# Development And Evaluation of Topical Gel of Diclofenac Sodium Using Niger Seed Oil

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***Abstract-*** *The present research has been undertaken with the aim to develop a topical gel formulation of Diclofenac sodium using gelling agent Carbopol in different concentration, which would attenuate the gastrointestinal relater toxicities associated with oral administration. Niger seed oil used as penetration enhancer.Carbapol940 & Niger seed oil Combination was used to construct the topical gel for improving the viscosity of for topical administration. By using gelling polymers various batches were prepared. The formulation optimized by $3^2$ factorial design and evaluated for viscosity, spreadability, skin permeability, stability. In-vitro permeation of the prepared topical gel. They were evaluated for physicochemical properties such as homogeneity, viscosity, pH, Spreadability, drug content, in vitro drug release, stability studies. The in vitro drug release rate of gel was evaluated using Franz diffusion cell containing cellophane membrane with phosphate buffer pH 7.4 as the receptor medium. Studies showed that drug release was reduction with increase in gelling agent concentration because polymer concentration increases, viscosity increases. Drug was involved from site of application as long as it remains in higher concentration gelling agent in solution form.*

***Keywords***- Diclofenac Sodium, Carbopol, Niger oil, Anti-inflammatory activity.

## I. INTRODUCTION

Transdermal drug delivery system attracts many scientists around the world. There has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery (transdermal delivery) of drugs. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. There are a number of routes by which a molecule can cross the stratum corneum; these are intercellular, transcellular and appendageal but the intercellular route is considered to be the major pathway for permeation of most drugs across the stratum corneum.(Benson et al.,2005)

Transdermal delivery of drugs promises many advantages over oral or intravenous administration. Some of the potential advantages include: avoidance of first-pass metabolism, elimination of gastrointestinal irritation resulting from some drugs, reduced dosing frequency and rapid termination of drug action. However, the success of a transdermal drug delivery system depends on the ability of the drug to penetrate the skin in sufficient quantities to maintain therapeutic level. The principal barrier to most transdermal drug delivery is the stratum corneum. Many strategies have been suggested in order to overcome the low permeability of drugs through the skin.

Diclofenac sodium (DFS) is nonsteroidal anti-inflammatory drugs used to relieve the inflammation, swelling, stiffness and joint pain associated with rheumatoid arthritis, osteoarthritis (the most common form of arthritis) and ankylosing spondylitis (arthritis and stiffness of the spine). It is extensively metabolized in the liver and because of its short biological half life the drug has to be given frequently but it has been known to cause peptic ulcers and bleeding with prolonged administration Therefore, developing a therapeutic system to provide a transdermal delivery is beneficial.( Shaila et al., 2005)

Niger (Guizotia abyssinica) is an oil seed crop cultivated in Ethiopian and Indian. It constitutes about 50% of Ethiopian and 3% of Indian oil seed production. In Ethiopia it is cultivated on water logged soils where most crops and all other oil seeds fail to grow and contributes a great deal soil conservation and land rehabilitation. The genus guizotia consist of six species of which five including Niger, are native to the Ethiopian high lands. It is dicotyledonous herb, moderately to well branched and growth up to 2m tall. The seed contains about 40% oil. Its fatty acid composition is 75%-80% linoleic acid,7-8% palmitic and stearic acid,5-8% oleic acid. The Indian types contain 20% oilic and 50% linoleic acid . Niger seed is indigenous to Ethiopia where it is grown in rotation with cereals and pulses.( Belayneh et al., 1987)

## II. LITRATURE SURVEY

The study of two topical diclofenac products (diclofenac diethylamine [DEA] 1.16% emulsion and diclofenac sodium [Na] 5% gel The quantitative evaluation of skin permeability and the qualitative evaluation of their physical characteristics were performed. A topical diclofenac product with a higher concentration of the active ingredient does not necessarily lead to greater absorption relative to a product with lower concentration of the active ingredient but different characteristics. These observations highlight the importance of considering parameters beyond drug concentration, such as composition, which may influence the solubility of the drug and permeation of topical non-steroidal anti-inflammatory drugs (Julie Pradal et al (2019).

