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RESEARCH ARTICLE
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A SURVEILLANCE STUDY TO OBSERVE THE SAFETY AND EFFECTIVENESS OF A FIXED-DOSE COMBINATION OF SODIUM ALGINATE + SODIUM BICARBONATE + CALCIUM CARBONATE (ALGINATE RAFT-FORMING ORAL SUSPENSION) THERAPY IN PATIENTS DIAGNOSED WITH SYMPTOMS OF GASTRO-ESOPHAGEAL REFLUX DISEASE.

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Abstract

Aim & Objectives: To observe the efficacy of a fixed dose combination of Sodium Alginate, Sodium Bicarbonate, and Calcium Carbonate therapy in patients with symptoms of heartburn, regurgitation, and indigestion (GERD). To observe patients' safety and overall satisfaction, improvement in symptoms and improvement of quality of life following a 28-day treatment with a fixed dose combination of Sodium Alginate, Sodium Bicarbonate and Calcium Carbonate therapy. This study was sponsored by Espi Industries & Chemicals Pvt. Ltd. P-9/2, IDA, Uppal, Hyderabad.

Materials & Methods: The product Sodium Alginate, Sodium Bicarbonate & Calcium Carbonate Oral Suspension (Alginate Raft-forming Oral Suspension) was manufactured and provided by ESPI Industries & Chemicals Pvt. Ltd. P-9/2, IDA, Uppal, Hyderabad. 100 eligible patients meeting inclusion/exclusion criteria were planned to be enrolled in selected sites to evaluate the effect of fixed-dose combination in patients with symptoms of heartburn, regurgitation, and indigestion. A total of 100 patients were enrolled in this study. As per sample size determination, a sample size of 100 patients was needed. Study data were collected at baseline, week 02 and week 04. Subjects were under direct medical care during the entire study period. The time points of interest for data collection were at baseline at the introduction of the study product, day 14 and day 28 (End of study).

Results: The primary efficacy variable of this study i.e., the Mean total score of heartburn/regurgitation was 12.32 at baseline. After 28 days of treatment, the mean total score of heartburn/regurgitation showed a significant fall of 86.2% from baseline. The secondary efficacy variable of this study was the mean total score of upper gastrointestinal disorders-Quality of Life (PAGI-SYM), (PAGI-QOL)from baseline to day 14 and day 28 which showed significant fall and for Treatment satisfaction Questionnaire from day 14 to day 28 patients exhibited treatment satisfaction.

Conclusion: Fixed-dose combination of Sodium Alginate + Sodium Bicarbonate + Calcium Carbonate (Alginate Raft-forming Oral Suspension) therapy showed a significant reduction of upper gastrointestinal disorder symptoms and Qualityof life along with treatment overall satisfaction at day

28 was found to be effective, safe and well tolerated in the study population. The percentage of patients from amongst the study population who were relieved of symptoms within 5 minutes of administration of the Fixed-Dose Combination was 75.52%. 80.61% of the study population experienced relief for a period of 2 to 4 hours after administration of the Fixed Dose Combination.

Keywords: GERD, Gastrointestinal disorder, Fixed-Dose Combination, Sodium Alginate, Sodium Bicarbonate, Calcium Carbonate, Alginate Raft-forming Oral Suspension

Introduction

This paper is about the Clinical Study to Observe the Safety and Effectiveness of a Fixed-Dose Combination of Sodium Alginate + Sodium Bicarbonate + Calcium Carbonate (Alginate Raft-forming Oral Suspension) therapy in patients diagnosed with symptoms of Gastro-esophageal Reflux Disease.

The study subjects were enrolled to receive the investigational product. The study is registered on CTRI (Clinical Trials Registry India) by Ethitrials Contract Research Pvt. Ltd. India. Reflux esophagitis is a common disorder in which esophageal inflammation is caused by the reflux of gastric contents.[1] It is a common disease increasing in incidence and prevalence in industrialized countries.[2] Patients with gastric acid hypersecretion have more acid reflux,esophagitis and cervical dysphagia.[3] Approximately 15-25% of adults suffer from reflux symptoms, characterized mainly by heartburn and/or regurgitation.[4]

Gastroesophageal reflux disease (GERD) is a common disorder of the upper gastrointestinal tract that is typically characterized by heartburn and acid regurgitation. According to the Montreal definition, GERD is a condition that develops when the reflux of stomach contentscauses troublesome symptoms and/or complications. GERD has an impact on the daily lives of affected individuals, interfering with physical activity, impairing social functioning, disturbing sleep and reducing productivity at work. According to the General guidelines, a negative impact on the quality of life is a criterion for reflux disease in patients with frequent heartburn. GERD patients can be classified as having either erosive esophagitis (EE) or non-erosive reflux disorder (NERD) depending on endoscopic findings.[5]

Complete healing of all mucosal lesions is not necessarily the aim of treatment in all patients. In milder forms of reflux disease, symptom relief is the most important goal. Many patients with mild gastroesophageal reflux disease do well on symptomatic self-care with antacids and/or alginate.[6] Acid-suppressive therapy targets the reduction of gastric acid production to prevent symptoms and complications of GERD.[7]

Alginate-based antacid formulations have a number of actions that make them potential candidates for protection against acid as well as non-acid gastro-oesophageal reflux. Sodium Alginate is an anti-reflux agent indicated for the relief of the symptoms due to gastric acid or bile reflux into the esophagus. Alginate exerts a unique mechanism of action by rapid reaction with gastric acid forming a raft, which floats on the top of the gastric contents as an anti-reflux barrier. Alginate has been reported for its ant-reflux efficacies in comparison with antacids or H_2 blockers in many clinical trials.[8]

Alginate gastroesophageal reflux disease treatments have fallen into two main categories: those containing alginate as the principal active agent, with only small quantities of antacid sufficient to aid raft formation, and those containing alginate in combination with a significant amount of antacid. The latter type can be said to have two distinct actions, both of which aid the treatment of heartburn and indigestion; the antacid should provide relief by neutralizing acid in both the stomach and the esophagus, and the alginate should suppress further reflux by forming a longer lasting physical barrier.[9] These findings suggest that alginate-based formulations could be considered as an alternative or add-on therapy in GERD patients, including those with NERD.

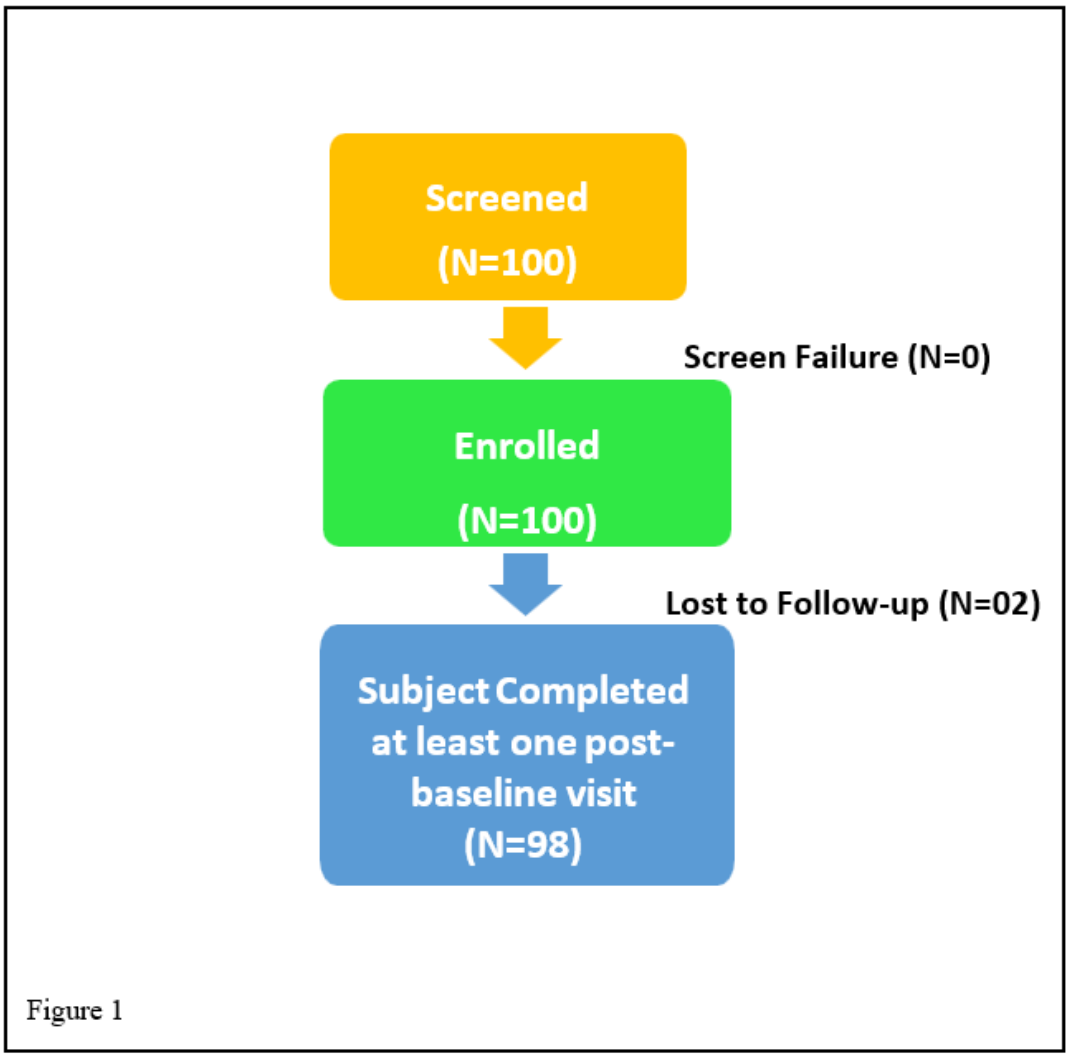
A Randomised double-blind placebo-controlled parallel-group study to evaluate efficacy and safety of Gaviscon DA in reducing heartburn, regurgitation and dyspepsia symptoms in individuals with mild-to-moderate GERD in China showed effective and safe reduction in acid reflux and dyspepsia

