Investigation of the Role of the Alkalizing Agent in Sodium Alginate Liquid Anti-reflux Suspension

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Abstract: Background: Anti-reflux formulation is one of the popular formulations across the globe in the pharmaceutical industry used specifically for the management of gastro-oesophageal reflux disease. But, this formulation is less explored with respect to research. Anti-reflux formulation has challenges to show its antacid functionality, which could have synergies in the management of refluxes in gastro-oesophageal reflux disease. Alkalizing agents act as antacid and improve the acid neutralization capacity in the anti-reflux formulation, and can be used appropriately as they affect raft strength beyond certain (optimum) limits.

Objective: The objective of this work is to investigate the significance of alkalizing agent in sodium alginate based on oral liquid anti-reflux suspension for the management of Gastro-oesophageal Reflux Disease (GERD).

Methods: In the present study, the formulation was prepared using sodium alginate along with different alkalizing agents like calcium carbonate and sodium bicarbonate at different levels. The formulation was further studied for in-vitro characterization like pH, viscosity, Acid Neutralization Capacity (ANC), thickness, formation speed, flotation, and raft strength.

Results: The formulation with a higher level of calcium carbonate as the alkalizing agent showed a positive effect on the acid neutralization capacity (20.83mEq) and raft strength (16.95g) as well. Whereas, the formulation with a higher level of sodium bi-carbonate (4.01%) showed improved acid neutralization (22.31mEq) but showed a negative effect on raft strengths (10.08g).

Conclusion: Based on the study, the optimum levels include 5% sodium alginate, 1.6% calcium carbonate and 2.67% sodium bicarbonate to achieve good liquid suspension formulation possessing good acid neutralization capacity as well as raft strength.

Keywords: Suspension, alginate, GERD, raft, in vitro, anti-reflux.

1. INTRODUCTION

Anti-reflux formulations have been in global pharmaceutical market since the last couple of decades. GERD is now and since a couple of years become a popular disease globally with an estimated prevalence of 10% to 20% [1-3]. GERD is diagnosed with symptoms of acid reflux, in which stomach acid and content back flow into the oesophagus resulting in heart burn, regurgitation. Long term GERD can also bring about reflux esophagitis or Barrett’s oesophagus. Like an antacid, an alginate-based formulation is preferred in the management of GERD because of its immediate onset of effect, generally less than an hour, which is faster than drugs like proton pump inhibitor or Histamine-2 receptor antagonist [3, 4]. The GERD is managed better with simple anti-reflux suspension, than the advanced dosage form like nanotechnology based formulation. Moreover, advance therapy has its own drawback and disadvantages [5].

The anti-reflux formulation is available in different dosage forms, say, liquid suspension, granules for suspension and tablets in the global market. The alginate liquid suspension in the presence of acid forms raft that acts as a physical barrier and prevents the reflux in GERD. Alginate gets converted into alginic acid gel and bicarbonate liberates carbon dioxide in the presence of stomach acid. The evolved carbon dioxide gets entrapped into the gel forming raft [4, 6, 7]. Alginate suspension is clinically proven for its anti-reflux action in GERD [8, 9]. Bicarbonate present in the formulation is also responsible to neutralize the stomach acid. Sodium alginate has also shown some properties to neutralize the stomach acid but less than bicarbonate.
The strength of raft depends on several factors such as the amount of CO₂, the presence of cation like calcium, potassium and aluminum in antacid and molecular properties of alginate [9]. Sodium alginate with a higher amount of guluronic acid gives more strengths to the raft. Ca²⁺ help to form hydrogel of alginate in the presence of stomach acid [10, 11]. The therapeutic goal of this research is to combine the benefit of the mechanical barrier with improved acid neutralization [12]. In general, a formulation containing magnesium and aluminum is used as antacid, however, known for its side effects, antacid that contains magnesium causes diarrhea and that contains aluminum causes constipation. In the current study, the use of aluminum hydroxide in liquid sodium alginate suspension and its effect on the raft strengths has been explored. Based on the results, it has been observed that the study has shown only negligible acid neutralizing capacity and led to a loss of raft strength [12]. Hence, the formulation was prepared using a different concentration of calcium carbonate & sodium bicarbonate and studied for their influence on functionality. The process parameter was kept constant during all the process to avoid any process variability. The formulations were tested in vitro for physico-chemical properties like pH, viscosity, ANC, raft thickness, raft formation speed, floatation and raft strength.

The complete study was designed with the aim to understand the significance of alkalinizing agent in the formulation. Alginate 5% showed good raft strengths (approx. 12g) and other physico-chemical characterization but with 7.5% alginate, better raft strengths were obtained (>15g), with better acid reflux property. Although the addition of bicarbonate helps to form buoyant raft with good acid neutralizing capacity, excess addition led to a negative impact on raft strength. But, the addition of calcium carbonate gave a combined benefit.

