Introduction

Aceclofenac is used as a non-steroidal anti-inflammatory drug indicated for the symptomatic treatment of pain and inflammation, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [1]. Oral administration of aceclofenac is associated with gastrointestinal side effects like gastric ulceration, gastrointestinal bleeding and liver and kidney trouble. Aceclofenac is increasingly administered by topical route. The topical route of administration eliminates side effects, increases patient compliance, avoids first-pass metabolism, and maintains the plasma drug level for a longer period [2]. Aceclofenac has a poor aqueous solubility that may cause a problem with skin permeation [2]. Aim of this study was to formulate topical gel incorporated with solid dispersion of aceclofenac to enhance permeability through skin.
Co-grinding method
Accurately weighed pure drug powder and the carrier were physically mixed for some time. The powder mixture was then ground. Then the sample was collected and kept at room temperature in a screw capped glass vial until use.

| Table 1: Different batches of Aceclofenac solid dispersion |
|---|---|---|---|---|
| Solvent evaporation | Co-grinding |
| F1 | F2 | F3 | F4 | F5 | F6 |
| Aceclofenac | 1g | 1g | 1g | 1g | 1g | 1g |
| PVP K30 | 1:1 | 1:2 | 1:3 |
| HPMC K15 | - | - | - | 1:1 | 1:2 | 1:3 |
| Ethanol | - | - | - | 10 ml | 10 ml | 10 ml |

Evaluation of solid dispersion
The solid dispersion prepared were further studied for percentage practical yield, drug content, in vitro release studies, FTIR and DSC study.

Drug content determination
Solid dispersions equivalent to 10 mg of aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 273 nm by UV spectrophotometer.

Percentage Practical Yield:
Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

\[
PY\% = \frac{\text{Practical Mass (Solid dispersion)} \times 100}{\text{Theoretical Mass (Drug+ Carrier)}}
\]

In vitro dissolution study
In vitro release profiles for each solid dispersion as well as pure drug were performed using USP type II dissolution apparatus. Sample was filled in capsules (F1&F4: 100 mg, F2&F5: 200 mg, F3&F6: 300 mg) & kept in the basket of dissolution apparatus containing 900 ml phosphate buffer pH 7.4 at 37 ± 0.5 ºC and stirred at 50 rpm. Aliquot of 5 ml was withdrawn at time intervals of 0.2, 5, 10, 15, 30, 45 & 60 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the sample was measured 273 nm after suitable dilution using appropriate blank.

Differential Scanning Calorimetry Study (DSC study)
DSC was used to analyze the curves of Aceclofenac, carriers & SDs representing the rates of heat uptake. DSC study was done at IIT Madras.

Preparation Of Gel
Two different gelling agents such a carbopol 934 and HPMC K100 M were used to prepare gels.

Procedure For Preparation Of Gel
Carbopol 934: The formulations were prepared by soaking carbopol 934 and HPMC K100M in different concentrations (0.5,1,1.5,2 %) in 60 ml of water for 24 hrs. Then added glycerol and dimethyl sulfoxide with continuous stirring. The solid dispersion containing 1.5% drug was dissolved in ethanol and this solution was added to the above gel with continuous stirring. The prepared formulations were filled in suitable bottles and stored in cool place.

Table 2: Formation of gel using Carbopol934

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F3C1</th>
<th>F3C2</th>
<th>F3C3</th>
<th>F3C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid dispersion equivalent to 1.5% drug</td>
<td>1.8 g</td>
<td>1.8 g</td>
<td>1.8 g</td>
<td>1.8 g</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Glycerol</td>
<td>5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>0.25 ml</td>
<td>0.25 ml</td>
<td>0.25 ml</td>
<td>0.25 ml</td>
</tr>
<tr>
<td>Distilled water</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
</tr>
</tbody>
</table>

HPMC K100M:
Weighed quantities of Hpmc socked in 60 ml of water for 24hrs and then add glycerin and dimethyl sulfoxide. The solid dispersion containing 1.5% drug was dissolved in ethanol and this dry solution was added to above gel with continuos stirring.

Table 3: Formulation of gel using HPMC K100 M

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F3H1</th>
<th>F3H2</th>
<th>F3H3</th>
<th>F3H4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid dispersion equivalent to 1.5% drug</td>
<td>1.8 g</td>
<td>1.8 g</td>
<td>1.8 g</td>
<td>1.8 g</td>
</tr>
<tr>
<td>HPMC K100 M</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Glycerol</td>
<td>5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
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<td>Dimethyl sulfoxide</td>
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</tr>
<tr>
<td>Distilled water</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
<td>Up to 100 ml</td>
</tr>
</tbody>
</table>

Evaluation of gel
Physical evaluation
The prepared gels were visually inspected for clarity, color and homogeneity.

