Original Article

Design, Formulation and Evaluation of Diclofenac Diethylamine Gel

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Abstract: The goal of this study was to produce a topical gel formulation of Diclofenac diethylamine using various gelling agents, such as carbopol 934, Sodium Carboxy methyl cellulose, and alovera extract, to reduce the gastrointestinal side effects associated with oral administration. Topical medication administration can be accomplished by integrating into the gel matrix, preventing first-pass metabolism and allowing for greater local action in anti-inflammatory and analgesic purpose. The gel formulations were tested for homogeneity, grittiness, viscosity, pH, spreadability, drug content, in vitro drug release and release kinetics. The effects of polymer composition on the rate of drug release from the gel formulations were examined through dialysis membrane at 37±0.5°C. The gel formulation consisting of alovera extract (F3) was found to be suitable for topical application based on in vitro evaluation. These results suggest the feasibility of the topical gel formulation of Diclofenac diethylamine.

1. INTRODUCTION

Topical delivery is the reason for its use on skin or particular local action or percutaneous penetration on mucosal membranes of medications, including protective or emollient characteristics. Gels are typically created from a liquid phase thickened with additional components. (Sheikh et al., 2011) The release should be equivalent to that of a simple solution due to the continuous liquid phase allowing molecules to easily permeate through the polymer scaffold. (Shivhare et al., 2009) NSAIDs (nonsteroidal anti-inflammatory and analgesic drugs) have strong anti-inflammatory and analgesic effects, but when used orally, they can induce GIT ulcers, liver, and kidney issues. Diclofenac diethylamine is increasingly used topically because of hazards connected to oral formulations. (Maghraby et al., 2006)

Advantages of gels of Diclofenac Diethylamine are no irritation in the stomach and intestines, prevent G.I. issues owing to P450 differences, feasible to prevent the consequences of meals on medication absorption, feasible to avoid active medicament deactivation owing to g.i.t. enzymes, economical, limited impact with little negative impact and when oral medication isn’t an option, such as in event of nausea and vomiting, they provide an alternative. (Kikwai et al., 2005, Satish et al., 2006).

2. MATERIALS & METHODS

2.1 MATERIALS

Diclofenac diethylamine (Yarrow chem. Pvt. Ltd.), Sodium Carboxy Methyl Cellulose and Carbopol 934 (Loba Chemie Pvt. Ltd., Mumbai), Methyl Paraben (Merck Limited, Mumbai), Propylene Glycol, Glycerol (New Bengal Drug House, Kolkata) were used without further purification. All the other chemicals were of analytical grade. Dialysis Membrane was procured from Hi Media Laboratories Pvt. Ltd., Mumbai (Avg. flat width 39.41 mm and avg. diameter 23.8 mm).

2.2 METHODS:

An accurately weighed quantity of polymer was taken and using heat and magnetic stirrer, the polymer was dissolved in distilled water. Then the precise amount of Diclofenac Diethylamine was weighted and Homogenized with the polymeric solution using a magnetic stirrer. Then the solution allowed to cool. Glycerine, PEG-400, and a preservative were all added and properly mixed together. Then the finalized formulation was frozen for overnight to stabilize the formulation. (Tanwat et al., 2012)
### 3. EVALUATION OF DICLOFENAC DIETHYLAMINE GEL:

#### 3.1 Visual Inspection:
After the gels were set in the container, all generated gel formulations were visually evaluated for homogeneity, colour, syneresis, and the presence of lumps.

