate and magnesium carbonate) which generate CO_2 gas in the presence of gastric acid (HCl), with simultaneous release of free metal ions which diffuse through the alginate, leading to formation of an egg-box structure which has a good mechanical strength. The CO_2 gas gets trapped in the alginate network and forms an expanding, buoyant foam which is commonly called 'alginate raft' [8]. The buoyancy of alginate raft is crucial for the effectiveness of an antacid formulation in preventing reflux in that it hinders the upward displacement of the corrosive gastric content of the upper part of the stomach, thereby reducing the likelihood of its being emptied with a meal [9]. The absence of raft formation in AF-2 and AF-3 formulations could be related to the fact that these formulations do not contain carbonates. Therefore, AF-2 and AF-3 may have limited efficacy in the prevention of reflux, when compared to *polygel dual*, AF-1 and AF-4. Besides, raft formation was fastest in AF-4 i.e. 15 sec, followed by *polygel dual* which formed a raft in approximately 25 sec. These results are consistent with published data which consistently show that raft-forming formulations rapidly form floating raft-like structures within a few seconds. Moreover, it has been reported that, in absence of vigorous mixing, the raft formed may be sustained for several hours [4]. Another crucial property of rafts formed by alginate-antacid combinations is thickness. The present study shows that AF-4 formed the thickest raft, with thickness of 14.79 mm, followed by *polygel dual* with thickness of 4.39 mm, while the thinnest raft (3.46 mm) was formed by AF-1. A study has demonstrated that products with stronger rafts were more resilient and more resistant to gastric refluxate than those with weaker rafts, thereby protecting the delicate esophageal mucosa and the airways in a pathological condition like GERD [12]. Antacid efficacy was measured using PAT, periodic pH and ANC. As reported in the literature, to be qualified to be properly so-called, an antacid should produce pH greater than 3.5 [10]. This study has demonstrated that all products, except AF-4, passed PAT, with AF-1 producing the highest rise in pH i.e. 5.89, followed by *polygel dual* which raised pH to 5.86. The high pH value produced by AF-1 might be due to the presence of three antacids in the formulation. Moreover, in periodic pH test, *polygel dual* raised the pH to 7.09 within a minute, which was faster than the rate of pH increase by any of the other products studied. In addition, unlike the other products, *polygel dual* maintained the pH above 7 for 210 min. Indeed, AF-4 did not raise the pH value up to 7. The higher and longer antacid efficacy of *polygel dual* may be attributed to its relatively high antacid content, as well as presence of aluminum hydroxide, a long-acting antacid. Another important antacid efficacy parameter is ANC, which is an index of the amount of acid neutralized by an antacid. Several studies have demonstrated variabilities in ANCs of antacids due to factors such as pharmaceutical form, composition, and type of antacid salt used [16]. Similarly, the present study has shown the range of ANCs produced by some antacid products, all of which met the cut-off value of 5 mEq, as per the official method described in USP. The ANCs of the products studied were in decreasing order of AF-2 > *Polygel Dual* > AF-4. The high ANC values of AF-2 and *polygel dual* may be linked to the presence of high levels of aluminum hydroxide (in gel form) per 5 mL of product which can influence the ANC value of an antacid [10].

Limitations of the study

The present study has some limitations: raft strength, stability and duration of all tested products were not measured. Therefore, it was not possible to report comparative data on complete reflux prevention potential of all the products used in this study.

CONCLUSION

Polygel dual (PD) produce better outcome than other antacid tested in this study, with respect to raft formation and acid neutralization, while other antacids demonstrate satisfactory performance only in one of these two parameters. Therefore, PD may provide consistent anti-reflux and antacid benefits as an effective treatment for GERD or hyperacidity. However, further clinical studies are required to establish its clinical benefits in patients with reflux disease or hyperacidity.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dr. Rajesh Sirwani and Sunil Nair conceived, designed, conducted the experiments, and analyzed the data. Dr Tshiamala, Dr. Oyeleke, Dr. Nsokolo and Dr. Aninagyei participated in manuscript planning and critical review. All authors read and approved the manuscript for publication.

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REFERENCES

1. *Gastro-esophageal Reflux Disease Collaborators. The global, regional, and national burden of gastro-esophageal reflux disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5(6): 561-581.*
2. *Torne S, Sheela A, Sarada NC. Investigation of the role of the alkalizing agent in sodium alginate liquid anti-reflux suspension. Curr Drug Ther 2020; 15: 53-60.*
3. *Nwokediuko S. Gastroesophageal Reflux Disease: A population-based study. Gastroenterol Res 2009; 2(3): 152-156.*
4. *Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther 2000; 14(6): 669-690*
5. *Tytgat GN, Simoneau G. Clinical and laboratory studies of the antacid and raft-forming properties of Rennie alginate suspension. Aliment Pharmacol Ther 2006; 23(6): 759-765.*
6. *Dettmar PW, Gil-Gonzalez D, Fisher J, Flint L, Rainforth D, Moreno-Herrera A, Potts M. A comparative study on the raft chemical properties of various alginate antacid raft-forming products. Drug Dev Ind Pharm 2018; 44(1): 30-39.*
7. *De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ. Gaviscon double action liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. Aliment Pharmacol Ther 2014; 40(5): 531-537*
8. *Elliott BM, Steckbeck KE, Murray LR, Erk KA. Rheological investigation of the shear strength, durability, and recovery of alginate rafts formed by antacid medication in varying pH environments. Int J Pharm 2013; 457(1): 118-123*
9. *Hampson FC, Farndale A, Strugala V, Sykes J, Jolliffe IG, Dettmar PW. Alginate rafts and their characterization. Int J Pharm 2005; 294(1-2): 137-147.*
10. *Ayensu I, Bekoe SO, Adu JK, Brobbey AA, Appiah E. Evaluation of acid neutralizing and buffering capacities of selected antacids in Ghana. Sci Afr 2020; 8: e00347*
11. *British Pharmacopoeia Commission. British Pharmacopoeia 2021: Volume III. London, TSO; 2021, 126p*
12. *Bor S, Kalkan İH, Çelebi A, Dinçer D, Akyüz F, Dettmar P, Özen H. Alginates: From the ocean to gastroesophageal reflux disease treatment. Turk J Gastroenterol 2019; 30(Suppl2): 109-136*
13. *Voropaiev M, Nock D. Onset of acid-neutralizing action of a calcium/magnesium carbonate-based antacid using an artificial stomach model: an in vitro evaluation. BMC Gastroenterol 2021; 21(1): 112.*
14. *United States Pharmacopeia and National Formulary (USP 43-NF 38). United States Pharmacopeial Convention; 2020. Accessed October 20, 2021. 6661 p.*
15. *Boya DA, Ahmed JM. Comparison of Acid-neutralizing capacity of antacids in Erbil City. Zanco J Med Sci 2021; 25(2): 586-590.*
16. *Yafout M, Elhorr H, Sbai El Otmani I, Khayati Y. Evaluation of the acid-neutralizing capacity and other properties of antacids marketed in Morocco. Medicine and Pharmacy Reports. 24Sep.2021 (cited 28 Oct. 2021). Available from: https://medpharmareports.com/index.php/mpr/article/view/2082*