### 2. MATERIALS AND METHODS

#### 2.1. Materials

Sodium alginate (Protanol LFR 5/60) USP/NF was provided by DuPont Nutrition and Health (formerly known as FMC Biopolymer) as a gift sample. Sodium bicarbonate USP/NF was manufactured by Innophos, ScoraliteLL250 USP/NF (calcium carbonate) and supplied by Signet chemical corporation, India. Carbomer (Carbopol 974p) was supplied by Lubrizol India, Sucralose manufactured and supplied by JK Sucralose, China. Methyl paraben sod., Propyl paraben sod., and Sodium hydroxide, fruit flavor were purchased from Central Drug House, Delhi, India. All the excipients were used during the experiments were of LR grade. Hydrochloric acid (SD fine chem Ltd.) was procured from a local supplier in Bangalore, India. Water of HPLC gradient grade was used from in-house Sartorius water system.

#### 2.2. Preparation of Alginate Liquid Suspension

The manufacturing formula and procedure were extracted from US patent (US4140760) and further referred with slight modification. The preservative paraben was changed to sodium salt for easy of solubility. The sweetener was changed from sodium saccharine to sucralose for its greater acceptability. Sodium alginate as a gelling agent, and carbonate as alkalinizing agent were used in the formulation. All the ingredients were weighed accurately as per the batch size mentioned in Table 1. The manufacturing procedure involved the dispersion of sodium bicarbonate, sucralose, calcium carbonate and sodium alginate in water using overhead stirrer at 300rpm in a beaker. In another beaker, carbomer was dispersed and neutralized with sodium hydroxide. Alginate suspension was added to neutralized carbomer solution and mixed well. Paraben for flavor was added to the suspension and the volume was made up to final batch size [13].

#### 2.3. Preparation of Simulated Gastric Fluid (SGF) (0.1N HCl- pH1.2)

100mL purified water was added to 8.5mL of concentrated hydrochloric acid and 700mL of purified water was further added. It was allowed to cool and made up to 1000mL with purified water.

#### 2.4. Characterization of Alginate Liquid Suspension

##### 2.4.1. pH

pH was measured using pH meter (Model: FiveEasyPlus, make- Mettler Toledo) after calibration with pH 7.00 and pH 4.00 buffer. The electrode surface was cleaned and 20mL of liquid suspension was added at room temperature (27±2°C) and pH was noted after stabilization of signals.

### Table 1. Formulation and in vitro anti-reflux evaluation details; ANC-acid neutralization capacity.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Sod. Alginate (g)</th>
<th>NaHCO₃ (g)</th>
<th>CaCO₃ (g)</th>
<th>Carbomer 974p (g)</th>
<th>NaOH (g)</th>
<th>Methyl Paraben Sod. (g)</th>
<th>Propyl Paraben Sod. (g)</th>
<th>Flavor (g)</th>
<th>Sucralose (g)</th>
<th>Water q.s. (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.5</td>
<td>2.67</td>
<td>1.6</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F2</td>
<td>7.5</td>
<td>2.67</td>
<td>1.6</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F3</td>
<td>5.0</td>
<td>1.34</td>
<td>1.6</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F4</td>
<td>5.0</td>
<td>2.67</td>
<td>1.6</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F5</td>
<td>5.0</td>
<td>4.01</td>
<td>1.6</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F6</td>
<td>5.0</td>
<td>2.67</td>
<td>0.8</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td>F7</td>
<td>5.0</td>
<td>2.67</td>
<td>2.4</td>
<td>0.65</td>
<td>0.3</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
<td>1.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Note-1*-complete, 0*-partial.
2.4.2. Viscosity

The viscosity of formulation was measured by using rheometer (model-Discovery HR-3, make-TA instruments). The rheometer is a precise instrument that contains the material of interest in a geometric configuration, controls the environment around it and applies and measures stress, strain, and strain rate more accurately. The sample was applied on a lower flat base and geometry of 60 mm stainless steel parallel plate was used with a gap of 800 microns. After equilibrating at 25°C for 1 min., a continuous shear rate of 0.1 to 500 s⁻¹ was applied. The viscosity at a lower shear rate was considered [11].

