Formulation and In-Vitro Evaluation of Capsaicin Emulgel for Topical Delivery

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Abstract: Emulgels are topical dosage form in which emulsions are gelled by mixing with gelling agent. Incorporation of emulsion into gel increases stability of emulsion and provides controlled release system. Emulgels have emerged as a promising drug delivery system for the delivery of hydrophobic drugs. The main objective of the present study is to prepare emulgel using capsaicin, an analgesic as drug of choice. Liquid paraffin was used as oil phase of o/w emulsion and combination of Span 80 and Tween 80 were used as emulsifying agent and clove oil was used as permeation enhancer. Polymers like carbopol 974, carbopol 930, HPMC K100, HPMC K4M and HEC are used as gelling agent in various proportions. Total of 7 formulations were prepared by changing the gelling agent and their concentration. The prepared emulgels were evaluated for physical appearance, pH, spreadability coefficient, physical stability, drug content, skin irritation test and in-vitro drug release. All the formulations were physically stable with the pH values within the range and have shown good spreadability coefficient. There was no irritation or swelling observed in the rats during the test period. In-vitro diffusion studies were carried out using pH 7.4 phosphate buffer and formulation F1 (Carbopol 974-1%) has shown best results with zero order release kinetics and diffusion mechanism.

Keywords: Emulgel, Hydrophobic drugs, Capsaicin, Clove oil, Carbopol, Diffusion mechanism.

INTRODUCTION:
Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment [1-3]. Topical drug delivery system has several advantages such as ability to deliver drug more selectively to a specific site, avoidance of gastrointestinal incompatibility and metabolic degradation associated with oral administration more over topical deliveries provide increased bio-availability by avoiding first pass metabolism by liver and consistent delivery for extended period [4-5].

Major drawback of topical dosage form is dissolution and diffusion of drug in the delivery of hydrophobic drugs, and permeation through stratum corneum is for hydrophilic drugs. Therefore, to overcome this limitation, emulgels are prepared. The combined dosage form of gels and emulsions are referred as emulgels. Both oil-in-water and water-in-oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in emulgel formulation. They also have a high ability to dissolve drug and to penetrate the skin. Oil-in-water emulsions are mostly useful as water washable drug bases.

The present research work aims at preparing emulgel containing capsaicin an analgesic agent. Capsaicin is a chemical irritant which is active ingredient in hot chilli peppers of the genus capsicum. Capsaicin is used topically to treat various diseases such as rheumatoid arthritis, osteoarthritis, diabetic neuropathy, post therapeutic neuralgia, psoriasis and to reduce pain in Burning Mouth Syndrome, Guillain Barre syndrome, refractory pain, cluster headache, urticaria, rheumatoid arthritis and osteoarthritis, and atypical odontalgia [6]. Capsaicin is hydrophobic in nature and has low half life, thus to enhance its solubility and increase its effectiveness it is formulated as emulgel. Various gelling agents such as HPMC, Carbopol and HEC are used in the study.

MATERIAL AND METHODS:
Materials:
Capsaicin is obtained from Naturite Agro Ltd, Hyderabad. HPMC K4M, HPMC K100M, Carbopol 930, Carbopol 974 and Hydroxy ethyl cellulose were procured from Horizon Chemicals Ltd. Span 80, Tween...
80, propylene glycol, methyl paraben, clove oil were procured from S.D. Fine Chem. Ltd, Mumbai, India.

Methods:

Drug excipient compatibility studies:

Integrity of the drug in the formulation was checked by taking an IR spectrum of the formulation along with the drug and other excipients. In this study pelletization of potassium bromide (KBr) was employed. Crystals of potassium bromide was completely dried at 100°C for 1 hr and was thoroughly mixed with the sample in the ratio of 1 part of sample and 100 parts of KBr. The mixture was compressed to form disc using dies. Spectrum measurement was carried out using KBr disk in the wavelength region of 4000-400cm⁻¹ by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction. The samples of pure Capsaicin drug and various mixtures of excipients and polymers with Capsaicin drug were prepared in the form of KBr pellets and subjected for scanning from 4000 cm⁻¹ to 400cm⁻¹ using FT-IR spectrophotometer.

