Some physicochemical properties of acetaminophen pediatric suspensions formulated with okra gums obtained from different extraction processes as suspending agent

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The purpose of this work was to evaluate the effect of the extraction process and the potential of okra gum as a suspending agent in pharmaceutical oral formulations containing acetaminophen as a model drug. Clarified mucilage of dried okra was either extracted directly with ethanol 96% (F1) or was first treated with base (F2), acid (F3) or heating in the presence of salt (F4) before extraction with ethanol 96%. The samples were used at 0.5% w/v as suspending agents in acetaminophen acetaminophen suspension to deliver 125 mg/5 mL acetaminophen. A binary mixture of F2 and F4 (1:1) was also used. Similar suspensions of acetaminophen containing either hydroxymethylpropylcellulose (HPMC) or tragacanth gum (TRAGA) were produced. Some physicochemical properties of the formulations were evaluated. The rheological properties of acetaminophen-containing treated okra gums (F2-F5) were generally similar. Changes in viscosity with storage were slower in the F2-F5 formulations as compared with F1. Particle size and particle size distribution were different for all formulations, and hysteresis was a function of time and the suspending agent used. The re-dispersion time of the formulations with treated okra gums was generally shorter than that observed with the untreated okra gum. The use of a binary mixture of F2 and F4 resulted in different physicochemical properties from those of either F2 or F4. The physicochemical properties of the formulations were comparable to those with HPMC and TRAGA. It can thus be concluded that treating okra gum with acid, base or salt impacted better physicochemical properties on an acetaminophen pediatric suspension when they were used as suspending agents.

Key words: Treated and untreated okra gum, oral pharmaceutical formulations, potential suspending agent, physicochemical properties

INTRODUCTION

Okra is a tall erect annual plant botanically known as Abelmoschus esculentus. It is widely cultivated and grown in most tropical parts of Nigeria. Okra has been used as food and soup in Africa[1] and Asia[2] and has been a subject of research in agriculture and food.[1,3-15] Okra is known for its viscous mucilaginous solution that results when it is crushed and extracted in water.[16] The potential of okra gum as a pharmaceutical excipient has received attention in the literatures as a binder,[17,18] control release,[19] film coating[20] and bioadhesive[21] agent. Report on the use of okra as a suspending agent is scanty. Moreover, there is no work to my knowledge at this time on the effect of treatment of okra before extraction on the quality of a suspension in which it has found application.

The purpose of this work was to study the effect of the extraction process on okra gum as a suspending agent in an acetaminophen pediatric formulation in comparison with the untreated okra gum extract and commercial analogues, hydroxymethylpropylcellulose (HPMC) and tragacanth (TRAGA). Acetaminophen was chosen as a useful non-steroidal anti-inflammatory agent such that its formulation as a suspension could be beneficial in children that could not swallow tablets.

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**MATERIALS AND METHODS**

Acetaminophen and sodium lauryl sulfate were obtained from Spectrum Chemicals Brunswick, New Jersey (USA), HPMC K4M, TRAGA from Sigma-Aldrich, St. Louis, MO (USA and okra gum was obtained from cultivated okra plants in Jos, Nigeria.

**Extraction of okra gum**

Thirty-seven grams of dried powdered okra was dispersed in 4.20 L of demineralized water using a Lightnin® 316 stainless steel high-efficiency axial flow impeller (Lightnin®, model LI018; Santa Cruz, Bolivia). The dispersed mucilage was strained through a muslin cloth to remove the fibrous materials. The cloudy mucilage was clarified by centrifugation (Allegra 6R centrifuge, Beckman Coulter™, S. Kraemer Boulevard Brea, CA, USA). About 500 mL of the mucilage was transferred into a 1000 mL beaker and the gum was extracted with the aid of ethanol 96%. The extracted gum was redispersed in water and re-extracted to get a whitish gum (F1). The gum was dried in an oven at 50°C for 8 h.

Five hundred milliliters of the mucilage was transferred into two beakers of 100 mL capacity and 20 mL (0.1M) of either sodium hydroxide (F2) or hydrochloric acid (F3) was added. The mucilage was mixed on a magnetic stirrer plate for 20 min and the mucilage was subsequently extracted with ethanol 96% following the above procedure. The gum obtained from the mucilage treated with sodium hydroxide and hydrochloric acid was, respectively, labeled as F2 and F3. Five grams of sodium chloride (F4) was added to 500 mL of the remaining mucilage. The content was heated at 80°C for 1 h. The sample was allowed to stand for 12 h before extraction with ethanol 96% following the above procedure and dried at 50°C for 8 h. A binary mixture of F2 and F4 in a 1:1 ratio was also prepared (F5). The samples were kept in sealed polythene bags and in desiccators until required.