2.4.3. Acid Neutralizing Capacity

In vitro acid neutralizing capacity (ANC) helps in understanding in vivo efficiency of the formulation to neutralize stomach acid [14]. Formulation after reconstitution with 20mL of water was diluted to 70mL and mixed thoroughly for 1 min. and stirred at a speed of 300±30rpm. 30mL of 1.0N hydrochloric acid was added and stirred for another 15 min. Excess hydrochloric acid was titrated with 0.5N sodium hydroxide to attain a stable pH of 3.5. The number of mole equivalents of acid consumed (ACN) was calculated by the formula (1) [15].

\[ \text{Total mEq} = (30 \times N_{\text{HCl}}) - (V_{\text{NaOH}} \times N_{\text{NaOH}}) \]  \hspace{1cm} (1)

2.4.4. Raft Thickness

A maximum dose of suspension (equivalent to 1000mg of sodium alginate) was transferred to 250mL beaker containing 150mL of 0.1N HCl heated and maintained at 37°C temperature in a water bath for 30min. The raft in the beaker was marked for the upper and lower position from the outer side of the beaker. The thickness of raft from the upper and lower marked position was measured by using calibrated vernier caliper, and noted in millimetre [6].

2.4.5. Formation Speed and Flotation of Raft

Raft formation was done as per the procedure mentioned previously and observed for speed, coherence and flotation. The formation speed was noted using calibrated stopwatch from the time of addition of sample to 150mL 0.1N HCl to the formation of the floating raft. Flotation was assessed as complete if all the insoluble materials rose to the surface. If insoluble materials sank to the bottom and remained there for 30 min., it was considered as partial flotation [6].

2.4.6. Raft Strengths

Raft was formed by adding a maximum recommended dose of sodium alginate (equivalent to 1000mg) in 250mL beaker with an internal diameter of 65 mm, containing 150mL of 0.1N HCl preheated and maintained at 37°C in a water bath; in which L-shaped probe was suspended such that the vertical arm of the probe hung down the center axis of the beaker and the horizontal arm was in the lower third of the acid. After 30 min., the beaker was removed from the water bath and transferred to Texture analyser (Model- TX plus, make-stable micro system, UK). The L shape probe was attached to the arm of the texture analyser, and the probe was lifted through the raft at a speed of 5mm/sec. The peak force during upward movement was recorded as raft strength in gram [6, 16]. The diagram of raft strength measurement set up is shown in Fig. 1.

3. RESULTS AND DISCUSSIONS

The sample of each trial was analyzed as per the methods for its anti-reflux characteristic and summarized in Table 2.

3.1. pH

The formulations had pH of 8.5±0.5 without any significant variation. The formulation with higher amount of alkalizing agent (NaHCO₃ & CaCO₃) had slightly alkaline pH expected to have more acid neutralization capacity. The main effect plot will help understand the effect of alkalizing agent on pH (Fig. 2). The higher pH may improve the therapeutic benefit with respect to acid neutralization in the stomach.

3.2. Viscosity

Main effect plot (Fig. 3) of viscosity reveals that the viscosity of formulation having higher concentration of NaHCO₃ (F5) was low, proving improved solubility of alginate in alkaline pH. In case of formulation F7, the formulation with a higher concentration of CaCO₃, the viscosity was high. The viscosity of the formulation is expected to be sufficient to stabilize the suspension and its easy administration to the patient. The alkalizing agent has a significant contribution to the viscosity of the final formulation.

3.3. Acid Neutralizing Capacity (ANC)

ANC is very important to understand in vivo effect of the formulation to neutralize excess stomach acid. The formulation is expected to have better acid neutralization to circumvent the symptoms of GERD effectively. Sodium alginate neutralizes stomach acid up to a certain extent and acts as an alkalizing agent (F2). The higher concentration of alkalizing agent NaHCO₃ (F5) and CaCO₃ (F7) showed good acid neutralization more than 20mEq. From the main effect plot (Fig. 4) and pareto chart (Fig. 5), it is very clear that formulations F5, F7 and F2 have good acid neutralization capacity and especially F5, with a higher concentration of NaHCO₃ showing better effect than the other two formulations (F2 & F7).

3.4. Thickness of Raft

Raft with lower thickness forms denser raft than that with higher thickness. The main effect plot of thickness (Fig. 6) reveals that the formulation F7, having higher CaCO₃ showed lower thickness and better raft strengths.

3.5. Formation Speed and Flotation of Raft

Raft formation speed was observed during formation and flotation was observed after raft formation that had significance in the onset of anti-reflux action. All the formulations showed onset of anti-reflux action < 1 minute with complete flotation.

3.6. Raft Strength

Raft strength is a very important attribute to understand the functionality of formulation to act as anti-reflux. The alginate suspension in the presence of stomach acid forms a
Fig. (1). Raft formation in 0.1N HCl and texture analyser: instrument to measure raft strength.

Table 2. *In-vitro* characterization of raft and formulation.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH</th>
<th>Viscosity (Pa.s)</th>
<th>ANC (mEq)</th>
<th>Thickness (mm)</th>
<th>Formation Speed (s)</th>
<th>Flotation</th>
<th>Raft Strengths (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>8.1</td>
<td>1.3368</td>
<td>14.71</td>
<td>26.28</td>
<td>&lt;60</td>
<td>1*</td>
<td>9.63</td>
</tr>
<tr>
<td>F2</td>
<td>8.4</td>
<td>5.9255</td>
<td>18.42</td>
<td>26.88</td>
<td>&lt;60</td>
<td>1*</td>
<td>19.44</td>
</tr>
<tr>
<td>F3</td>
<td>8.2</td>
<td>14.004</td>
<td>12.87</td>
<td>27.08</td>
<td>&lt;60</td>
<td>1*</td>
<td>11.47</td>
</tr>
<tr>
<td>F4</td>
<td>8.3</td>
<td>10.634</td>
<td>15.91</td>
<td>26.78</td>
<td>&lt;60</td>
<td>1*</td>
<td>12.84</td>
</tr>
<tr>
<td>F5</td>
<td>8.9</td>
<td>2.6454</td>
<td>22.31</td>
<td>27.46</td>
<td>&lt;60</td>
<td>1*</td>
<td>10.08</td>
</tr>
<tr>
<td>F6</td>
<td>8.1</td>
<td>3.0919</td>
<td>13.26</td>
<td>27.52</td>
<td>&lt;60</td>
<td>1*</td>
<td>12.92</td>
</tr>
<tr>
<td>F7</td>
<td>8.6</td>
<td>9.9505</td>
<td>20.83</td>
<td>17.36</td>
<td>&lt;60</td>
<td>1*</td>
<td>16.95</td>
</tr>
</tbody>
</table>

Fig. (2). Main effect plot of pH: effect of the alkalizing agent on pH of formulation.
Fig. (3). Main effect plot of viscosity: effect of the alkalizing agent on the viscosity of the formulation.

Fig. (4). Main effect plot of ANC: effect of the alkalizing agent on ANC of the formulation.

Fig. (5). Pareto chart: comparative ANC of all formulation.
raft that acts as a surrogate to oesophagus sphincter. The main effect plot (Fig. 7) and bar chart (Fig. 8) of raft strength show that formulations F2 & F7 having alginate 7.5% and 2.4% of CaCO₃ respectively showed higher raft strength than other formulations. However, higher (4.01%) and lower (1.34%) NaHCO₃ concentrations impart raft strength less than 12g and with optimum concentration (2.67%) it was found to be more than 12g. Bicarbonate reacted with stomach acid and evolved free CO₂ which helped the raft to float over stomach content. Higher bicarbonate concentration evolves more CO₂ bubble forming a more porous/low density raft, a weaker raft. The lower concentration of bicarbonate results in a weaker raft. NaHCO₃ and calcium carbonate have a significant impact on raft strength but independently.

All the formulation has shown that the role of the alkalizing agent is critical when not used at an appropriate concentration in the formulation. Any change in the concen-
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Comparative Raft strengths (g) of all formulation

<table>
<thead>
<tr>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

Fig. (8). Comparative raft strength of all formulation.

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A formulation containing 750mg of sodium alginate having good raft strength will show very good protection against acid reflux in GERD.

Although, use of alkalizing agent at higher concentration showed a negative effect on the functionality, it also confirmed the benefit of better acid neutralization.

Use of alkalizing agent in anti-reflux formulation may give faster relief from acid reflux, as it will neutralize excess stomach acid in no time.

**CONCLUSION**

The present study was done with an objective to assess the role of CaCO$_3$ and NaHCO$_3$ as alkalizing agents in liquid alginate suspension used in the treatment of GERD. The use of Aluminum hydroxide in the formulation has been studied and has shown a negative effect on raft strength and acid neutralization property. Apart from the neutralizing effect, NaHCO$_3$ acts as raft density modifier making it float and CaCO$_3$ as the source of calcium ions that gels with alginate forming stronger raft which would not otherwise be possible. It has also been observed that higher concentration of NaHCO$_3$ leads to reduced raft strength and that of CaCO$_3$ leads to increased viscosity. Thus, it can be concluded that the selection of appropriate alkalizing agents and their required concentration play a vital role in formulating alginate liquid suspension.

**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANC</td>
<td>Acid Neutralization Capacity</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastro-oesophageal Reflux Disease</td>
</tr>
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</table>

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

**HUMAN AND ANIMAL RIGHTS**

No Animals/Humans were used for studies that are base of this research.

**CONSENT FOR PUBLICATION**

Not applicable.

**AVAILABILITY OF DATA AND MATERIALS**

The authors confirm that the data supporting the findings of this study are available within the article.

**FUNDING**

None.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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