symptoms. In another trial the clinical benefit of Gaviscon DA was demonstrated in a single-center pilot study conducted on participants with GERD in the UK, Gaviscon DA significantlyreduced heartburn, regurgitation and dyspepsia symptoms in GERD patients and showed a tolerability profile similar to that of placebo.[10,11]

The purpose of this study was to observe the safety and efficacy of alginate-based antacids having sodium bicarbonate and calcium carbonate as other antacid components.

Materials & Methods

A prospective, single-arm, multicentric, post-marketing surveillance study to observe the safetyand effectiveness of a fixed dose combination of sodium alginate + sodium bicarbonate + calcium carbonate therapy was carried out at Shubham Multispeciality Hospital, ABC Complex, Near Rabari Colony Cross Road, Amraiwadi, Ahmedabad, Dr. Amit Patel, M.D. (Medicine) Shreeji Hospital, Vallabh Nagar Society, Odhav Ahmedabad, Dr. Gouranga Sarkar, M.D. (Medicine) Health Point Hospital, 21 Prannath Pandit Street, Oppsosite Lansdown Padampukur, Kolkata after prior approval from Institutional Ethics Committee of respective sites. The participants were explained the nature, purpose, risks, and benefits involved in the study, and written informed consent was obtained. Before entering the study, a full medical history was taken and a qualified physician performed a clinical examination to declare the participant healthy. A total of 100 patients aged between 19 and 65 years of both sexes were to be enrolled from participating hospitals, study wards/clinics having a high frequency of patients.



(**Figure 1:** Subject Enrollment and Follow-up Status)

The patients who were finally included in the study (those diagnosed with GERD) are summarized below.

Results

Table-1 Details of Patients enrolled in each site

Site	Enrolled	Discontinued	Completed
01 (Ahmedabad)	34	01	33
02 (Ahmedabad)	46	01	45
03 (Kolkata)	20	00	20
Total	100	2	98

Site 01 of Ahmedabad has 34 enrollments of participants. However, one participant discontinued their participation and 33 have completed the study. Likewise, Site 02 of Ahmedabad had 46 enrolled participants initially, but later one person discontinued the study and 45 out of them have completed their assessments. Site 03 in Kolkata had started its enrollment process with 20 participants, and all of them completed the study. In sum, a total of 100 patients were enrolled in all three sites combined, out of which 2 discontinued and 98 completed the study.

Table-2 Baseline Characteristics of the Study Participants

Sr. No.	Variables	(N=100)
1	Age (years)	41.93 ± 12.58
2	Male n (%)	40 (40.0%)
3	Female n (%)	60 (60.0%)
4	Height (cm)	158.55 ± 07.12
5	Weight (kg)	58.63 ± 10.49

In this study, the age of the patient population was ranging from 19.00 – 65.00 years with average age being 41.93 years. Average Weight of the patient population was 58.63 kg whereas average Height was 158.55cm. 40.0% of the patient population was male and 60.0% of the patient population was female.

Table-3 Mean change total score of Heartburn/Regurgitation among study cases from baseline to day 14 and day 28

Duration in days	Mean Total score of heartburn/regurgitation ($\bar{x}$ ± SD) (N = 98)
Baseline	12.32 ± 02.98
Day 14	06.74 ± 03.14
Mean diff (Baseline – Day 14)	-05.57 ± 01.89
P Value	(0.001)
Day 28	01.69 ± 02.56
Mean diff (Baseline – Day 28)	-10.62 ± 03.21
P Value	(0.001)

A mean total score of heartburn/regurgitation was 12.32 at baseline. After 14 days of treatment, the mean total score of heartburn/regurgitation showed a significant fall of 45.2% from baseline, with a P value of 0.001. After 28 days of treatment,mean total score of heartburn/regurgitation showed a significant fall of 86.2% from baseline,with P value of 0.001.

Table-4 Mean change total score of Fullness/Early Satiety among study cases from baseline to day 14 and day 28

Duration in days	**Mean Total score of Fullness/Early Satiety ($\bar{x}$ ± SD) (N = 98)**
Baseline	5.91 ± 1.69
Day 14	3.82 ± 2.00
Mean diff (Baseline – Day 14)	-2.09 ± 1.27
P Value	(0.001)
Day 28	2.02 ± 1.75
Mean diff (Baseline – Day 28)	-3.89 ± 01.51
P Value	(0.001)

The mean total score of Fullness / early satiety was 5.91 at baseline. After 14 days of treatment, the mean total score of Fullness / early satiety showed a significant fall of 35.4% from baseline with a mean reduction to 3.82 with a difference of 2.09 with a P value of 0.001. Similarly, after 28 days of treatment, the mean total score of Fullness / early satiety showed a significant fall of 65.8% from baseline with a mean reduction to 2.02 with a difference of 3.89 with a P value of 0.001.

Table-5 Mean change total score of Nausea/Vomiting among study cases from baseline to day 14 and day 28

Duration in days	**Mean Total score of Nausea/Vomiting ($\bar{x}$ ± SD) (N = 98)**
Baseline	3.74 ± 1.87
Day 14	1.97 ± 1.24
Mean diff (Baseline – Day 14)	-1.78 ± 1.22
P Value	(0.001)
Day 28	0.77 ± 0.91
Mean diff (Baseline – Day 28)	-2.98 ± 2.04
P Value	(0.001)

A mean total score of Nausea / Vomiting was 3.74 at baseline. After 14 days of treatment, mean total score of Nausea / Vomiting showed a significant fall of 47.6% from baseline with a mean reduction to 1.97 with a difference of 1.78 with a P value of 0.001. Similarly, after 28 days of treatment, the mean total score of Nausea / Vomiting showed a significant fall of 79.7% from baseline with a mean reduction to 0.77 with a difference of 2.98 with a P value of 0.001.

Table-6 Mean change total score of Bloating among study cases from baseline to day 14 and day 28

Duration in days	**Mean Total score of Bloating ($\bar{x}$ ± SD) (N = 98)**
Baseline	2.85 ± 1.27
Day 14	1.90 ± 1.30
Mean diff (Baseline – Day 14)	-0.95 ± 0.83
P Value	(0.001)
Day 28	1.05 ± 1.22
Mean diff (Baseline – Day 28)	-1.80 ± 1.09
P Value	(0.001)

A mean total score of Bloating was 2.85 at baseline. After 14 days of treatment, the mean total score of bloating showed a significant fall of 33.3% from baseline with a mean reduction to 1.90 witha difference of 0.95 with a P value of 0.001. Similarly, after 28 days of treatment, the mean total score ofbloating showed a significant fall of 63.2% from baseline with a mean reduction to 1.05 with a difference of 1.80 with a P value of 0.001.

