Evaluation of diclofenac niosomal gel formulated with *Grewia* gum for topical delivery

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Abstract

The purpose of this study was to formulate niosomal gel for topical delivery of diclofenac using *Grewia* gum as gelling agent. Niosomes containing 1g of diclofenac were formed using the thin film hydration (TFH) method. Niosomal gels were then formulated using a semi-synthetic polymer, hydroxypropylmethylcellulose (HPMC) and a natural polymer, *Grewia* gum as gelling agents. The formulated gels were evaluated for spreadability, viscosity, extrudability, homogeneity, clarity and pH. Results show that gels having pH and viscosity ranges of 6.8-7.3 and 265-490 Poise respectively were formed. The gels were homogenous, clear and showed good spreadability and extrudability except for batches F7 and F8. The gels formulated using the test gum, *Grewia* gum compared favourably with those of the standard polymer, HPMC as well as with the marketed gel. Formulation F5 containing 2% w/w *Grewia* gum, the optimized batch, showed viscosity of 265 poise, pH of 6.9, spreadability and extrudability values of 5.55 cm and 5.00 g/s respectively. In conclusion, *Grewia* gum at a concentration of 2% w/w could be used in the formulation niosomal gel for the delivery of diclofenac, which would help to circumvent the potential gastric irritation of diclofenac when used orally.

Keywords: Niosomes; *Grewia* gum; Diclofenac; Lipid hydration; Topical delivery

INTRODUCTION

Plant gums or hydrocolloids can be classified as exudative (Acacia gum, Tragacanth gum, and Karaya gum), extractive (*Grewia* gum and Okra gum) or seed gums (Mucuna gum, Irvingia gum,). Gums can also be formed as a result of infection by microorganisms, for example Xanthan gum. Gum production has also been associated with fungal growth in the plant with the liberation of fungal enzymes, which synthesize the complex polysaccharide gums [1,2]. Gums are polymers or polysaccharide complexes of plant origin or mucilaginous excretion from various plants which on hydrolysis yields hexoses, pentoses and uronic acids [3]. Plant gums are susceptible to hydrolysis on microbial attacks. They exhibit batch-to-batch variation, uncontrolled rate of hydration, and reduced viscosity on storage as well as require a considerable amount of time to hydrate completely to form a homogenous preparation [4-6]. However, unlike synthetic polymers with high cost, toxicity, environmental pollution during synthesis, non-renewable sources, poor
biocompatibility, and side effects, natural gums are biodegradable, biocompatible and non-toxic, low cost, local availability, and most of the times are of edible sources [7]. Gums are utilized in the pharmaceutical industry as: binders in tablets, controlled release agent, targeted drug delivery, suspending agents, emulsifying agents, coacervating agents, stabilizing agents, and coating agents [8,9].

Niosomes are synthetic vesicles consisting of an aqueous core enclosed in a bilayer consisting of cholesterol and non-ionic surfactant for topical drug delivery systems similar to liposomes in structure. Niosomes formation can be affected by factors such as the type of non-ionic surfactant used, method of preparation, and the temperature of hydration. Niosomes are stable, have good entrapment efficiency, can enhance the skin penetration of drugs, have high compatibility with biological systems and low toxicity because of their non-ionic nature. They are biodegradable, biocompatible and non-immunogenic, they can entrap lipophilic drugs into vesicular bilayer membranes and hydrophilic drugs in aqueous compartments hence they can be used for a variety of drugs and can act as a depot to release the drug slowly and offer controlled release [10]. Niosomes can be prepared by the following methods: Hand Shaking method (HSM), Thin-Film Hydration (TFH), Proniosome technology (PT), Dehydration Rehydration (DRM), Freeze and Thaw method (FAT), Heating, Microfluidization, Sonication, Reverse Phase Evaporation (REV), Ether Injection method (EIM) and “Bubble” method. The TFH method is a very simple method of formation of Niosomes and widely used [11], hence adopted in this study.

The formulation of diclofenac as niosomal gel for topical delivery will circumvent the gastric irritation potential of orally administered diclofenac. The purpose of this study therefore was to evaluate the physicochemical properties diclofenac niosomal gel formulated with Grewia gum as gelling agent.

**EXPERIMENTAL**

Diclofenac was a gift from Fidson Pharmaceutical Ltd, Lagos. Grewia gum was extracted from the pods of *Grewia flava* (Malvaceae) and authenticated in the Department of Pharmacognosy, Delta State University, Abraka. All other reagents were of analytical grade.

**Extraction of Grewia gum.** The fresh pods of *Grewia* plant were purchased from a local market in Irele, Ondo State, Nigeria. The pods were washed to remove debris, sliced into small pieces with the aid of a knife. The slices were then air-dried for three days to remove the moisture content. The dried slices were pulverized, and then 4.3 kg sample was transferred into a bowl containing 800 ml of water and allowed to form mucilage. The mucilage was separated from the marc using a clean muslin cloth. The gum was then precipitated with the aid of 2.5 L of acetone, air-dried, pulverized and stored in a labelled airtight container [12].