**Preparation of acetaminophen pediatric suspension**

A pediatric acetaminophen suspension to deliver a dose of 125 mg/5 mL was formulated. Five grams each of the powder of the extracted okra gum samples (F1-F5) to give 0.5% w/v was weighed and dispersed in 500 mL of demineralized water and allowed to stand for 12 h. About 1.0 mL of sodium lauryl sulfate was added to 200 mL of demineralized water and the mixture was stirred thoroughly. Acetaminophen powder was sifted through a sieve to break any lumps and the powder was dispersed in 200 mL of demineralized water containing the surfactant. The mixing was carried out on a magnetic stirrer plate for 20 min to ensure uniform mixing. The volume was made up to 1000 mL with demineralized water. The pH of the suspensions was adjusted with either citric acid monohydrate or sodium hydroxide. Similar suspensions of acetaminophen containing either HPMC or TRAGA as a suspending agent were prepared under the same environmental conditions for comparison. Some physicochemical properties of the suspensions were evaluated.

**Rheological evaluation**

The rheological characteristics of the pediatric suspensions were determined on a Brookfield digital rheometer (model LVDV-III+CP; Brookfield Engineering Laboratories Inc., Middleboro, MA, USA) using CPE 40 cup and plate. Before the determination of viscosity, the rheometer was zeroed and the gap between the cup and the plate was set to 0.013 m using the rheometer programmable features.

One milliliter of the suspension was transferred into the cup of the digital rheometer (Brookfield Engineering Laboratories Inc.) and was fitted in position. The rheological characteristics were acquired at increasing ramping up (100–250 rpm) at 1-min intervals. Before ramping down, a wait time of 2 min was allowed. The data were collected with the aid of Rheocal® software (Brookfield Engineering Laboratories Inc.). The data were exported to Microsoft Excel (Microsoft Incorporation, San Francisco, CA USA) for analysis.

**Sedimentation volume**

Hundred milliliters of the suspension was transferred from the bulk after shaking in a 100 mL graduated cylinder and allowed to stand. The volume occupied by the solute in the cylinder below the supernatant (clear surface of the suspension) was noted as the volume occupied by the dispersed solids and the change in the sedimentation volume was recorded daily until there was no visible change in volume in any of the samples.

**Time to redisperse study**

To assess the ease of redispersibility of the suspensions quantitatively, the following method was devised in our laboratory. Before the determination, the bulk suspension of the formulation was allowed to mix thoroughly over a magnetic stirrer plate for 30 min. Hundred milliliters of the sample was then transferred to a 250 mL capacity beaker and allowed to stand. The ease of dispersal of the suspensions was evaluated at a predetermined time, between 24 h and 6 weeks of storage. The sample was carefully placed on the magnetic stirrer plate (Variomag Electronicruhrer poly15, Daytona Beach, FL, USA) as shown in Figure 1 without disturbing the equilibrium of the system. A magnetic octagonal stirring bar (2.0 inch length x 5/16 inch diameter) was gently lowered into each of the formulations. The magnetic stirrer plate was operated at 310 rpm and the movement of the stirrer bars caused the redispersion of the settled dispersed phase. The experiment was interrupted at intervals of 30 s to visually inspect for redispersion. The time taken for a sample to redisperse was recorded by summing up the intervals up to the redispersion time. The process was continued until the last sample achieved redispersion, and the time taken for redispersion was similarly computed. The time taken for absence of the undispersed solute mass was taken as the redispersion time.

**Particle size and size distribution**

A standard bench laser diffraction instrument (Model:
Mastersizer® S.v2.18; Malvern Instruments Ltd., Malvern Worcestershire WR14, UK) fitted with lens 300RF that measures a size range of 0.05–880 micron was used to assess the particle size distribution by volume of the suspensions. To analyze the measurement data, a polydisperse model was chosen and 3OHD (Fraunhofer) presentation was selected. The mastersizer was first aligned and the background measurement was taken. The sample was introduced into the small volume sample dispersion unit that was connected to a sample dispersion controller. The sample dispersion controller was set at a stirring speed of 5000 rpm to disperse the sample. A sufficient quantity of demineralized water was transferred into the small volume dispersion unit and drops of the sample to be analyzed were introduced into the unit to produce at least an obscuration of 10%, and the bar color turned green. The data were captured with the aid of the Malvern software. The acquired data were transferred to a Microsoft Excel (Microsoft Incorporation, San Francisco, CA, USA) for analysis. The result obtained was the mean of 10 determinations.

RESULTS AND DISCUSSIONS

General description
The pH of acetaminophen pediatric suspensions was 5.4–6.0. A good-looking suspension was produced in all the formulations.