Table-7 Mean change total score of Upper Abdominal Pain among study cases from baseline to day 14 and day 28

Duration in days	**Mean Total score of Upper Abdominal Pain($\bar{x}$ ± SD) (N = 98)**
Baseline	2.90 ± 1.45
Day 14	1.55 ± 1.05
Mean diff. (Baseline – Day 14)	-1.35 ± 1.05
P Value	(0.001)
Day 28	0.27 ± 0.79
Mean diff. (Baseline – Day 28)	-2.63 ± 1.49
P Value	(0.001)

Mean total score of Upper Abdominal Pain was 2.90 at baseline. After 14 days of treatment, mean total score of Upper Abdominal Pain showed a significant fall of 46.6% from baseline with a mean reduction to 1.55 with a difference of 1.35 with a P value of 0.001. Similarly, after 28 daysof treatment, the mean total score of Upper Abdominal Pain showed a significant fall of 90.7% from baseline with a mean reduction to 0.27 with a difference of 2.63 with a P value of 0.001.

Table-8 Mean change in total score of Lower Abdominal Pain among study cases from baseline to day 14 and day 28

Duration in days	**Mean Total Score of Lower Abdominal Pain ($\bar{x}$ ± SD) (N = 98)**
Baseline	1.78 ± 1.40
Day 14	0.94 ± 0.92
Mean diff (Baseline – Day 14)	-0.84 ± 1.10
P Value	(0.001)
Day 28	0.11 ± 0.49
Mean diff (Baseline – Day 28)	-1.66 ± 1.46
P Value	(0.001)

The mean total score of Lower Abdominal Pain was 1.78 at baseline. After 14 days of treatment, the mean total score of Lower Abdominal Pain showed a significant fall of 47.2% from baseline with a mean reduction of 0.94 with a difference of 0.84 with a P value of 0.001. Similarly, after 28 daysof treatment, the mean total score of Lower Abdominal Pain showed a significant fall of 93.3% from baseline with a mean reduction to 0.11 with a difference of 1.66 with a P value of 0.001.
Exploratory data involves a product review questionnaire at the end of visit 3 which deals withhow much time the study product takes to provide relief in GERD symptoms and how the saidrelief in GERD symptoms lasts after a single dose of the product is administered.

Table-9 Product Review Questionnaire

Questions	**Answer**	**No. of Cases (N=98)**	**Percentage**
How much time study product take to provide relief for GERD symptoms?	Within 5 minutes	74	75.52%
	Within 10 minutes	21	21.43%
	Within 30 minutes	03	3.06%
	More than 30 minutes	00	0%
How long does the relief of GERD symptoms last after using the study product?	Between 2 to 4 hours	79	80.61%
	Between 4 to 6 hours	17	17.34%
	More Than 6 hours	02	2.04%

At the end of the study time taken to provide relief in GERD symptoms within 5 minutes was75.52% (N=74) and GERD symptoms relief between 2 to 4 hours was 80.61% (N= 79).

Discussion

Gastroesophageal reflux disease (GERD) is a common disorder of the upper gastrointestinal tract that is typically characterized by heartburn and acid regurgitation. According to the Montreal definition, GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. GERD has an impact on the daily lives of affected individuals, interfering with physical activity, impairing social functioning, disturbing sleep and reducing productivity at work. According to the General guidelines, a negative impact on the quality of life is a criterion for reflux disease in patients with frequent heartburn. GERD patients can be classified as having either erosive esophagitis (EE) or non- erosive reflux disorder (NERD) depending on endoscopic findings.

Alginate based antacid formulations have number of actions that make them potential candidates for protection against acid as well as non-acid gastro-oesophageal reflux. Sodium Alginate is an anti-reflux agent indicated for the relief of the symptoms due to gastric acid or bile reflux into oesophageus. Alginate exerts it unique mechanism of action by rapid reaction with gastric acid forming a raft, which floats on the top of the gastric contents as anti-reflux barrier. Alginate has been reported for its ant-reflux efficacies in comparisons with antacids or H2 blockers in many clinical trials.

A study Randomised double-blind placebo-controlled parallel-group study to evaluate efficacy and safety of Gaviscon DA in reducing heartburn, regurgitation and dyspepsia symptoms in individuals with mild-to-moderate GERD in China showed effective and safe reduction in acid reflux and dyspepsia symptoms in Chinese individuals with mild-to-moderate GERD. In another trial, the clinical benefit of Gaviscon DA was recently demonstrated in a single-center pilot study conducted in participants with GERD in the UK. Gaviscon DA significantly reduced heartburn, regurgitation and dyspepsia symptoms in GERD patients and showed a tolerability profile similar to that of placebo. In this study, the safety and efficacy of alginates-based antacid having sodium bicarbonate and calcium carbonate as other antacid components were evaluated over a period of 04 weeks (28 days) and a total 100 patients were enrolled.