Thymoquinone which shows, the major constituent of *Nigella sativa* oil has been found to have a promising topical anti-inflammatory activity; however, exaggerated heat and photosensitivity and lipophilicity prevent the best use of this promising product.. The gel formulation was clear with suitable skin permeation and exhibited acceptable rheological properties.( Mahmoud et al (2018)

## III. MATERIALS AND METHODS

**2.1Material** :

Diclofenac sodium was procured from Research lab chem industries, Mumbai, *Niger seed oil* (V.S Natural Agro Foods, Nashik) ,carbapol 940(Research lab chem industries, Mumbai.),Tween 80 (Research lab chem industries, Mumbai.),glycerin (Research lab chem industries, Mumbai.) TEA(Research lab chem industries, Mumbai.), methyl paraben (Research lab chem industries, Mumbai.) propyl paraben(Research lab chem industries, Mumbai.)

**2.2Methods**:

All substances collecting first as per requirement of formulation as Diclofenac sodium, *Niger* seed oil, Carbapol 940,Tween 80,Glycerin, Preserved water, Distilled water, Triethanolamine.

Topical gel is done by using the cold method, dispersion method, Flocculation method, Chemical reaction, temperature effect. All of it we used the cold method for topical gel. Cold method is all ingredients mixed together and formation of a homogeneous mass under low temperature at about $50^0$C.

Firstly weighed Carbapol and added *niger* oil as per quantity required is taken its solution A. It stirred well under mgnetic stirrer for some time at room temperature. Nextly in solution B the another beaker the drug and one by one the remaining ingredients are added are Tween80,Glycerin, In this preserved water are made mixture of methyl paraben and propyl paraben. Finally added triethalonamine and then add solution B to A put it on stirring by lastly adding distill water as per requirement placed upto formation of homogeneous mass. At room temperature. (Saroha et al., 2013)

The gels are prepared by using different proportions of formulations :

Formulation No oil, F1 to F4

| Ingredients | NO oil | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| DICLOFENAC SODIUM(mg) | 1000 | 1000 | 1000 | 1000 | 1000 |
| Niger oil(ml) | 0 | 3 | 3 | 3 | 2 |
| Carbapol 940 | 500 | 250 | 500 | 375 | 500 |

Formulation F5 to F9

| Ingredients | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|
| DICLOFENAC SODIUM(mg) | 1000 | 1000 | 1000 | 1000 | 1000 |
| Niger oil(ml) | 1 | 2 | 2 | 1 | 1 |
| Carbapol 940 | 375 | 250 | 375 | 500 | 250 |

Other ingredients are used are for same quanity :

| Ingredients | Quantity |
|---|---|
| Glycerin(ml) | 2 |
| Tween 80(ml) | 0.2 |
| TEA(ml) | 0.2 |
| Methyl paraben(mg) | 0.02 |
| Propyl paraben(mg) | 0.02 |

Distilled water used as quantity suffiecient in each formulation

**2.3. Optimization of topical gel***:*

A $3^2$ factorial design was used to investigate the combined influence of three levels, two factor variables on the formulation of Diclofenac sodium topical gel. In the design two factors were evaluated, each at three levels shown in table and experimental trials were performed at all nine possible combinations table. The concentration Of Carbapol940 (X1) & *Niger* oil (X2) was selected as the independent variables.

Drug release % & Viscosity of the gel was selected as the dependent variables. These two factors that might affect the design characteristics of the Gel formulation were over three levels and arranged according to a $3^2$ full factorial design. Then the equation generated by this experimental design (using Design expert 11) was used to study two independent variables factors of the dependent variables response.

**2.4 Characterization of topical gel:**

**2.4.1.pH***:*

The pH of the topical gel formulation was determined in triplicate. The calibrated digital pH meter was used to determine the pH of the solution. The average reading was taken.

**2.4.2.Clarity:**

The clarity of the topical gel was determined before and after gelation by visual examination of the formulation under light alternatively against white and black backgrounds.

**2.4.3.Rheological Study:**

The viscosity of the topical gel was determined by using Brookfield viscometer (Brookfield DV-II Pro). Rheological characterization of optimized gel was done by placing the sample in the sample tube at 37± $5^0$C rotating spindle number 64 at 50 rpm. Controlled stress rate study was conducted to get information about the flow behavior with changes in speed of spindle (rpm).( Satyabrata et al.2013)

**2.4.4. Drug content:**

The drug content was determined by taking the 100mg of the gel and dissolved it into the suitable solvent i,e (7.4 pH phosphate buffer) again diluted with the methanol. The concentration was determined by using the double beam UV spectrophotometer at 277 nm. Drug content of formulation was determined in triplicate and average reading was calculated.( Naresh et al., 2008)

**2.4.5. In-vitro Skin permeation study:**

The diffusion studies of the prepared gels were carried out by using Franz diffusion cell apparatus for studying the dissolution release of gels through a cellophane membrane. Gel sample (equivalent to 50 mg) was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 20 ml of phosphate buffer (pH 7.4) as the dissolution medium. Two milliliters of each sample was withdrawn periodically at 15, 30, 60, 120, 180, 240 and 300min and each sample was replaced with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using 7.4 phosphate buffer as blank at 277nm using UV spectrophotometer(Vanna et al., 2009)

**2.4.6. Spreadability:**

Spreadability of the gel was evaluated by using Brookfield texture analyzer. For instance, a lipid rich gel will have decreased spreadability values with an increase in viscosity and surface tension (a measure of cohesiveness), making the gel greasy, tacky and difficult to spread. The lower the viscosity of a gel, the lower the surface tension and the more the gel is easily spread and absorbed into the skin.( Vrushika et al., 2017)

**2.4.7. DSC:**

DSC study was performed to check whether drug is added incorporated in the formulation. Also this study performed to check the interaction among the various excipients used into the formulation.( Divvela et al.,2017)

**2.4.8. FTIR:**

FTIR study was performed to check whether drug is incorporated in the formulation. Also this study performed to check the interaction among the various excipients used into the formulation.( Dheeraj et al .,2013)

**2.4.9. SEM study:**

Morphology of the gel was performed by using of the scanning electron microscopy**.** SEM used was of (Carl Zeiss Supra 5, Germany)Company and this study is helpful for the determining uniformity and homogeneity(M.E. Palomo et al., 1999 and Dilip et al., 2012)

## III. RESULTS AND DISCUSSION

**3.1. Preformulation Study**

**A)** Preliminary Evaluation and characterization of drug

The preliminary characterization of drug physical properties of drug was evaluated (table ). All the characteristics match with the standard results.

**Table.1:** Preliminary Evaluation and characterization of drug:

| Sr.no | Characteristics | Observation |
|---|---|---|
| 1 | Colour | White |
| 2 | Odour | Odourless |
| 3 | Appearance | Amorphous |

**B) Melting Point:**

The average melting point of Diclofenac sodium was determined by capillary method was found to be. This is in good agreement with reported and it matches with the reported value.

**C) Determination of the absorption maxima of Diclofenac sodium(λmax) and calibration curve :**

UV spectrum for Diclofenac sodium in 7.4 Phosphate buffer is shown in figure. It shows absorbance maxima at 277 nm Figure.1.

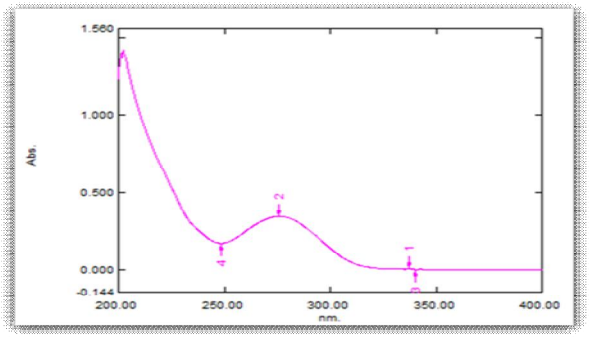



**Figure.1 Absorption maxima of Diclofenac sodium.**

The calibration curve of Diclofenac sodium was plotted in methanol at 277 nm. The equation obtained was y = 0.031x + 0.041. The correlation coefficient was found to be 0.998 as shown in *Figure.2*.

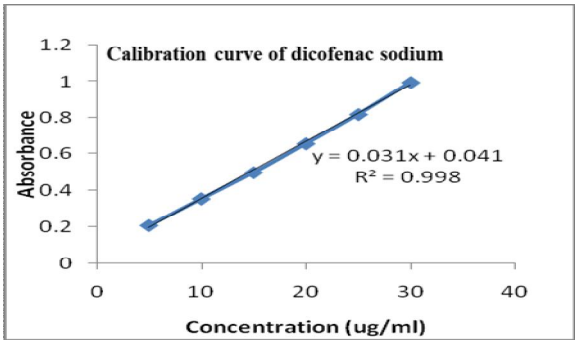
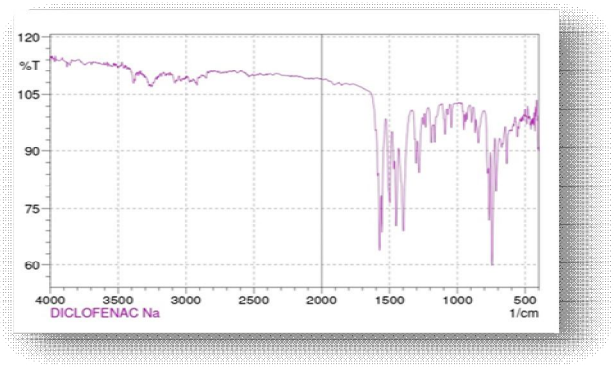



**Figure.2 Calibration curve Of Diclofenac sodium**

**3.2. Infrared Spectroscopy**

IR Spectrum was taken by FTIR and graph is shown in **figure (3)** and table shows peak and it gives conformity of structure of drug. Infrared band at around 1573 $cm^{-1}$ (C=O stretch ), 3300 $^{cm-1}$ (NH strech) , 1303$^{cm-1}$ (C-N stretch ) and 752$^{cm-1}$(C-Cl stretch) peak are observed.




**3.3.Differential Scanning Calorimetry (DSC)**

The thermo gram of drug was characterized by melting endothermic peak at 270$^0$C Thus the DSC thermo gram of drug was found to be agreement to the specification.

DSC analysis were performed to find out the physical nature of diclofenac sodium entrapped in the gelatin microsphere and also to confirm absence of drug–polymer interaction. The thermo gram of diclofenac sodium showed **(Figure. 4)**

**3.4. Optimization of topical gel:**

A $3^2$ factorial design was used to investigate the combined influence of three levels, two factor variables on the formulation of Diclofenac sodium topical gel. In the design two factors were evaluated, each at three levels shown in table and experimental trials were performed at all nine possible combinations table. The concentration Of Carbapol940 (X1) & *Niger* oil (X2) was selected as the independent variables. 9 batches given by design was prepared and evaluated for the further characterization.

**3.5. Characterization of Topical gel**

Topical gel was evaluated for various parameters like colour, pH, Homogeneity, viscosity, drug content for its characterization. The results obtained from this study were shown in **table.2.** Colour of formulated gel was found milky white.

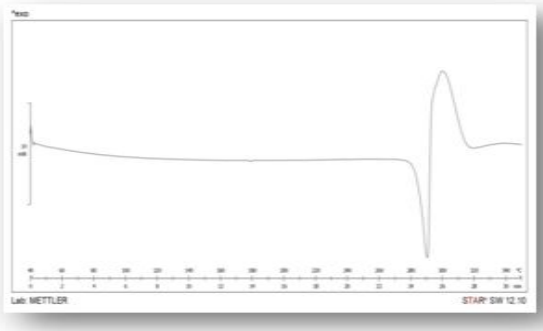


**Table 2. Characterizations of diclofenac sodium gels formulations**

| Formulation | Homogeneity | pH | Viscosity | Drug content |
|---|---|---|---|---|
| F1 | Yes | 6.55±0.23 | 7708±1.08 | 89.32±1.20 |
| F2 | Yes | 6.54±0.12 | 7850±2.05 | 89.36±0.52 |
| F3 | Yes | 6.16±0.57 | 7788±1.09 | 90.84±0.85 |
| F4 | Yes | 6.20±0.24 | 6355±5.7 | 84.61±1.13 |
| F5 | Yes | 6.34±059 | 5459±1.4 | 77.79±1.00 |
| F6 | Yes | 6.74±0.35 | 6169±2.9 | 83.31±0.76 |
| F7 | Yes | 6.31±0.19 | 6279±3.8 | 84.54±1.05 |
| F8 | Yes | 6.57±0.11 | 5598±5.3 | 74.38±1.32 |
| F9 | Yes | 6.28±0.61 | 5368±1.7 | 75.36±1.41 |
| No oil | Yes | 6.12± 0.31 | 4821± 2.8 | 58.37±1.30 |

*All values are expressed as mean ±SD(n=3)

All developed gel formulations were homogeneous in texture in pH range 6.12 to 6.74 in which the normal skin pH of healthy people. Gels show uniform Homogeneity for all batches. The all batches showed good homogeneity with absence of lumps. Viscosity shows optimum flow property of gel formulation. The viscosities of gel ranged from 5368 to 7850 cps. The viscosity gel formulation it reflects in consistency. The drug content of the formulation was in the range of 58.37 to 90.84 mg/ml of gel which indicates uniformity content.