Sedimentation volume and redispersibility
Table 1 shows the sedimentation profiles of acetaminophen suspension formulations over a 6-week period. After 24 h of preparation, the sedimentation volumes were, respectively, 12.5, 12.0 and 10.7 mL for the F4, F5 and F2 formulations. The corresponding values for F1 and F3 were, respectively, 10.1 and 10.00 mL. On the other hand, the sedimentation volume of acetaminophen pediatric formulation containing TRAG and HPMC were, respectively, 10.2 and 6.4 mL. The trend was the same throughout the study period. The sedimentation volumes were generally of the order F4>F2>F5>TRAG>F3>F1>HPMC. That a suspended dispersed solute in a continuous medium will settle is a matter of time. The characteristics of both the dispersed and the continuous phases are important in the rate and extent of this phenomenon. Dense particles (due to gravity) and, conversely, low viscosity (low resistance to movement of solute) of continuous medium will aid fast settling while less dense and more viscous medium will favor longer suspension of the solute in the medium without segregating. It is desirable in pharmaceutical suspensions that the solutes are suspended long enough to ensure withdrawal of uniform doses and of such viscosity that the suspension is pourable. It seems that the observed sedimentation volumes of the pediatric suspensions are due more to the characteristics of the dispersion medium than of the active pharmaceutical ingredient. It seems that the particle size and particle size distribution had some effects on the sedimentation volume. The formulation with HPMC, e.g. had a mean particle size of 180.34μm, and modal distribution of 192.57μm. At the same time, the percentile distribution showed that this suspension had a high percent of both small and big particles, making quick sedimentation and dense packing possible as small particles filled the voids created by the large ones. On the other hand, fine particles, as with F4, had a mean particle size by volume of 57.01μm and a modal distribution of 70.27μm. It is also expedient that solutes that have settled down in a suspension on standing be easily redispersed when needed to allow for withdrawal of uniform doses. Figure 2 shows the redispersion time of the formulations. The redispersion time of the F1 formulation was 360 s and the corresponding time for TRAG and HPMC were, respectively, 210 and 270 s. Acetaminophen suspensions prepared with okra gums other than F1 each experienced redispersion at 240 s [Table 2].

While redispersion is one of the recognized quality attributes of pharmaceutical suspensions, its evaluation has been qualitative and subjective. The present effort at quantitative determination was to make the evaluation more objective when comparing a new suspending agent with an established one. Easily redispersed sediments in a suspension allow withdrawal of uniform doses. Patients or
their representatives with the same effort will require less time to achieve complete redispersion of acetaminophen-containing okra gum that was extracted after processing compared with that extracted directly with ethanol from the mucilage without acid, base or salt. On the other hand, the formulation with TRAG and HPMC, respectively, lower and higher the redispersion time compared with the F1-F5 formulations.

**Rheological evaluation**

Figure 2 shows the rheological characteristic of the acetaminophen pediatric formulations. At 100 rpm, the viscosity of the F1, F2, F3 and F4 formulations were, respectively, 7.91, 3.4, 3.2 and 3.14 cP. The corresponding values of F5, HPMC and TRAGA formulations were 5.13, 4.32 and 4.68 cP, respectively, within one day of the manufacture of the samples. The order of increasing viscosity of the samples was F4<F3<F2<HPMC<TRAGA<F5<F1. At a higher rpm, the viscosity of the formulations was of the order F4<F3=F2<TRAGA<HPMC<F5<F1. Generally, the viscosity of the formulations decreased with an increase in rpm. The figure also showed the rheological profile of the formulations with storage. Viscosity affects the ease with which a suspension is withdrawn for administration. The less viscous suspension tends to pour more easily than the more viscous ones, and the rheological study can help us gain insight into the structure of the system. The majority of the viscosity measurements are made at the quality control level and consist of a single data point using one spindle at one speed, and this is a good bench mark for decision making in a production setting. However, many fluids exhibit a characteristic change in viscosity with a change in applied force that cannot be captured with a single viscosity measurement, as demonstrated in the viscosity profile of the formulations as the ramping was performed between 100 and 250 rpm.

**Effect of aging on the rheological properties of the suspension**

Figure 2 also shows the effect of aging on the rheological properties of acetaminophen pediatric suspensions formulated with okra gums. The viscosity of F1 at 1 day and 3 and 6 weeks were, respectively, 7.91, 9.22 and 5.26 cP. During the same period, the viscosity of F2 was, respectively, 3.4, 3.17 and 2.6 cP. Although there was an increase in viscosity of F1 and HPMC within 3 weeks, it dropped afterwards except for F5 and TRAGA in the 6th week. The figure also showed the response of the formulations to the applied pressure. Hysteresis in the F1 formulation that was not obvious when freshly prepared became pronounced after 3 weeks. On the other hand, F2-F5 showed minimal hysteresis during this period. A change in viscosity of a suspension on storage could be a quality concern to the consumer. Nowadays, in the age of technology, it is hardly practiced to make extemporaneous medicines only as when needed. Pharmaceutical products are now mass produced in pharmaceutical factories and are distributed for consumption. This process of distribution and use may continue throughout the shelf-life of the medicine, which may last up to 36 months in the case of most liquid.