#### 3.2 Test of Spreadability:
It was determined by wooden block and glass slide apparatus. To determine the spreadability, 0.5 g sample of each formula was squashed between two slides. The upper slide was fitted with a string that was tied with a fixed weight. The weight was suspended from the string after it was passed through a pulley. Under the upper, the glass slide took time to slip off. The time was noted. Lesser the time is taken for separation of two slides, better the spreadability. The diameters of spread circles were measured in centimetres and used as comparative spreadability values. The acquired findings were the average of three determinations. (Kaur et al. 2010)

Spreadability is calculated by using the formula: $S = M \cdot L / T$

Where, $M =$ Weight tied to the upper slide
$L =$ length of glass slides
$T =$ time taken to separate the slides

#### 3.3 pH determination:
The pH of gel was determined using digital pH meter. 2.5 gm gel was stirred in distilled water till a uniform suspension is formed. The volume was made up to 40 ml and pH of the solution was measured. Each formulation’s pH was determined by temperature of room. (Lakshmi et al., 2011)

#### 3.4 Viscosity:
Brookfield viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to determine the viscosities of the produced gel formulations at 25°C. The spindle (TD) was turned at a certain speed. When the torque was close to 100 percent, the viscosities of the formulas were more accurate. (Ramchandani et al., 2013)

#### 3.5 Extrudability:
The material is extruded from the tube as normal in this test. A gel-filled closed collapsible tube was forcefully passed through the cramped end. When the cap is removed, the gel extrudes until the pressure is gone. It was calculated the weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds. The data were reported as extrusion pressure in grams for each formulation. (Bharadwaj et al., 2012) (Singh et al., 2013)

#### 3.6 Estimation of Drug Content:
A portion of the produced gel was dissolved in 50 mL of phosphate buffer. To ensure full solubility of the medication, the volumetric flask containing gel solution was mechanically shaken for 2 hours. Millipore filters (0.45μm) were used to filter this solution. Then, using a UV-Visible spectrophotometer set to maximum 266 nm and phosphate buffer as a blank, the drug absorbance was measured. (Kaur et al. 2010)

#### 3.7 In-Vitro Release Study:
The study was carried out using dialysis membrane. Fixed quantity of the gel was placed on a circular aluminum foil. The foil was placed on the dialysis membrane and pressed to spread uniformly in order to get a uniform thickness of the gel throughout the foil. The membrane was tied with the open end of a test tube such that the gel remained in the donor side of the membrane placed on a test-tube of defined diameter. The test-tube was then immersed in the vessel containing 100 ml of the release medium, phosphate buffer pH 6.8 maintained at 37°C±0.5°C in a precision water bath. The membrane just touched the release medium at the receptor side. Aliquots (5 ml) volumes of samples were withdrawn at predetermined time interval and were immediately replaced with fresh medium pre-warmed to 37°C±0.5°C. The samples were analyzed in a UV spectrophotometer at specific nm. (Jain et al., 2010 and Das et al., 2015)

#### 3.8 Drug Release Kinetic:
The data obtained from the in vitro release study were analyzed using linear regression method according to the following equations:

- **i. Zero order**
  
  $Q_t = k_0 \cdot t$
  
  Where, $Q_t =$ Amount of drug release in time $t$
  $k_0 =$ Zero order rate constant expressed in unit of concentration/time
  $t =$ Release time

- **ii. First Order**
  
  $\log Q = \log Q_0 - \frac{k_1 \cdot t}{2.303}$
  
  Where, $Q_0 =$ is the initial concentration of drug, $k_1 =$ is the first order rate constant, $t =$ release time

- **iii. Higuchi model**
  
  $Q = k_1 \cdot t^{1/2}$
  
  Where, $k_1 =$ Release rate constant, $t =$ release time

- **iv. Hixson-Crowell model**
  
  $W_0 \frac{1}{3} - W \frac{1}{3} = k_1 \cdot t$
  
  Where, $W_0 =$ initial amount of drug in the pharmaceutical dosage form, $W =$ remaining amount of drug in the pharmaceutical dosage form at time $t$ and $K =$ rate constant incorporating the surface volume relation

- **v. Korsmeyer-Peppas model**
  
  $\frac{M_t}{M_\infty} = k_1 \cdot n$  

  Where, $M_t =$ amount of drug released at time $t$  
  $M_\infty =$ amount of drug released after infinite time  
  $M_0 =$ fraction solute release  
  $t =$ release time, $K =$ kinetic constant incorporating structural and geometric characteristics of the polymer system, $n =$ diffusion exponent that characterizes the mechanism of the release of traces. (Sakore et al., 2013)

The results are shown in the table 2 and figs 1-5.

#### 4. RESULTS AND DISCUSSION:
All of the created gel formulations had a pleasant feel to them and showed no clogging or lumps, indicating that the system’s texture was good.

The pH of the gels was in the range of 6-7, which was close to neutral. Because it impacts the spreadability, extrudability, and release of the medication, viscosity is an important metric for describing the gels. The viscosities of the formulations ranged from 3600 to 1030 Cps. In terms of patient compliance, easy spreadability is one of the most significant aspects of any topical medication. If it takes the least amount of time to spread across the surface, the gel is regarded good. The F3 formulation exhibits superior spreadability and drug release than the other gels evaluated. The spreadability numbers suggest that the gel can be easily spread with a small degree of shear. (Bhanja et al., 2013)

### Table 1: Composition of Diclofenac Di-ethylamine Topical gel

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Diethylamine</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Sodium CMC</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloe vera extract</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerol</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PEG 400</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Methyl Paraben</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
</tr>
</tbody>
</table>

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During application and for patient compliance, extrusion of gel from the tube is critical. Extrudability of various formulations ranged from 82 to 92%. The drug content consistency of all formulations was observed, with the F3 batch having a drug content of 93.12±0.27%.

Table 2: Physical Properties of Prepared Diclofenac Diethyl amine topical gel

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Appearance</th>
<th>pH</th>
<th>Spreadability (cm²)</th>
<th>Extrudability</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Transparent</td>
<td>6.00±0.05</td>
<td>16.45</td>
<td>82%</td>
<td>93.20±0.18</td>
</tr>
<tr>
<td>F2</td>
<td>White</td>
<td>6.50±0.02</td>
<td>9.53</td>
<td>71%</td>
<td>91.47±0.18</td>
</tr>
<tr>
<td>F3</td>
<td>Light Green</td>
<td>6.60±0.07</td>
<td>18.50</td>
<td>93%</td>
<td>93.12±0.27</td>
</tr>
</tbody>
</table>

The percent of Diclofenac Diethylamine released over a 2-hour period from produced gel formulations with the same initial drug concentration is discussed utilising various polymers. Alovera gel has the highest percentage of Diclofenac Diethylamine release. In comparison to the other batches, the F3 batch has a superior release.

Various kinetic models, such as zero order, first order, Higuchi model and Hixon-Crowell model were used to analyse the release data, as shown in figs 1-4. In table 2, the $R^2$ value was tabulated. The Higuchi model best fit all of the above formulations.

Table 3: Kinetic study of in-vitro release data of Diclofenac Diethylamine gel

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero Order $R^2$</th>
<th>First Order $R^2$</th>
<th>Higuchi Model $R^2$</th>
<th>Hixon Crowell $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.998</td>
<td>0.977</td>
<td>0.991</td>
<td>0.976</td>
</tr>
<tr>
<td>F2</td>
<td>0.972</td>
<td>0.994</td>
<td>0.998</td>
<td>0.99</td>
</tr>
<tr>
<td>F3</td>
<td>0.975</td>
<td>0.975</td>
<td>0.990</td>
<td>0.987</td>
</tr>
</tbody>
</table>

CONCLUSION:

According to the results of the investigation, Diclofenac Diethylamine was effectively finished in the topical gel formulation. As a polymer, Carbopol 934, Sodium CMC, and Alovera extract were employed. The F3 batch had the finest release, spreadability, and extrudability, as well as the highest drug content. As a result, the F3 batch is regarded as the most optimized. Though, long term stability study is required for future development of these formulations.
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Declaration of competing interest
The authors declared no conflict of interest.

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