### 3.5.1. In-vitro Skin permeation study

In drug release study of formulation No oil, F1 to F9 are shows results in Table.3 and Table.4 The *In- vitro* diffusion study done by using the Franz diffusion cell by using the phosphate buffer 7.4. The drug release of drug has shown altered and controlled. Formulation F2 was found to be optimal since it exhibited greater controlled release (96%) in opposed to the other formulations.

**Table 3.Diffusion of Topical gel Diclofenac sodium: NO OIL, F1 to F4 (pH =7.4)**

| Time(min) | NO | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 4.74±0.15 | 10.46±0.78 | 11.61±0.12 | 10.98±0.32 | 10.37±0.73 |
| 30 | 8.5±0.16 | 20.77±1.31 | 15.26±0.73 | 20.69±2.46 | 31.75±1.04 |
| 60 | 12.37±0.20 | 28.19±0.41 | 25.91±2.06 | 29.00±1.61 | 41.13±2.40 |
| 120 | 30.63±4.33 | 42.30±0.85 | 44.32±1.52 | 41.78±3.04 | 52.14±3.15 |
| 180 | 37.54±3.47 | 54.15±1.20 | 65.93±0.97 | 59.40±2.73 | 67.75±1.35 |
| 240 | 57.25±1.90 | 76.08±0.70 | 81.82±1.56 | 77.58±2.62 | 78.91±1.00 |
| 300 | 67.38±1.43 | 93.97±0.33 | 96.27±0.19 | 94.83±0.95 | 89.71±4.24 |

*All values are expressed as mean ±SD(n=3)

**Table 4.Diffusion of Topical gel Diclofenac sodium: F5 to F9 (pH =7.4)**

| Time(min) | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 6.39±0.26 | 10.30±0.33 | 6.16±0.07 | 5.10±0.11 | 6.20±1.15 |
| 30 | 18.36±2.63 | 21.99±1.95 | 14.78±1.81 | 33.07±5.97 | 11.69±1.18 |
| 60 | 33.17±3.83 | 30.18±1.28 | 23.31±0.81 | 41.30±3.98 | 24.99±2.24 |
| 120 | 43.57±4.40 | 51.84±2.89 | 35.71±4.40 | 58.80±3.01 | 44.42±0.28 |
| 180 | 55.66±1.14 | 60.19±3.14 | 53.48±4.27 | 67.33±1.73 | 54.78±0.40 |
| 240 | 63.48±1.31 | 73.47±2.22 | 62.17±3.13 | 74.84±1.08 | 64.25±1.87 |
| 300 | 79.63±0.42 | 84.01±1.23 | 84.18±2.10 | 82.37±0.33 | 75.39±1.61 |

*All values are expressed as mean ±SD(n=3)

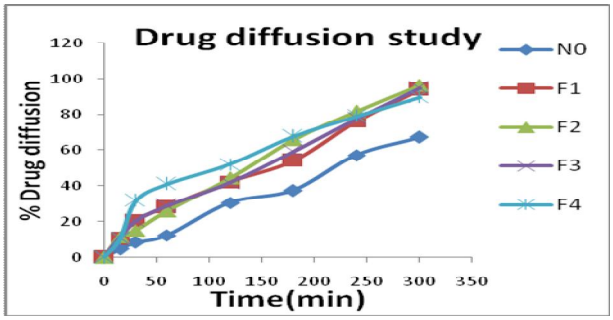



**Figure.5:** Drug diffusion study of without oil(No) andF1-F4.

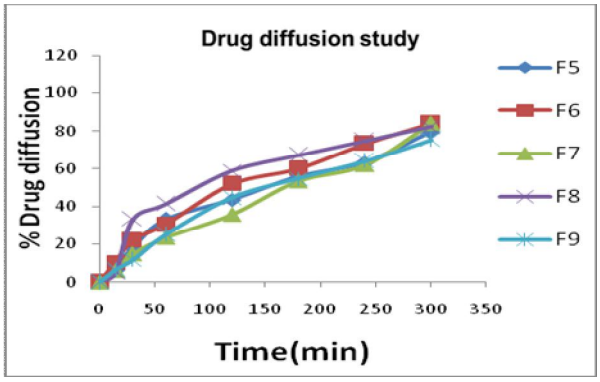



**Figure.6:** Drug diffusion study F5-F9

### 3.5.2. Spreadability:

Results obtained for Spredability study of optimized formulation were shown in **figure7**