Determination of pH
pH of formulation determined by dispersing 0.5 gm of gel in 50 ml of water.

Determination of Viscosity
The viscosity of gel formulations were determined using Brookfield’s viscometer.

Determination of Spreadability
Two glass slides of standard dimensions were selected. The gel formulation was placed over one of the slide. The other slide was placed on the top of the gel in such a way that the gel was sandwiched between the two slides. A 20 g weight was kept on the upper slide. The time taken for upper slide to travel and separate away from the lower slide under the influence of weight was noted.

\[
\text{Spreadability} = \frac{\text{M.L}}{T}
\]
M-wt. given on upper slide
L-length of glass slide
T-time taken in sec

Determination of Extrudability
The formulation under study was filled in a clean, aluminum collapsible tube. It was then placed in hardness tester.
plunger was adjusted to hold the tube properly. The pressure was applied for 30 seconds. The percentage of gel extruded was calculated.

**Determination of drug content**

100 mg of gel was dissolved in methanol & filtered and the volume was made to 100 ml with methanol. The resultant solution was suitably diluted with methanol. The absorbance of the resulting solution was measured at 273 nm.

**In-vitro diffusion study**

*In vitro* skin permeation studies were carried out using Franz diffusion cell. Cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated gel was placed over the membrane. The receptor compartment of the diffusion cell was filled with a phosphate buffer. The solution in the receptor compartment was stirred continuously using a magnetic bead at 50 rpm, with the temperature maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content using a UV–Vis spectrophotometer at 273 nm. The receptor compartment was replenished with an equal volume of the same medium. The cumulative percentage diffused was plotted against time.

**Ex vivo skin permeation studies**

*Ex vivo* release study was conducted using fresh chicken skin from slaughter house. The skin was soaked in phosphate buffer pH 7.4 solution for 5-6 hours and washed with water. The dermis was dried at 25% RH, wrapped in aluminium foil and stored in freezer until further use.

For *ex vivo* permeation studies, skins were allowed to hydrate for 1 hour before being mounted on the Franz diffusion cell with the stratum corneum facing the donor compartment. The sample was applied on the skin and then fixed in between donor and receptor compartment of Franz diffusion cell. Required quantity of phosphate buffer (pH 7.4) was placed in the receptor compartment and the temperature of the medium was thermostatically controlled at 37±10 °C by the surrounding water jacket and the medium was stirred. Aliquots of 1 ml were withdrawn at predetermined intervals and were spectrophotometrically estimated at 273 nm.

**Cloth staining study**

This study was undertaken to assess the fabric staining property of the gels. Fabrics of different fiber blends ranging from 100% cotton to 100% polyester were procured and stained with 0.5 gm gels of Aceclofenac and observed for staining after washing.

**Stability study**

For stability study, the gel sample were stored at 40°C, 60% RH, in stability chamber. The physical appearance, pH value, Viscosity and drug content were periodically analysed for 1 month.

**Comparative study of optimized gel with prepared Aceclofenac gel**

Selected formulation was compared with prepared gel of Aceclofenac. The aceclofenac gel was prepared using a gel base and diffusion study of gel is done for 12 hrs and is compared with the optimized solid dispersion incorporated gel of aceclofenac.

**Results and Discussion**

**Preformation Studies**

**Drug-Excipient Interaction Study Using FTIR Spectroscopy**

The FTIR spectra of Aceclofenac, physical mixture I (aceclofenac+ PVP k30), physical mixture II (Aceclofenac + HPMC k15 LV) is recorded to check any interaction between drug and polymer. The characteristic peak obtained after FTIR indicates that there is no chemical interaction between drug, PVP K30, and HPMC K15 LV.

![Fig 1: FTIR Spectra of Aceclofenac](image1)

![Fig 2: FTIR spectra of Aceclofenac and HPMC E15 LV](image2)

![Fig 3: FTIR Spectra of Aceclofenac and PVP K30](image3)

**Preparation of solid dispersions**

Solid dispersions using different ratios of Aceclofenac and carriers such as PVP K30 and HPMC E15 LV is prepared by solvent evaporation and co-grinding method.

**Evaluation of Solid dispersions**

**Drug content**

The percentage drug content of the formulations were analyzed using UV spectroscopy. All formulation shows a percentage drug content between 77.68% to 97.09%.
Percentage practical yield
The results of Percentage practical yield for all formulations of solid dispersions were found to be 89.09 to 95.46%

In-vitro drug release study
The in-vitro release studies of different batches of solid dispersions are shown in Fig: 4. The solid dispersion prepared by solvent evaporation method in the ratio 1:3 shows improved dissolution when compared with pure drug and co-grinding method. The formulation F3 shows greater solubility than the others.

The study reveals that there is increase in the dissolution rate of all the Aceclofenac solid dispersions when compared to pure aceclofenac itself (Fig no.4). This may be due to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. From the In-vitro drug release profile, it can be seen that formulation F3 containing PVP K30 (1:3 ratio of drug: PVP K30) shows higher dissolution rate compared with other formulations. The increase in dissolution rate is in the order of F3 >F6>F2 >F4>F1>F5.

DSC Study
In the DSC study, pure Aceclofenac showed a sharp endothermic peak at 153.8 °C corresponding to the melting point of drug and the sharpness of peak indicates crystalline nature of the drug. The carrier PVP K30 showed endothermic peak at 82.2 °C. The DSC curve of physical mixture of the drug and carrier (PVP K30) showed two broad endothermic peaks, one peak at 64.3 °C corresponding to carrier and the other peak at 126.0 °C corresponding to drug. The peak temperature in the physical mixture were slightly shifted with respect to the drug and carrier alone. In case of Aceclofenac solid dispersion (1:3 ratio of drug & carrier), the endothermic peak were broadened and shifted towards a lower temperature (66.3 °C) with reduced intensity. The DSC thermogram revealed the diminishing of the characteristic peak of the drug. This may due to the uniform distribution of drug in the polymer, resulting its better solubilization in the carrier and conversion of crystalline to amorphous form.

Preparation Of Gels
Topical gels incorporated with optimized aceclofenac solid dispersion(F3) were prepared using different concentrations of gelling agents such as Carbopol 934 & HPMC K100 M Eight formulations were prepared and the prepared gel formulations were optimized on the basis of evaluation studies.

Evaluation of Topical Gels Incorporated With Aceclofenac Solid Dispersion
Physical evaluation
The prepared gel formulations were examined visually. All batches of gel formulations showed good homogeneity with absence of lumps.

Determination of pH
The pH of all the prepared gel formulations were found to be in the range of 6.2 – 7.3 which lies in the normal pH range of skin.

Determination of viscosity
The measurements of viscosity of the prepared gels were done with a Brookfield Viscometer. Viscosities were found to be proportional to the concentration of the gelling agent.

Cloth staining
This study is very important to ascertain the patient compliance of the gels. Patients generally resist gels as they stain clothes. It was observed that all the eight gels did not stain any of the fibre blends tested, even after prolonged exposure and accelerated drying.
Determination of spreadability
The value of spreadability indicates the degree of shear required to apply the gel. Lesser the time taken for separation of two slides, better the spreadability. Values of spreadability indicate that the gel formulations are easily spreadable.

Determination of extrudability
Extrudability of all the formulations is higher than 80%. All the formulations showed good acceptance properties. The extrusion of the gel from the tube is an important parameter during its application and in patient acceptance.

Drug content
The drug content of formulations was in the range of 88.90-96.66 %.

In-vitro diffusion study
In-vitro drug release study was performed by Franz diffusion cell method using phosphate buffer pH 7.4. From the data obtained it was found that the prepared topical gel of carbopol 934 of concentration 1(F3C2) releases 68.54 % drug by in-vitro diffusion study over a period of 8 hrs.

Stability study
The selected formulation (F3C2) were subjected to stability testing. Changes in the appearance, pH, viscosity, and drug content of the gel were investigated at a period of 1 month. From the data obtained, no significant changes in physical appearance, viscosity, pH & drug content were seen. This indicates the stability of prepared gel formulation

Comparative study of optimized topical gel with prepared Aceclofenac gel
It was found that the cumulative percentage of drug diffused from optimized formulation (F3C2) of topical gel incorporated with aceclofenac solid dispersion is higher than that of plain aceclofenac gel(Fig 11). Hence, it proves that the solid dispersion improves solubility and thereby permeation of the drug.

Fig 9: In-vitro diffusion study using cellophane membrane
Formulation batch F3C2 showed good release profile compared to other formulations prepared by using Carbopol 934 & HPMC K100 M. Increase in concentration of gelling agent leads to decreased drug release from formulations which may be due to increase in viscosity of formulation.

Ex-vivo drug permeation study
Ex-vivo study was also done for the gel formulations prepared by using two gelling agent such as carbopol 934 & HPMC K100 M. Fig 10 show graphical presentation of release profile. The cumulative amount of drug permeated at the end of 8 hrs was found to be (63.63%) for formulation F3C2(gelling agent Carbopol 934 of concentration 1%) which was found to be higher than that of other formulations.

Conclusion
Carbopol 940 topical gel containing Aceclofenac solid dispersion was successfully prepared. These formulated gels showed sustained permeation of Aceclofenac over 8h in ex vivo skin permeation study. The gels were characterized by pH, viscosity, extrudability and cloth staining tests. FTIR study clearly indicated the absence of any significant interaction between the drug, Aceclofenac and other excipients present in the formulation.

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Conflict of interest
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References


