ABSTRACT

There are several techniques for tablet coating such as sugar coating, film coating and enteric coating. The enteric coating is the polymeric layer on solid surface that prevent the release of medication before it reaches the small intestine. Objectives: The present study addresses development and evaluation of acacia-guar gum combination as an enteric tablet coat aiming to add knowledge on how develop the ability of natural enteric forming ability of acacia-guar combination. Methods: Nine formulations of enteric coating solution based natural polymer were organized (FG1 to FG9) according to Taguchi design array which contain acacia: guar gum ratio as 1:4, 1:5 and 1:6 without/or with 10 to 20 % HPMC E5 polymer. These nine formulations were optimized with disintegration test in acid and Alkaline media using Taguchi experimental design. Various other Chemical tests parameters such as weight variation, hardness, friability and surface morphology were evaluated. Results: The peeled or cracked tablet surface that appear rough, indicating coat defects were observed with coated tablets FG3, FG4 and FG5, might be attributed to the lack of HPMC E5 as supporting material in coat adhesion, but having the same range of disintegration in 0.1 M HCL (about ±25 min) and in 0.2M phosphate buffer (± 15 min). Whereas FG1, FG2 and FG6 contains 20% HPMC E5 showed better quality smooth enteric coat and can resist acidic for ±50 min. Based on Taguchi analysis, FG1 is selected is the best formulation contains acacia: guar gum (1:6) along with 20% HPMC E5 and has no concern on tablets chemical tests pre and post coating as well as stable against storage conditions for 9 months. The study statistically analyzed and concluded that, stable enteric coat based acacia gum and guar gum is achievable.
with no effect on tablets chemical tests parameters as far as acacia: guar ratio as 1:6 with HPMC E5 polymer.

**KEYWORDS:** Tablet enteric coating, Guar gum, Acacia gum, HPMC E5, and chemical tests parameters evaluation.

**INTRODUCTION**

A tablet is the most popular a pharmaceutical solid dosage form for oral administration and is most preferred dosage form all over the world.[1] The different categories of tablet include: uncoated compressed tablets; coated compressed tablets including film-coated, sugar-coated and modified-release tablets as delayed-release tablets or enteric-coated tablets and sustained-release tablets. Coating is one of the oldest pharmaceutical processes by which coating material is applied to the surface of a dosage form.[2] There are several techniques for tablet coating such as enteric coatings which are prepared from gastric resistant polymers remain intact in acidic environment, but dissolve readily at the elevated pH of the small intestine. This property is related to the chemical structure, the most effective enteric polymers contain many carboxylic acid groups.[3]

In recent years, several tropical plants which possess properties that are of interest to the pharmaceutical, food and cosmetic scientists like the uses of natural polymeric plant metabolites, generally known as plant gums.[4] They are biocompatible, non-toxic (safe for human consumption), readily available, economical and cost-effective, even for industrial scale production.[5] Some of them have evoked great interest in various pharmaceutical applications.[6] include: tragacanth, acacia gum, karaya and guar gums.

Acacia gum (also known as gum Arabic) is a gummy exudate from the stem and branches of *Acacia Senegal*, (Fam. Leguminoseae) which is a branched-chain, complex polysaccharide, either neutral or slightly acidic.[7] The most fundamental property, its water solubility and high viscosity in aqueous dispersions and has approved by FDA as pharmaceutical products that use in a wide variety of applications.[8] When used at 10% or 12% in film coating formulation, it form a high quality shiny film coat on tablets surface without affect the tablets properties.[9]

Guar gum is an extractive polysaccharide gum derived from the endosperm of the leguminous plant, *Cyamopsis tetragonolobus* (Leguminoseae). Their major compound being
galactomannan which hydrates rapidly in cold or hot water and produces a uniform and high viscous gel that aids in thickening a wide variety of food categories.\textsuperscript{[10]} Since the guar is neutral, which give solutions that are sensitive to pH are usually characterized by the presence of carboxyl or sulphate groups. Slowest hydration is at pH, above 10.0 and below 4.0.\textsuperscript{[11]} Guar gum produces films that lack in clarity and have poor tensile strength, so the combined coating formulation was developed for improving its film forming properties.\textsuperscript{[12]} HPMC E5 was used both as binding agent and barrier enteric polymer owing to its low molecular weight and its application of acting as aid binding polymer.\textsuperscript{[13]}

The aim of this study was to evaluate and optimize acacia-guar gum enteric coating formulations for enteric coating and to assess the quality of acacia –guar coat acid resistant and their release in alkaline environment at the same time no change of tablets characteristics with time and storage conditions (temperature and humidity).