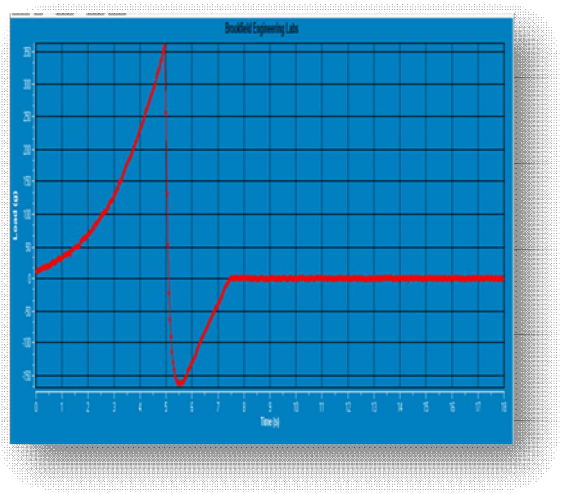


**Figure.7.** Texture profile analysis spectra of gel

The given spectra of topical gel formulation from optimized batch formulation**(F2).** Results of gel showed that the area under the positive curve is a measure of the energy required to deform the sample to the defined distance. Research has shown that the firmness and energy required for deforming a sample to a defined depth grades samples in order of spreadability as shown in fig.7. A higher peak load (firmness) and hardness work done value indicated a less spreadable sample. Conversely, a lower peak load (firmness) value coupled with a lower hardness work done value indicated a more spreadable sample.

### 3.5.3. Infrared spectroscopy

Analysis of pure drug and optimized formulation (F2) containing diclofenac sodium and other excipients respectively The spectrum of diclofenac sodium showed an intense, well defined peak, Infrared band at around 1573 cm-1 (C=O stretch ), 3300 cm-1 (NH strech) , 1303cm-1 (C-N stretch ) and 752cm-1(C-Cl stretch) peak are observed.

The Overlay of Diclofenac sodium and optimized topical gel (F2) were shown in **figure 8**. Infrared spectra of optimized formulation showed the characteristic peaks of the pure drug diclofenac sodium. From the above interpretation, it is found that there is no shifting in the frequencies of above said functional groups. Hence, above result conclude that no drug and excipients interaction were found.

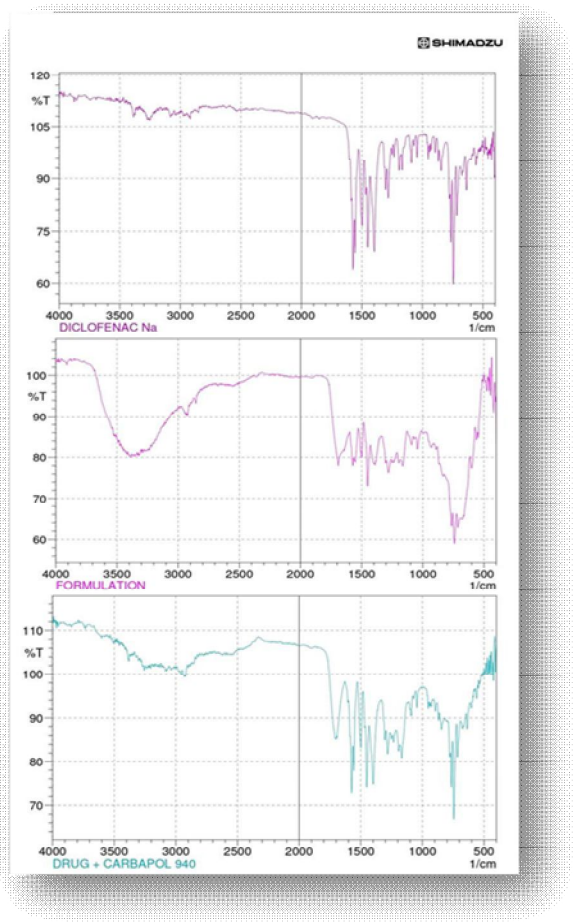
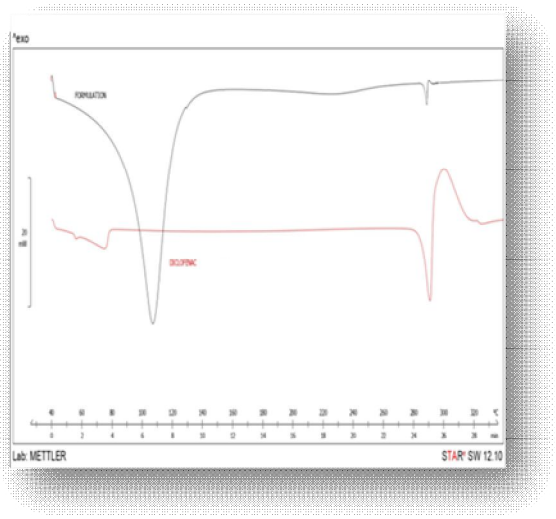