**Preparation of niosomes.** Niosomes were prepared by the thin film hydration (TFH) method. A 1 ml sample of Tween 80 and 1g of cholesterol were mixed and dissolved in 10 ml of chloroform in a porcelain dish. The solvent was then evaporated using a vacuum oven at 60°C. Niosomes were formed by slowly adding phosphate buffered saline (PBS) pH 7.4 containing 1 g of diclofenac to the dried film formed at the bottom of the porcelain dish with gentle agitation. Dispersion of the mixture was carried out using a sonicator for a period of 5 minutes at 60°C [13,14].

**Preparation of diclofenac niosomal gel.** Weighed amount of polymer (specified for the different batches) shown in Table 1, was
sprinkled gently in a beaker containing 70 ml of warm distilled water and stirred using a magnetic stirrer at high speed. Stirring was continued until a hazy dispersion, without lumps, was formed. A 10 ml volume of glycerin and 10 ml propylene glycol were added as permeation enhancers with continuous stirring followed by addition of 0.2 ml of methylparaben as preservative. The already prepared niosomal suspension containing 1 g of diclofenac was added to the gel to form the niosomal gel. The preparation was then transferred to a cream jar, made up to 100 g with distilled water and labeled.

**Evaluation of extracted Grewia gum powder.**

**Bulk density.** A 6.50 g sample of Grewia gum was weighed and poured into a 10 ml graduated measuring cylinder and the volume occupied by the powder (bulk or unsettled volume) was recorded. This was done three times and the average bulk density was calculated using the equation below [15].

$$\text{Bulk density} = \frac{M}{V_0} \quad \text{Eqn 1.1}$$

Where, $M =$ mass of the powder, $V_0 =$ bulk or unsettled apparent volume of the powder.

**Tapped density.** The tapped density was done by filling the 10 ml graduated cylinder with 6.50 g of the gum, the cylinder was mechanically tapped to a constant volume, and the change in volume was recorded. This was done three times and the average tapped volume was calculated using the equation below [15].

$$\text{Tapped density} = \frac{M}{V_f} \quad \text{Eqn 1.2}$$

Where, $M =$ mass of the powder, $V_f =$ final tapped volume of the powder

**Flow rate and angle of repose.** A 25 g weight of Grewia gum was poured into a glass funnel 5 cm above a flat surface, plugged at the orifice. The plug was removed from the orifice of the funnel and the time taken for the powder to completely flow through the orifice of the funnel was recorded. In addition, the height of the heap formed by the powder and the diameter of the heap base were measured and recorded. Angle of repose was calculated using the equation below

$$\text{Angle of repose} = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{Eqn 1.3}$$

Where, $h =$ height of the pile, $r =$ radius of the base of the pile, $\Theta =$ angle of repose

**Carr’s index.** The difference between the tapped and bulk density divided by the tapped density was calculated and expressed in percentage as in equations below [16].

$$\text{Carr’s index(%) } = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{Eqn 1.4a}$$

$$\text{Carr’s index(%) } = \frac{V_0 - V_f}{V_0} \times 100 \quad \text{Eqn 1.4b}$$

**Hausner’s ratio.** Hausner’s ratio is the ratio of tapped density to that of the bulk as given in the equations below [16].

$$\text{Hausnerratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{Eqn 1.5a}$$

$$\text{Hausnerratio} = \frac{V_0}{V_f} \quad \text{Eqn 1.5b}$$

Where $V_0 =$ unsettled apparent volume, $V_f =$ final tapped volume.

**Evaluation of niosomal gels**

**Opacity.** It was determined by visual inspection under black and white background and it was graded as follows: transparent; translucent; and opaque.

**Homogeneity.** It was determine by visual inspection for the appearance of lump and presence of any aggregate.

**Spreadability.** A spreadability test was conducted by pressing 0.5 g of gel between two glass slides with the aid of a 20 g weight and leaving it for about 5 min until no more spreading was observed. The diameter of
formed circle was measured and used as the value for spreadability [17].

**Extrudability.** A 5 g quantity of gel was filled in a clean 10 ml syringe suspended using a retort stand; 0.5 kg weight was placed on the free end of the plunger and the amount of gel extruded in 5 min was noted.

**pH.** A 1 g quantity of gel was dispersed uniformly in 100 ml of distilled water using magnetic stirrer. The pH of the 1 %w/v dispersion of the niosomal gel was measured by using digital pH meter.

**Viscosity.** The viscosity of 1 % w/v dispersion was determined by the use of a rotational viscometer (NDJ-1, China) using spindle 4.

**RESULTS & DISCUSSION**
The results of the physicochemical characterization are presented in Tables 2 and 3; and Figures 1 and 2.

**pH of Grewia gum.** The pH of the gum was found to be 6.0, which indicates that the gum is slightly acidic and within the normal range for natural gums as presented in Table 2.

**Viscosity of Grewia gum.** The viscosity of the gum was found to be 509 poise indicating that it is a very viscous gum as presented in Table 2.

**Flow properties of Grewia gum.** The angle of repose value was 26.11° which is indicative of good flow characteristics. This value is further corroborated by the Hausner’s ratio and and Carr’s index values of 1.17 and 14.98 % respectively. In addition, the bulk and tapped density values are quite close showing that the powders are free flowing and would not consolidate readily (Table 2).

**Opacity and homogeneity of niosomal gel.** Formulation batches F1, F2, F3, F4, F5, and F6 were translucent when viewed against a black and white background, and showed very good homogeneity but formulations F7 and F8 were opaque when viewed and did not show good homogeneity. The marketed diclofenac gel CDG was transparent when viewed against a black and white background (Table 3).

**Spreadability and extrudability of niosomal gel.** Formulations F1, F2, F5 and F6 showed good spreadability and compared favourably with the marketed brand while Formulation F5 and F6 showed excellent extrudability when compared with the marketed commercial brand of diclofenac. Batch F5 exhibited the best profile in terms of spreadability and extrudability (Figure 1).

**pH of niosomal gel.** Formulation F1, F2, F3, F4, F6 and F7 gave neutral pH values while formulation F5 and F8 pH values of 6.9 and 6.8 respectively. All formulation batches fell within the pH range for gels and compared favourably with the commercial brand (Table 3).

**Viscosity of niosomal gel.** The viscosity values for formulations F1 and F5 are similar to that of the marketed diclofenac gel.

**Table 1: Composition of diclofenac niosomal gel**

<table>
<thead>
<tr>
<th>Ingredients (g)</th>
<th>Formulation Batches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1</td>
</tr>
<tr>
<td>HPMC</td>
<td>2</td>
</tr>
<tr>
<td><em>Grewia</em> gum</td>
<td>-</td>
</tr>
<tr>
<td>Methylparaben (ml)</td>
<td>0.2</td>
</tr>
<tr>
<td>Glycerin (ml)</td>
<td>10</td>
</tr>
<tr>
<td>Propylene Glycol (ml)</td>
<td>10</td>
</tr>
<tr>
<td>Niosomal suspension (ml)</td>
<td>10</td>
</tr>
<tr>
<td>Distilled water to</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 2: Micromeritic properties of extracted Grewia gum powder

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage yield (%)</td>
<td>20.9</td>
</tr>
<tr>
<td>pH</td>
<td>6.0</td>
</tr>
<tr>
<td>Viscosity (poise)</td>
<td>509</td>
</tr>
<tr>
<td>Flow rate (g/s)</td>
<td>6.67 ± 0.001</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>26.11 ± 1.033</td>
</tr>
<tr>
<td>Bulk density (g/ml)</td>
<td>0.69 ± 0.010</td>
</tr>
<tr>
<td>Tapped density (g/ml)</td>
<td>0.82 ± 0.013</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.17</td>
</tr>
<tr>
<td>Carr’s index (%)</td>
<td>14.98</td>
</tr>
</tbody>
</table>

Table 3: Organoleptic and pH characterization of diclofenac niosomal gel

<table>
<thead>
<tr>
<th>Batches</th>
<th>Opacity</th>
<th>Homogeneity</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Translucent</td>
<td>Very good</td>
<td>7.3</td>
</tr>
<tr>
<td>F2</td>
<td>Translucent</td>
<td>Very good</td>
<td>7.1</td>
</tr>
<tr>
<td>F3</td>
<td>Translucent</td>
<td>Very good</td>
<td>7.3</td>
</tr>
<tr>
<td>F4</td>
<td>Translucent</td>
<td>Very good</td>
<td>7.2</td>
</tr>
<tr>
<td>F5</td>
<td>Translucent</td>
<td>Very good</td>
<td>6.9</td>
</tr>
<tr>
<td>F6</td>
<td>Translucent</td>
<td>Very good</td>
<td>7.0</td>
</tr>
<tr>
<td>F7</td>
<td>Opaque</td>
<td>Fair</td>
<td>7.1</td>
</tr>
<tr>
<td>F8</td>
<td>Opaque</td>
<td>Fair</td>
<td>6.8</td>
</tr>
<tr>
<td>Commercial diclofenac gel (CDG)</td>
<td>Transparent</td>
<td>Very good</td>
<td>7.2</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)

**Figure 1:** Chart showing the spreadability and extrudability values for diclofenac niosomal gel

![Figure 2](image2.png)

**Figure 2:** Bar graph showing the viscosity of the different batches of diclofenac niosomal gel
Formulation F8 gave the highest viscosity, which could be due to the high concentration of the gum (Figure 2).

Conclusion. Diclofenac niosomal gel can be formulated successfully using *Grewia* gum as a gelling polymer. It can be concluded that *Grewia* gum is a promising polymer with good physicochemical and micromeritic properties. Formulation F5 containing 2% w/v *Grewia* gum is the optimized batch because it is clear, homogeneous, almost neutral pH, showed good spreadability and extrudability. *Grewia* gum based diclofenac niosomal gel has shown good promise for topical delivery, which would circumvent the potential gastric irritation of orally, administered.

REFERENCES