MATERIALS AND METHODS
Uncoated placebo tablets were obtained from Azal pharmaceuticals company Ltd. - Khartoum, Sudan. Acacia gum powder and guar gum were obtained from Sudan central of gum Arabic – Khartoum (purified and tested by Alnasr company).

Other materials as hydroxyl propeyl methyl cellulose HPMC E5, carboxy methyl cellulose CMC, titanium dioxide, starch and coloring agents were used for coating formulations obtained from Amipharma laboratories Ltd.- Sudan and Karary University.

Experimental design
Taguchi experimental design was selected to investigate the effect of different parameters to obtain an optimal, well-functioning delayed coat on tablet surface. In this design, the affecting parameters arranged and their levels in the way, most likely to affect the acid resistance of the coat. Taguchi employs a minimal number of trials by testing pairs of combinations saving both time and resources.\textsuperscript{[13]} Optimization of formula in the present study, the following three parameters was selected: type of polymer, concentration of HPMC E5 polymer and ratio of acacia: guar gum. Each of these parameters was of three different levels. Three parameters, at three levels each, would give only nine experimental runs using the L9 orthogonal array, as shown in (Table 1). The sequence of the experimental runs was randomized to prevent any bias. As the delayed tablets formed were enteric in nature, acid resistance and release of drug in phosphate buffer.
Preparation of different enteric coating solutions

Uncoated placebo tablets were further coated with enteric coating solution containing mainly acacia and guar gum with/or without HPMC E5. The stated amount of components of the enteric coating formulations in (Table 1) were individually weighed as powder and mixed together.

Then were transferred into a beaker containing specified weight of distilled water and homogenized for 45 minutes to achieve desired viscosity to form different nine enteric coating solutions with different colors according to the coloring agent was added in each formula.

Table 1: Taguchi array of different enteric coating formulations.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Type of polymers</th>
<th>Acacia : guar gum ratio</th>
<th>Coating materials (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPMC E5</td>
</tr>
<tr>
<td>FG1</td>
<td>Acacia</td>
<td>1:6</td>
<td>20</td>
</tr>
<tr>
<td>FG2</td>
<td>HPMCE5</td>
<td>1:4</td>
<td>20</td>
</tr>
<tr>
<td>FG3</td>
<td>HPMCE5</td>
<td>1:5</td>
<td>0</td>
</tr>
<tr>
<td>FG4</td>
<td>Acacia</td>
<td>1:5</td>
<td>10</td>
</tr>
<tr>
<td>FG5</td>
<td>Acacia</td>
<td>1:4</td>
<td>0</td>
</tr>
<tr>
<td>FG6</td>
<td>Guar</td>
<td>1:5</td>
<td>20</td>
</tr>
<tr>
<td>FG7</td>
<td>HPMCE5</td>
<td>1:6</td>
<td>10</td>
</tr>
<tr>
<td>FG8</td>
<td>Guar</td>
<td>1:4</td>
<td>10</td>
</tr>
<tr>
<td>FG9</td>
<td>Guar</td>
<td>1:6</td>
<td>0</td>
</tr>
</tbody>
</table>

Coating process of uncoated placebo tablets

Each sample of uncoated placebo tablets was going through coating process by spraying the previously enteric coating solutions were prepared. Each solution was filled individually into the spray gun of coating pan (SAMS BOMBAY code Rd02, India) and sprayed at rate of 1ml/min every 3 minutes on the tablets surface. A tube of preheated air (at 45° C) was inserted within the pan to allow for the solvent evaporation and continued until all the coating solution used up and elegant shiny enteric coated tablet were formed. This process of the coating was repeated for each enteric coating solution.
Evaluation of chemical tests parameters of different acacia-guar enteric coated placebo tablets

1. Tablet weight variation
Randomly a sample of 20 tablets of each enteric coated tablet was weighted (g) individually on a accuracy analytical balance (China). Total average weight ($X$) and standard deviation ($\pm SD$) was calculated of each.$^{[14]}$

2. Tablet diameter, thickness and hardness
A10 tablets of each enteric coated tablet were examined for the diametrical crushing strength test using hardness tester (TDTF YD-35, China). The device initially measures tablet dimensions (diameter and thickness) and ultimately it revealed the force required to break the tablet in Newton (N). The measured values and their relative statistics were calculated for each one.