- Primary efficacy variable of this study was mean total score of heartburn /regurgitation which was 12.32 at baseline. After 28 days of treatment, mean total score of heartburn /regurgitation showed a significant fall of 86.2% from baseline.
- The Secondary Efficacy variable of this study was the mean total score of heartburn /regurgitation which was 12.32 at baseline. After 14 days of treatment, the mean total score of heartburn/regurgitation showed a significant fall of 45.2% from baseline.
- Other Upper gastrointestinal disorders symptoms such as Fullness / early satiety, Nausea/vomiting, Bloating, Upper abdominal pain and Lower abdominal pain at 14 days of treatment, and at 28 days of treatment showed a significant fall from baseline.
- Similarly, upper gastrointestinal disorders-Quality of Life (PAGI-QOL) as Daily Activities,Clothing, Diet and Food habits, Relationship (REL) and Physiological well-being and Distress at 14 days of treatment, and at 28 days of treatment showed a significant fall frombaseline.
- Treatment satisfaction was observed among all the patients from day 14 to day 28 after using the test product.
- At the end of the study relief in GERD symptoms within 5 minutes was reported by 75.52% (N=74) of the patient population and GERD symptoms relief within 2 to 4 hours was reported by 80.61% (N= 79) of the patient population.

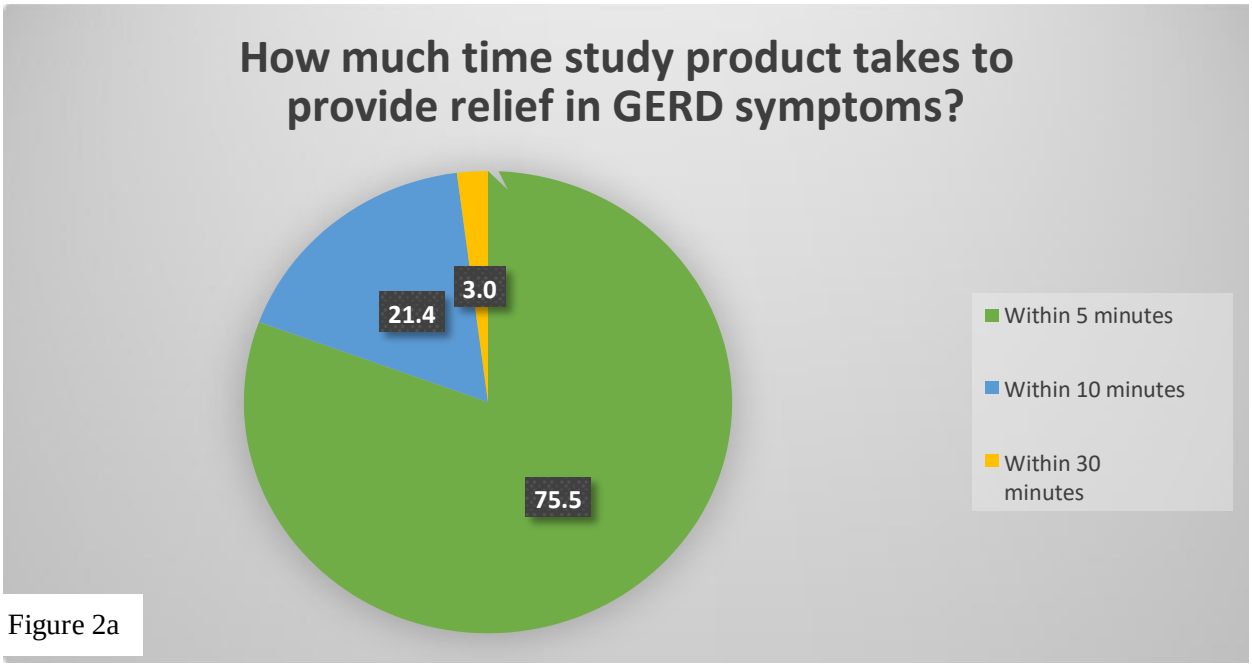


Figure 2a

(**Figure 2a:** Time Taken for Relief in GERD Symptoms)

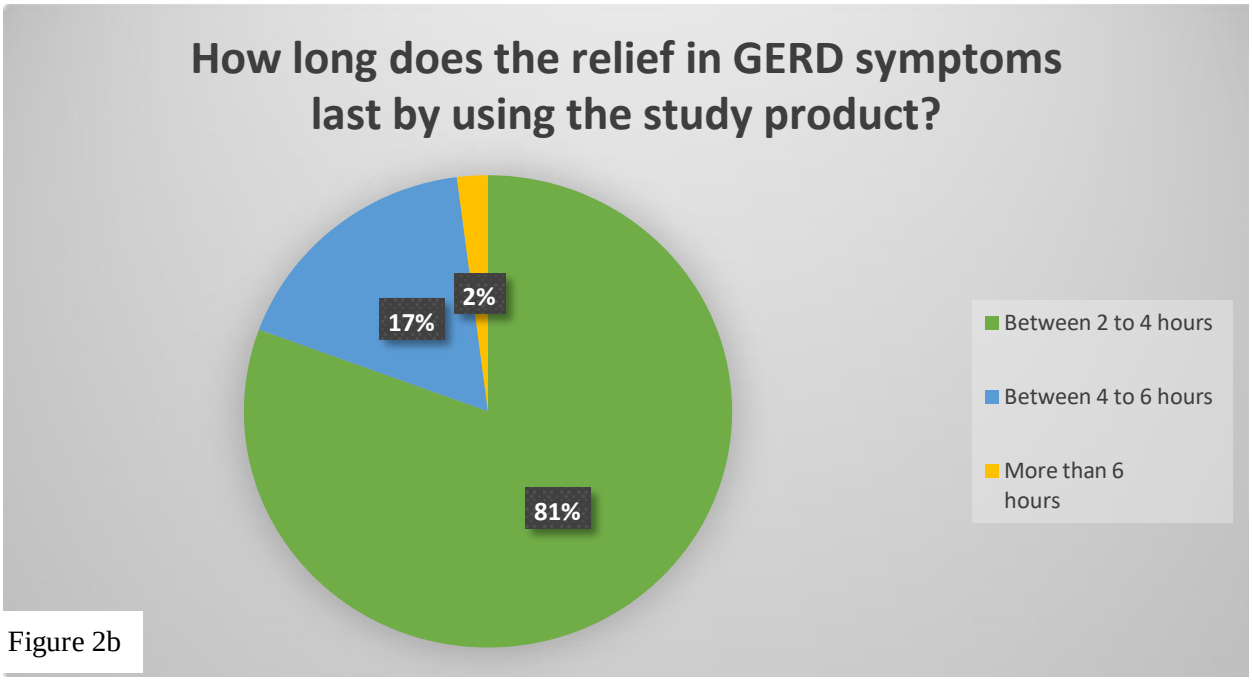


Figure 2b

(**Figure 2b:** Duration of Relief in GERD Symptoms)

None of the patients in the study reported any serious adverse events. All the events were of mild to moderate severity and were resolved without any sequel. From day 0 to day 28, all laboratory parameters were within normal limits. Based on the study results, Fixed-Dose Combination of Sodium Alginate + Sodium Bicarbonate + Calcium Carbonate therapy was found to be safe and well tolerated in the study population.

Based on the results of this study, it may be concluded that Fixed-Dose Combination of Sodium Alginate + Sodium Bicarbonate + Calcium Carbonate therapy of 04 weeks is helpful in improving the condition of patients diagnosed with symptoms of Gastro-esophageal Reflux Disease.

Data availability
The authors agree to deposit data that support the findings of their research in a public repository.

Author contributions
All the listed authors played a role in the clinical management, planning, execution, analysis, writing of the manuscript, and they all agree and accept responsibility for the contents of the manuscript submitted.

Ethical approval
The local Institutional Review Board has approved the proposal.

Consent to Participate
Informed consent was obtained from all individual participants included in the study.

Consent for Publication
The participants have consented to the submission of the article to the journal.

Financial support and sponsorship
Nil

Conflicts of Interest
There are no conflicts of interest.

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Conflict of Interest: None

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