**Figure .8.FTIR overlay of Diclofenac sodium & Formulation**

### 3.5.4.DSC

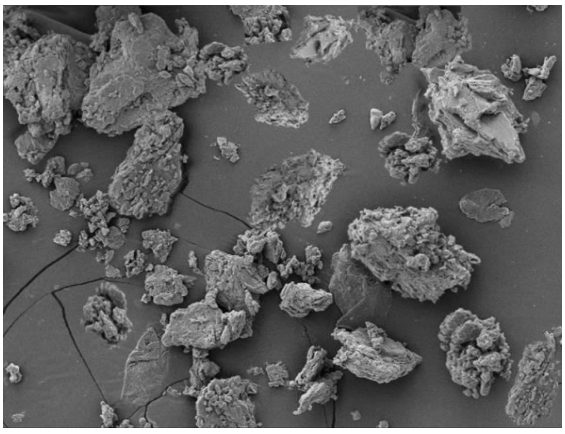
Differential Scanning Calorimetry (DSC) results for plain drug, formulation are shown in **Figure.9.**



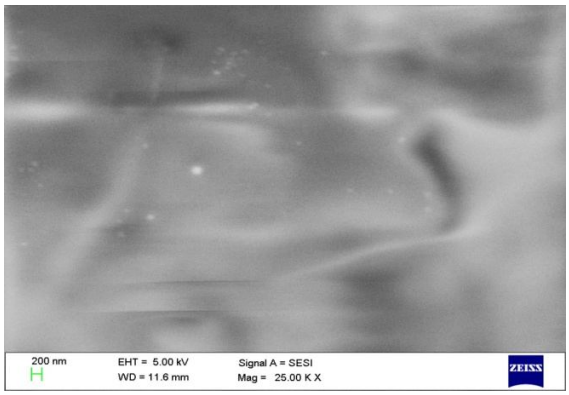

In Figure .9. Gives diclofenac sodium peak at $290^0$C the peak is obtained. The formulation gives the peak at $110^0$C but there is the slight shifting to lower melting points suggests the possibility of formation of an eutectic mixture. Thus, the consistency of the thermo grams of the formulation with that of the pure drug indicates that no structural changes occurred for diclofenac sodium. This investigation confirms the the rapid permeation of diclofenac sodium from the prepared gels could be attributed to the absence of interaction between the drug and the formulation.

### 3.5.5. SEM

SEM image of optimized gel at two magnification level are shown in **figure A and B.**



**(a) DICLOFENAC SODIUM**




**(b) FORMULATED GEL**

**Figure.10.SEM image of optimized gel at various magnification level a) at 1000x and b) at 25000x**

The range of gel of molecule was found within the nanometer range. The micrograph also shows different ranges uniformity and homogeneity.SEM was done by (Carl Zeiss Supra 5, Germany) Company. The given gel shows no sign of drug precipitation was observed inferring the stable nature of formed dispersion; therefore the drug is uniformly spreads to the gel formulation.

## IV. CONCLUSION

The developed gel formulation improved the skin permeability of gel. Diclofenac sodium topical gel with Carbapol 940& Niger oil. Carbapol 940 produces better Consistency and Spredability to the formulation. The resulting gel Niger oil concentration increases were increasing in drug release. Oil used as penetration enhancer which shows resulting in skin permeability. The formulation F2 batch optimized shows good skin permeability having good drug content.

## V. ACKNOWLEDGEMENTS

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