A Study on the Effect of Penetration Enhancer on Ketoprofen Emulgel

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A B S T R A C T
Topical delivery gained popularity for the treatment of local skin disorders. Topical formulations have the potential to deliver the drug to the site of action and can achieve the therapeutic benefit. Apart from the delivery of drugs through the skin it can maintain the long residence time with the skin. Among the topical formulations emulgel emerged as a promising drug delivery systems for the delivery of hydrophobic drugs. Ketoprofen is a non-steroidal anti-inflammatory drug. It is widely used as analgesic for patients with rheumatic disease, joint disorders such as ankylosing spondylitis, osteoarthritis. The aim of this study was to formulate the ketoprofen topical emulgel formulation using sodium alginate and to evaluate the effect of penetration enhancer DMSO on the drug release. To overcome the two major problems of ketoprofen, it is an insoluble drug and has irritant effect on GIT lead to ulceration and bleeding-emulgel was formulated. The formulated emulgels were subjected evaluation in terms of physical stability, homogeneity, drug content, invitro drug release. 

Keywords: ketoprofen, emulgel, anti-inflammatory, analgesic

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1. Introduction

Topical formulations have gained popularity since many years. Topical drug delivery is the most widely used drug delivery for local and systemic delivery. Topical route refers to the drug delivery through skin and mucous membrane. This includes delivery through skin, vagina, rectal and ophthalmic routes. The formulations under this category include creams, ointents, gels etc. A gel is colloid that is typically 99% by weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present. In spite of many advantages of gels a major limitation is their inability to delivery hydrophobic drugs [1,2].

Among topical formulations emulgel is emerging as a potential drug delivery system. Gel formulation is not suitable for the delivery of hydrophobic drugs. An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or O/W with a gelling agent 3. The main advantage of the emulgel that lipophilic drugs can be easily formulated into gels 4. Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydrogel5. For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. Other advantages for emulgel include; better stability, high loading efficiency, more production economical with low cost. These are used for dermatological and cosmetic preparations.

Drug applied to the skin for their local effect are antiseptics, protectants, NSAID’s, skin emollients, antifungal agents, emulgels for their dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-souble, longer shelf life, biofriendly, transparent, and pleasing in appearance6. Emulgel formulation requires polymers of natural and synthetic origin. As the emulgel is a gellified emulsion it consists of emulsion and gel. The lipophilic phase of the emulsion is prepared by liquid paraffin, olive oil, coconut oil and other vegetable and mineral oils. Apart from the gellifying agents like polymers, oil penetration enhancers, humectants, emulsifying agents are also used.

Addition of a chemical penetration enhancer to the delivery system will enhance drug partitioning into the SC7, these enhancer should be inert, non toxic, compatible with the drugs, and the onset of penetration enhancing action should be immediate. Most common enhancers are alcohols, polyalcohols, amides, pyrrolidones, fatty acids, sulphoxides, esters, amines, terpenes, and surfactants [8,9]. Researchers have been trying to overcome gastrointestinal side effects by topical delivery of non-steroidal anti-inflammatory drugs among these, piroxicam, ketoprofen, naproxen, and tenoxicam have been proposed [22]. Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). It is widely used as analgesic for patients with rheumatic disease [20], joint disorders such as ankylosing spondylitis, osteoarthritis. Its molecular weight equal 254.29, pKa of 5.94, partition coefficient of 0.97. It is practically insoluble in water, freely soluble in acetone, ethanol and methylene chloride [21]. Ketoprofen is a non-steroidal anti-inflammatory drug that has two major problems when administered orally; it is an insoluble drug and has irritant effect on GIT lead to ulceration and bleeding [12]. The aim of the present work is to prepare the emulgel using ketoprofen to overcome the side effects associated with ketoprofen and to evaluate the effect of concentration of DMSO on the in-vitro release of drug.

2. Materials and Methods

Ketoprofen was obtained as a Gift sample from medreich Pvt ltd, bangalore. Sodium alginate, DMSO was purchased from SD. Fine Chemicals, Mumbai, glycerol was purchased from SD. Fine Chemicals, Mumbai, India. Ethanol (AR grade) was purchased from Loba Chemical Mumbai (India). Double distilled water was used for all experiments.

Spectroscopic Studies:

Determination of \( \lambda_{\text{max}} \) of ketoprofen in phosphate buffer

7.4: Stock solution (100µg/ml) of gliazide was prepared in 0.1N Hcl pH 1.2. This solution was appropriately diluted to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200nm to 360nm on UV.VI Sspectrophotometer (UV-1800, shimadzu corporation, japan). The drug exhibited a \( \lambda_{\text{max}} \) at 255 nm in phosphate buffer pH 7.4.

Compatibility studies:

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. Hence, before producing the actual formulation, compatibility of ketoprofen with different sodium alginate was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

Fourier-transform Infrared Spectroscopy:

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Shimadzu FT – IR 8400). The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. scans were obtained at a resolution of 4 cm\(^{-1}\), from 4,000 to 500 cm\(^{-1}\).

Preparation of emulgel:

To formulate the stable emulgel, stable emulsion is required. To fulfill these requirements various concentrations of tween and stearic acid were added in aqueous and oil phases respectively i.e.1:1, 1:2, 1:3, 2:1, 3:1,2,3,3:2. And the two phases are heated to 70-80 ⁰C and they are emulsified at 1000 rpm. Among the prepared formulations3:2 exhibited more physical stability, less phase separation, good globule size and milkiness. so, 3:2 ratio of stearic acid and tween were selected for the further studies. The composition of the emulgel formulations was presented in table no.1.
Different formulations were prepared using varying amount of penetration enhancers\cite{11,12}. Gel phase was prepared by dispersing the required amount of sodium alginate in the distilled water and stirred to obtain the gelly consistency. Glycerine, DMSO were added to the gel. Oil phase was prepared by dissolving the Stearic acid in sunflower oil. Aqueous phase was prepared by dissolving the tween-80 in distilled water. Ketoprofen was dissolved in required amount of alcohol and added to the aqueous phase. both oil and aqueous phases were heated to 70-80 c. then both phases cooled to room temperature, oil phase is added to aqueous phase with continuous stirring at 1000 rpm for 30 min. the obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel.

**Evaluation of emulgels:**

1. Physical evaluation:
The prepared emulgel formulations were evaluated physically for their color, appearance, homogeneity, consistency and presence of any gritty particles\cite{13}.

2. Rheological study:
Viscosity of different emulsified gel formulation was determined at 37 c [16] using a brook field viscometer (Brookfield DV-E viscometer) with helipath spindle no 20 at 50 and 100 rpm.

3. Spreading coefficient:
It is helpful for the extent of area to which the formulation Readily spread on application to skin or the affected part. The spreading coefficient is expressed internms of time in seconds taken by two slides to slip off from the emulgel. The lesser the time taken for separation of the two slides , better is the spreadability. It is calculated by the following formula [14]

\[
S=M.L/T
\]

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

The experimental setup consists of two glass slides. The emulgel of 2g sample is placed on the lower slide which is fixed to the stationary surface and upper glass slide is placed on it. Then 500gm of weight is placed for some time to spread the sample evenly between the upper and lower slides. The lower plate holds the sample, while the upper plate, which weighs 50gm, exerts force to the sample. each sample was tested at constant temperature and exerted weight\cite{15}. The spreading coefficient values are represented in table no.3

4. Drug content:
Ketoprofen content in emulsified gel was measured by dissolving emulgel in suitable solvent by sonication. Absorbance was measured after suitable dilution at 255nm in UV-VIS spectrophotometer (UV-1800, shimadzu corporation, japan) [16]. The % drug content values are represented in table no.4.

**In-vitro drug release:**
The invito drug release studies were carried out using a modified franz diffusion cell [11,12]. 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 stirrerat 50 rpm. At specified time intervals 5ml of the sample solution was taken and analyzed spectro-photometrically at 255nm. The cumulative % drug release was determined. The cumulative % drug release values were presented in table no.5 and fig no.1.

3. Results and Discussion

Infrared (IR) spectrum of ketoprofen showed characteristic absorption peaks at 1406/cm denoting c-c stretching vibrations of aromatic ring, C = O stretching of carboxylic acid was at 1742.29/cm which is confirmed by the 1760-1690 range vibrations. The absorption peaks at 2940.18 and 2873.53/cm were due to C = H stretching alkanes, 3258.36 vibrations are observed due to OH-peaks due to carboxylic acid. Similar absorption peaks were observed in the IR spectra of physical blend of drug and excipients, showed that there was no shift or disappearance of the characteristic parameter of drug which is represented in fig no. 2.3.

Initially different proportions of stearic acid and tween-80 were selected and added to aqueous and lipid phases to get stable emulsion. The stability of the emulsion was observed for 2 months. The optimized concentration of stearic acid and tween-80 were 3:2. This ratio was taken for further formulations. Various proportions of DMSO concentrations were taken, to study the influence of penetration enhancer on the drug release of ketoprofen from the emulgel formulation. Here glycerine is used as humectants. As ketoprofen is a hydrophobic drug to solubilise drug ethanol is used. The formulations were prepared by simple emulsification method. After preparation of F1 formulation small sample of emulgel was taken on glass slide and observed under microscope for even globule size and presence of drug particles. This gives the evidence that drug is subjected to solubilization in the ethanol. For achievement of homogeneous distribution of drug in the emulgel, solubilization step is essential. Since emulgel formulaion is used for delivering of Hydrophobic drug this crucial step is fulfilled by means of selection of solvent. The prepared formulations were evaluated.

**Physical evaluation:**
All formulations exhibited white color and homogeneous in appearance. They did not show any gritty particles.

**PH measurement:**
PH measurements were done by using a digital PH meter by dipping the glass electrode into the emulgel\cite{15}. The measured values are neutral.

**Rheological study:**
Concentration of DMSO has no influence on the formulation.

**Drug content:**
Drug content of F1-F4 formulations was calculated which shows 84-85% of drug.

**In-vitro drug release:** In-vitro drug release results show that F4 formulation exhibited maximum drug release compared
to other formulations. This may be due to increased proportion of DMSO i.e. 6.5%. khaled et al. Investigated ketoprofen emulgel formulation formulated with carveol, terpne, oleic acid and isopropyl alcohol.

Brajesh Kumar et al. Investigated Penetration enhancing activity of dimethylsulphoxide (DMSO) at 5% w/w and 10% w/w concentration was determined in aqueous solution of Acyclovir and in microemulsion formulations. In this study DMSO was used at a concentration of 4-6.5%. 6.5% containing F4 formulation exhibited highest release compared to F1, F2, F4. A vast array of literature describes the penetration enhancing activities of DMSO, and studies have shown it to be effective in promoting both hydrophilic and lipophilic permeants.

The effects of the Penetration enhancer are concentration dependent. DMSO is widely used to denature proteins, application to human skin has been shown to change the intercellular keratin confirmation, from a helical to β sheet [18,19]. As well as an effect on the proteins, DMSO has also been shown to interact with the intercellular lipid domains of human stratum corneum. Considering the small highly polar nature of this molecule it is feasible that DMSO interacts with the head groups of some bilayer lipids to distort to the packing geometry. Further, DMSO within skin membranes may facilitate drug partitioning from a formulation into this “universal solvent” within the tissue.

In the present work using sodium alginate as gellifying agent four formulations were prepared .various proportions of DMSO is used to study the influence of penetration enhancer on the drug release. F4 formulation exhibited maximum drug release due to presence of more DMSO concentration. Here penetration enhancer has no much influence on the other physicochemical properties but has more influence on the drug release.

### Table 1: Composition of ketoprofen emulgel

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ketoprofen</td>
<td>1.2g</td>
<td>1.2g</td>
<td>1.2g</td>
<td>1.2g</td>
</tr>
<tr>
<td>2</td>
<td>Alcohol</td>
<td>8ml</td>
<td>8ml</td>
<td>8ml</td>
<td>8ml</td>
</tr>
<tr>
<td>3</td>
<td>Stearic acid</td>
<td>3g</td>
<td>3g</td>
<td>3g</td>
<td>3g</td>
</tr>
<tr>
<td>4</td>
<td>Tween-80</td>
<td>2ml</td>
<td>2ml</td>
<td>2ml</td>
<td>2ml</td>
</tr>
<tr>
<td>5</td>
<td>Sodium alginate</td>
<td>2.5 g</td>
<td>2.5 g</td>
<td>2.5 g</td>
<td>2.5 g</td>
</tr>
<tr>
<td>6</td>
<td>Glycerine</td>
<td>4 ml</td>
<td>4 ml</td>
<td>4 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>5 ml</td>
<td>5.5 ml</td>
<td>6 ml</td>
<td>6.5 ml</td>
</tr>
<tr>
<td>8</td>
<td>Sunflower oil</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>9</td>
<td>Distilled water</td>
<td>Qs to 100ml</td>
<td>Qs to 100ml</td>
<td>Qs to 100ml</td>
<td>Qs to 100ml</td>
</tr>
</tbody>
</table>

### Table 2: Viscosity values of F1-F4

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>Viscosity (cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>218523</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>215682</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>214533</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>212342</td>
</tr>
</tbody>
</table>

### Table 3: spreading co-efficient values of F1-F4

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>Spreadability (G-Cm/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>22.53±0.21</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>23.56±0.52</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>22.46±0.65</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>22.23±0.85</td>
</tr>
</tbody>
</table>

Mean±SD, n=3. SD: Standard deviation

### Table 4: % Drug content of F1-F4

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>84.32±0.21</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>83.26±0.32</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>82.31±0.51</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>85.20±0.85</td>
</tr>
</tbody>
</table>

Mean±SD, n=3. SD: Standard deviation

### Table 5: In-Vitro cumulative % drug release of F1-F4

<table>
<thead>
<tr>
<th>S.No</th>
<th>Time (min)</th>
<th>F1 % Cumulative % Drug Release</th>
<th>F2 % Cumulative % Drug Release</th>
<th>F3 % Cumulative % Drug Release</th>
<th>F4 % Cumulative % Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10.56±0.21</td>
<td>11.02±0.87</td>
<td>14.55±0.87</td>
<td>14.55±0.21</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>11.69±0.35</td>
<td>15.23±2.3</td>
<td>15.32±0.95</td>
<td>18.24±0.85</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>13.14±0.65</td>
<td>16.32±8.23</td>
<td>25.78±0.41</td>
<td>25.78±0.95</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>13.18±2.3</td>
<td>20.31±0.12</td>
<td>23.41±0.25</td>
<td>41.84±0.52</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>14.41±0.65</td>
<td>32.41±0.63</td>
<td>48.69±0.23</td>
<td>48.04±0.32</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>36.52±2.5</td>
<td>42.58±0.54</td>
<td>54.89±0.41</td>
<td>56.01±0.51</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
<td>48.25±3.1</td>
<td>59.63±0.58</td>
<td>63.11±0.62</td>
<td>69.32±2.1</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>52.69±0.85</td>
<td>62.54±0.67</td>
<td>74.15±0.15</td>
<td>79.54±2.1</td>
</tr>
</tbody>
</table>

Mean±SD, n=3. SD: Standard deviation

### Figure 1: In-Vitro drug release profiles of formulations F1-F4.

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4. Conclusion
The present study reports for the development of ketoprofen emulgel for topical release of the drug. The results demonstrate that the release of the drug is dependent on concentration of the DMSO used. It can be concluded that the ketoprofen emulgel formulation appears to be the promising system for the topical delivery of ketoprofen to avoid the side effects associated with ketoprofen.

5. Acknowledgements
The authors are greatful to the Narayana Pharmacy College management for providing the facilities to carry out the research work and also to Medreich, India for providing ketoprofen as gift sample.

6. References