3. Tablet friability
Randomly 10 tablets of each enteric coated tablet were subjected to official friability testing. These tablets were weighed firstly and placed in the drum of tablet friability tester (TDTF FT2000SE, China) that operates at 25 round/ min for 4 minutes. Secondly the tablets were dedusted again after the end of rotation and weighed. The difference in weight expressed as a percentage of the initial weight and this intended the relative weight loss of the tablets. The United State Pharmacopoeia states that the friability value of tablets should be less than 1%.$^{[15]}$

$$\text{Friability} \% = \frac{\text{weight before} - \text{weight after}}{\text{weight before}} \times 100$$

4. Tablet disintegration
The disintegration test was performed to check the intactness of enteric coat in acidic medium and their release in phosphate buffer.$^{[16]}$ Disintegration test was carried out in 0.1 M HCL and subsequently in 0.02 M phosphate buffer (TDTF ZBS- 6E, China). Disintegration tester was used to determine the disintegration time of the selected randomly six of each coated tablets. Firstly each one tablet was placed in each of the six tubes of cylindrical glass and was inserted into the beaker and settled the motor rotation speed to the minimal value up and up down. The basket rack was positioned firstly in a beaker of 0.1 M HCl at 37 ± 0.5 °C. Perforated auxiliary discs were placed on the top.$^{[16]}$ The time was taken for a tablet to disintegrate until no residue of the tablet left in the basket; this time was calculated and was
recorded as disintegration time in 0.1 M HCL. Secondly a randomly another selected six of
each coated tablets were placed in each of the six tubes of cylindrical glass and was inserted
into the beaker of 0.02 M phosphate buffer at 37 ± 0.5 °C. The time was taken for a tablet to
disintegrate was calculated and recorded as disintegration time in alkaline media.

**Stability study**
Taguchi optimized acacia-guar enteric formulation was subjected to stability testing as per
ICH guidelines\(^{[18]}\) using stability chamber (Newtronic, India) at temperature of 40°C and 75%
relative humidity for nine months. The changes in tablets general appearance and chemical
tests parameters were evaluated every three months.

**Statistical analysis**
Different chemical parameters of optimized acacia-guar enteric coated placebo tablets before
and after enteric coating and pre and post nine months of accelerated stability study were
analyzed using Statistical Package for Social Science SPSS version 20 (paired sample (t)
test). P- value < 0.05 was considered statistically significant.\(^{[19]}\)

**RESULTS AND DISCUSSION**
Taguchi experimental design was selected to obtain a best possible acacia-guar enteric coat
on tablet surface (nine formulations). In the previous study by random trials, designs of
acacia-guar enteric coating formulations contains acacia gum: guar gum ratio as (1:4) and
(1:5) respectively can form acacia-guar enteric coat. These formulations were optimized for
development with/or without addition of HPMC E5 polymer so there was three parameters
were selected and gave only nine experimental runs as stated in (Table 1) which the
concentration of HPMC E5 plays a primary role in acid-resistant of acacia-guar enteric coat.
The larger acacia: guar ratio, the better the quality characteristic for optimization of enteric
cat formed. Table 2 concluded that the enteric coated tablets FG1, FG2 and FG6 would be
optimized for good acid resistance which HPMC E5 represented at 20% with acacia: guar
ratio as 1:6, 1:4 and 1:5 respectively. Also they were given the greatest release in phosphate
buffer.