Formulation Development

The Gel in formulations were prepared by dispersing polymer in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 80 in liquid paraffin and aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben was dissolved in propylene glycol whereas drug (Capsaicin) was dissolved in ethanol and both solutions were mixed with the aqueous phase. Clove oil was added to oil phase which acts as penetration enhancer. Both the oily and aqueous phases were separately heated to 40° to 50°C then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. And mixing of gel and emulsion in ratio 1:1 to obtain the emulgel [7].

Table.1: Formulation of Capsaicin Emulgels

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation codes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.1%</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>1%</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>-</td>
</tr>
<tr>
<td>Carbopol 930</td>
<td>-</td>
</tr>
<tr>
<td>Carbopol 930</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K 15M</td>
<td>-</td>
</tr>
<tr>
<td>HEC</td>
<td>-</td>
</tr>
<tr>
<td>Span 80</td>
<td>1%</td>
</tr>
<tr>
<td>Liquid paraffin</td>
<td>7.5%</td>
</tr>
<tr>
<td>Tween 80</td>
<td>1%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5%</td>
</tr>
<tr>
<td>Methyl paraben</td>
<td>0.03%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>2.5%</td>
</tr>
<tr>
<td>Clove oil</td>
<td>8%</td>
</tr>
<tr>
<td>Water</td>
<td>Q.S</td>
</tr>
</tbody>
</table>

Characterization of emulgel

1. Physical appearance: The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation after 24 h of preparation [8].

2. pH: The pH values of 1% aqueous solutions of the prepared emulgels were measured by a calibrated pH meter [8].

3. Spreadability: The spreadability of the emulgel formulations was determined 48 hrs after preparation, by measuring the spreading diameter of 0.5 g emulgel which was placed within a circle of 1 cm diameter pre-marked on a glass plate over which a second glass plate (75 gm) was placed. A weight of 425 g was allowed to rest on the upper glass plate for 5 min where no more spreading was expected [9, 10]. The increase in the diameter due to spreading of the gels was noted. The spreadability (g.cm.min⁻¹) was calculated by using the formula:

\[ S = \frac{m \times 1}{t} \]

Where: S is spreadability, m is the weight of the upper plate and rested on it (g), l is the diameter of the spreading emulgel (cm), and t is the time taken (min) [11-13].

4. Centrifugation: This parameter could be measured to evaluate physical stability. Emulgel could be centrifuged at an ambient...
temperature and 6000 RPM for 10 minutes to evaluate the system for creaming or phase separation. System could be observed visually for appearance [14].

5. **Drug Content Determination:** Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using the same standard plot by utilizing the value of absorbance.

6. **In-vitro permeation study:** In-vitro release study is carried out using a modified Franz diffusion cell. 1g of the formulation was weighed and placed on the dialysis membrane having the surface area of 2.5cm², which is placed between donor and receptor compartment of the diffusion cell. Phosphate buffer 7.4 was prepared and used as the diffusion media. The temperature of the cell was maintained at 37˚c. This whole setup was stirred using the Teflon coated magnetic stirrer at 50 rpm. At specified time intervals 5ml of the sample solution was taken and analyzed spectrophotometrically at 281nm. The cumulative % drug release was determined [15].

7. **Kinetic Analysis of in-vitro Release Rates of Capsaicin Emulgel[16]***

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows,
1. Zero order kinetic model – Cumulative % drug released versus T.
2. First order kinetic model – Log cumulative percent drug remaining versus T.
3. Higuchi’s model – Cumulative percent drug released versus square root of T.
4. Korsmeyer equation / Peppa’s model – Log cumulative percent drug released versus log T.

8. **Skin irritation study:**

The preparation is applied on the properly shaven skin of wister rat and its adverse effects like change in color, change in skin morphology should be checked up to 72 hours. If no irritation is occurred then test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated [17].

**RESULTS AND DISCUSSION**

Compatibility study of drug with different polymers:
In comparison with pure drug (Fig:1), the absorption peak of the spectra of Capsaicin in combination with different polymers (Fig: 2, 3, 4, 5, 6) showed no shift and no disappearance of characteristic peaks suggesting that there is no interaction between drug and the polymers used.