<table>
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<tr>
<th>Time (s)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

X - sediments present; √ - no sediment observed

**Table 2: Redispersion time of acetaminophen pediatric suspensions after 6 weeks of storage**
preparations. Sequel to this the rheological information that is obtained during manufacture may not be the same with time. As can be seen from the figure, there are changes in the rheological properties of suspension on storage, and the manufacturer must work out a limit that may be acceptable within the shelf-life of the product.

Particle size and particle size distribution
The distribution moments of acetaminophen pediatric suspensions are shown in Figure 3. F1 had a mean particle size by volume of 154.92±21.0, being the largest of the formulations containing okra gum, while the corresponding value for F4 was 57.01±4.6, being the smallest of the formulations containing okra gum as the suspending agent. On the other hand, HPMC had a mean particle size of 180.34±23.5, being the highest in all the formulations. Generally, the order of increasing particle size by volume was F4<F2<F3<TRAGA<F1<HPMC. The particle size of the dispersed phase in formulation with HPMC may account for its fast sedimentation. The differences in the particle size of these formulations might have been influenced more by the suspending agent than by the active pharmaceutical ingredient. The particle size distribution of all the formulations containing okra gum except F5 looked similar, although to a different degree of skewness and kurtosis. On the other hand, the distribution in F5, HPMC and TRAGA resembled normal distribution. These differences in the particle size of the formulations may have implications on the dissolution and subsequent absorption of the active ingredient in the formulations [Table 3].

CONCLUSION
Okra gums obtained by first treating the mucilage with acid, base or salt before extraction with ethanol 96% and okra gum extracted without treatment were used as suspending agents to formulate the acetaminophen pediatric suspensions. The properties of the formulations were evaluated. Changes in viscosity with storage were slower in the F2-F5 formulations compared with the F1 formulation. Particle size and particle size distribution by volume of the acetaminophen pediatric suspensions

![Figure 3: Particle size and particle size distribution by volume of the acetaminophen pediatric suspensions](image-url)
Table 3: Distribution moments of acetaminophen pediatric suspensions

<table>
<thead>
<tr>
<th>Description</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>TRAG</th>
<th>HPMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>D43</td>
<td>154.92±21.0</td>
<td>62.13±2.0</td>
<td>115.93±12.2</td>
<td>57.01±4.6</td>
<td>212.14±3.0</td>
<td>121.98±12.1</td>
<td>180.34±23.5</td>
</tr>
<tr>
<td>Modal distribution</td>
<td>215.74±5.6</td>
<td>68.58±1.1</td>
<td>111.36±1.6</td>
<td>70.27±0.58</td>
<td>234.54±5.9</td>
<td>130.81±2.96</td>
<td>192.57±3.41</td>
</tr>
</tbody>
</table>

Percentile distribution

- 10%: 6.3±0.5, 4.05±0.2, 12.96±0.07, 7.96±0.28, 45.22±0.07, 40.02±1.4, 53.44±0.56
- 20%: 23.25±0.0, 12.2±1.12, 29.06±0.28, 13.91±0.14, 83.60±0.0, 62.14±0.61, 78.47±0.71
- 50%: 113.61±1.12, 44.0±0.71, 83.41±0.71, 36.95±0.31, 178.40±1.21, 112.5±0.5, 149.54±0.07
- 80%: 268.91±0.28, 101.28±1.21, 189.55±0.31, 94.47±0.12, 325.28±0.28, 178.33±1.21, 266.17±2.7
- 90%: 369.3±1.4, 145.95±1.4, 266.22±0.4, 133.4±1.2, 428.09±0.07, 220.51±0.5, 369.3±1.4

size distribution were different for all formulations, and hysteresis was a function of time and the suspending agent used. The redispersion time of the formulations with treated okra gums were generally shorter than that observed with the untreated okra gum. The use of a binary mixture of F2 and F4 resulted in different physicochemical properties from those of either F2 or F4. The physicochemical properties of the formulations were comparable to those with HPMC and TRAGA. It can be concluded that treating okra gum with acid, base or salt influenced and impacted better physicochemical properties on the acetaminophen pediatric suspension when they were used as suspending agents compared with the untreated gum.

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