**Chemical tests parameters of nine acacia-guar enteric coated tablets**
Chemical test parameters of nine different acacia-guar enteric tablets were listed in (Table 2)
and showed within the official limits similar uncoated placebo tablets. Acacia-guar enteric
cat have slight effect on these parameters post enteric coating process. Nine enteric coated
Deina et al. World Journal of Pharmacy and Pharmaceutical Sciences

tablets weight within the normal range of tablet weight and hardness were in range (40-150 N). Uncoated and nine enteric coated tablets friability were less than 1% which means the tablets can resist the stresses during manufacturing, coating process and transportation. The different results of disintegration time in 0.1 M HCL and 0.02 M phosphate buffer depend on guar gum and HPMC E5 percentage was showed in (Fig 1). FG1, FG2 and FG6 showed good to resist acid media and release in phosphate buffer whereas FG3, FG4 and FG8 showed delayed release in 0.1 M HCL (25min) and completely release in 0.02M phosphate buffer (15 min). HPMC E5 polymer addition affects acacia- guar coat ability to resist acid for more time (±50 min). FG3, FG5 and FG9 formulations contain acacia and guar gum without HPMC E5 addition, showed significant effect on enteric coat characteristics. Taguchi design selected FG1 formula contains 10% acacia, 60% guar gum and 20% HPMC E5 proper enteric coat acid resistance (45 min). Chemical tests parameters were supportive for elegant enteric coat formation with fewer incidences of coat defects that evaluated by visual inspection.

Table 2: Chemical tests parameters within different nine enteric coated tablets according to Taguchi model array.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Acacia:guar (ratio)</th>
<th>HPMC E5 (%)</th>
<th>Weight (mg) mean±SD</th>
<th>Hardness (N) mean±SD</th>
<th>Diameter (mm) mean±SD</th>
<th>Thickness (mm) mean±SD</th>
<th>Friability (%) mean±SD</th>
<th>Disntg pH1.2 (min)</th>
<th>Disntg in pH6.8 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG1</td>
<td>1:6</td>
<td>20</td>
<td>139.8±4.8</td>
<td>108.7±5.3</td>
<td>6.75±2.32</td>
<td>3.75±0.44</td>
<td>0.1±0.03</td>
<td>45.15±0.04</td>
<td>20.25±2.1</td>
</tr>
<tr>
<td>FG2</td>
<td>1:4</td>
<td>20</td>
<td>129.9±26.3</td>
<td>127.9±6.7</td>
<td>7.64±0.05</td>
<td>3.53±0.54</td>
<td>0.01±0.01</td>
<td>40.27±1.4</td>
<td>18.14±0.06</td>
</tr>
<tr>
<td>FG3</td>
<td>1:5</td>
<td>-</td>
<td>139.2±15.1</td>
<td>136.1±7.4</td>
<td>8.21±0.06</td>
<td>3.54±0.09</td>
<td>0.11±0.15</td>
<td>23.41±3.01</td>
<td>13.2±0.5</td>
</tr>
<tr>
<td>FG4</td>
<td>1:5</td>
<td>10</td>
<td>149.89±1.9</td>
<td>113.5±8.2</td>
<td>6.67±2.22</td>
<td>3.95±0.06</td>
<td>0.02±0.12</td>
<td>23.37±4.1</td>
<td>18±1.5</td>
</tr>
<tr>
<td>FG5</td>
<td>1:4</td>
<td>-</td>
<td>149.15±0.9</td>
<td>140.4±7.1</td>
<td>6.85±0.38</td>
<td>3.61±0.03</td>
<td>0.48±0.11</td>
<td>12.4±3.7</td>
<td>8.21±5.1</td>
</tr>
<tr>
<td>FG6</td>
<td>1:5</td>
<td>20</td>
<td>139.3±2.3</td>
<td>132.1±5.6</td>
<td>7.28±0.06</td>
<td>3.56±0.04</td>
<td>0.14±0.04</td>
<td>43.12±0.02</td>
<td>17.14±0.006</td>
</tr>
<tr>
<td>FG7</td>
<td>1:6</td>
<td>10</td>
<td>149.77±1.7</td>
<td>132.3±2.7</td>
<td>8.24±0.08</td>
<td>3.53±0.05</td>
<td>0.38±0.07</td>
<td>27.14±8.2</td>
<td>19.26±6.1</td>
</tr>
<tr>
<td>FG8</td>
<td>1:4</td>
<td>10</td>
<td>149.53±6.1</td>
<td>126.7±11.7</td>
<td>8.22±2.7</td>
<td>3.57±0.03</td>
<td>0.05±0.16</td>
<td>19.51±2.1</td>
<td>14.58±0.8</td>
</tr>
<tr>
<td>FG9</td>
<td>1:6</td>
<td>-</td>
<td>149.12±0.7</td>
<td>100.3±41.6</td>
<td>6.28±1.85</td>
<td>3.71±0.38</td>
<td>0.13±0.08</td>
<td>31.08±0.7</td>
<td>17.58±5.5</td>
</tr>
</tbody>
</table>

General appearance of nine acacia-guar gum enteric coated tablets

Placebo tablets pre coating have convex smooth surface shape with white color and free of defects (Fig 2). Post coating FG1, FG2 and FG6 coated tablet revealed uniform smooth colored surfaces without coat defects (Figs 3, 4 and 8). Peeled or cracked rough tablet surface were observed of FG3, FG4 and FG5 coated tablets and to a lesser extent of FG8 (Figs 5, 6, 7 and 10). Cracked coat observed might be attributed to lack of HPMC E5 beside smallest content of guar gum (40% w/w). Smoother, softer and more flexible enteric coat of FG1 compare to too dried coat of FG9 is attributed to same guar gum percentage with and
without HPMC E5. CMC and glycerin plasticizers plays role in flexibility of coat formation.\[^4\] HPMC E5 addition to guar gum and acacia gum, it facilitates polymer adhesion on tablet surface and acid resistance coat was formed.

Figure 1: Disintegration test within different nine acacia-guar enteric coated placebo tablets in 0.1 M HCL and in 0.02 M phosphate buffer.

Tablets coated with formulations containing 10% w/w acacia and 50 to 60 % w/w of guar gum and 10%-20% HPMC E5 established good appearance and chemical tests parameters compared to tablets coated without HPMC E5 addition. Taguchi design optimized FG1 formulation for acid resistance enteric tablet coat free from visual defects. FG1 is natural enteric coat formula substantial benefits resulted in cost reduction when compared to widely used highly cost effective enteric-forming polymer coating system and the flexibility are providing apparent enteric coat with optimum chemical tests characteristic and acid resistance.

This study showed, the guar gum percentage significantly influences on the quality of acacia gum film coats to give a superior enteric coat forming on tablet surface. Since acacia-guar enteric coat was stable when was studied for further tests as stability test against environmental conditions.

**Stability study**

FG1 enteric coated tablet was subjected to stability studies against accelerated storage conditions for nine months at temperature 40°C and humidity 75% RH. During stability studies, chemical tablet tests and general appearance parameters were evaluated every three
months as resulted in (Table 3) and were showed slight changes in results compared at initial and no effect on acacia-guar enteric coat characteristics and tablets properties (Fig12).

**Statistical analysis**
There was no significant statistical different 0.313 > 0.05 in chemical tests parameters of FG1 acacia-guar enteric coated placebo tablets before and after enteric coating and long time of disintegration in 0.1 M HCL may attributed to enteric coat formed on tablet surface.

There was no significant statistical difference 0.398 > 0.05 in chemical tests parameters of FG1 acacia-guar enteric tablets at first of accelerated storage and at the end nine months test duration.

No effect of storage conditions as temperature and humidity on FG1 acacia-guar enteric coat characteristics (Fig 12).

![Figure 2: Uncoated placebo tablets.](image)

![Figure 3: FG1 enteric tablets.](image)

![Figure 4: FG2 enteric tablets.](image)

![Figure 5: FG3 enteric tablets.](image)

![Figure 6: FG4 enteric tablets.](image)

![Figure 7: FG5 enteric tablets.](image)

![Figure 8: FG6 enteric tablets.](image)
CONCLUSION

It is preferable to find optimized formulations of natural enteric tablet coating using experimental design like Taguchi, which not only reduce time but also provide ideal formulation as that consisting of acacia: guar gum ratio as 1:6 with 20% of HPMC E5. It was showed good acid resistance and their release in alkaline environment as well as stable against storage conditions. Therefore, this study shows that there is positives continue to exist to further scale up the enteric coating formulation and to develop a generic version of the drug.

Figure 12: Comparison of chemical tests parameters of FG1 acacia-guar enteric coated tablets pre and post three months stability study.

ACKNOWLEDGEMENTS

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