**Fig: 1. FTIR Spectra of Capsaicin**

**Fig: 2. FTIR Spectra of Capsaicin+ Carbopol 974**
Characterization of emulgel

1. Physical appearance: The formulated emulgels were examined for their color, homogeneity, consistency and phase separation after 24 hr of preparation. They were white, homogenous, transparent to white opaque and from viscous gel preparations with a smooth homogeneous appearance and there was no significant phase separation observed in the formulations.

2. Measurement of pH: The pH of the Emulgel formulations was in the range of 6.07 to 6.33, which lies in the normal pH range of the skin and would not produce any skin irritation. The results are represented in table-2.

### Table 2: pH of the prepared emulgels

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Formulation code</th>
<th>pH</th>
<th>Spreadability (g.cm/min)</th>
<th>Drug content %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>6.07</td>
<td>123</td>
<td>98.86</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>6.28</td>
<td>111</td>
<td>97.52</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>6.27</td>
<td>102</td>
<td>98.94</td>
</tr>
<tr>
<td>4</td>
<td>F₄</td>
<td>6.33</td>
<td>99</td>
<td>98.37</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>6.13</td>
<td>93</td>
<td>97.64</td>
</tr>
<tr>
<td>6</td>
<td>F₆</td>
<td>6.21</td>
<td>105</td>
<td>95.47</td>
</tr>
<tr>
<td>7</td>
<td>F₇</td>
<td>6.33</td>
<td>96</td>
<td>94.21</td>
</tr>
</tbody>
</table>

3. Spreadability: One of the essential criteria for an emulgel is that it should possess good spreadability. Spreadability is an important factor in therapy and it is shown as index of ease of application. The delivery of the correct dose of the drug depends highly on the spreadability of the formulation. The spreadability of capsaicin emulgel formulation following the spreadability test was found to range from 93 g.cm/min to 123 g.cm/min for the formulations F₁-F₇ and the results are given in the table-2.

4. Centrifugation: The prepared emulgels were subjected to centrifugation test to determine the physical stability and there was no phase separation or creaming observed during this test which indicated that the formulations were stable.

5. Skin irritation study: Skin irritation test as performed on the male wistar rats for all the developed formulations and there was no redness or swelling observed during the 24 hr test period.

6. Drug Content Determination: Drug content of the formulations were determined by using standard plot and the values were given in the table-2 and the values ranged from 95.47% to 98.94%.

7. In-vitro drug release study: The in-vitro release profiles of Capsaicin from its various emulgel formulations are represented in fig-7 and 8. The better release of the drug from all emulgel formulation can be observed and the emulgel formulation can be ranked in the order of F₁>F₇>F₆>F₅>F₄>F₃>F₂. Of the developed formulations F₁ has shown the good drug release of 98.6% at the end of 180mins.
8. Drug release Kinetics: From the kinetic data, the formulations F2, F3, F4, F5, F6 shows drug release by korsmeyer-Peppas model. The regression values for these formulations range from 0.9871-0.9962. The formulation F6 shows drug release by Higuchi (R²=0.9894) i.e., drug release is by diffusion process. The optimized formula F1 shows drug release by zero order kinetics (R²=0.9489) and higuchi mechanism i.e., diffusion (R²=0.9815). The ‘n’ values of korsmeyer-Peppas model are in the range of 1.1343- 0.9423. It indicates that drug release is by erosion of polymeric chain.

CONCLUSION:

The present study was carried out with the aim to prepare an emulgel formulation for capsaicin an analgesic agent. All the formulations F1-F7 have passed all the evaluations with good values. The formulations were found to be stable and homogenous in nature, pH of the formulations suggest that values were within the limits of the skin pH and there was no irritation, swelling and redness found in the test animals during the skin irritation study. In-vitro releases of the tests formulations were performed to determine drug release rate from emulgel. F1 (carbopol 974- 1%) formulation has shown best spreadability among all and can be used to produce quick pharmacological action. Emulgels also shows good spreadability, better loading capacity, ease of application and a good patient compliance. The in-vitro release study has shown that formulation with carbopol 974 in 1% concentration has shown a good release when compared with the other formulations and the mechanism of drug release was by zero order kinetics and diffusion of drug molecules from the emulgel formulation. Among the various formulations developed F1 formulation was found to better and is thus optimized.

Considering the various dermatological topical preparation with various advantages and disadvantages, emulgels serve as the better alternative of the present...
available marketed topical formulation for delivery of hydrophobic drugs.

REFERENCES: