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# FORMULATION AND EVALUATION OF EMULGELS CONTAINING ETODOLAC

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## ABSTRACT

Emulgel is a novel drug delivery system with dual control release. Etodolac is a hydrophobic, BCS class-II, anti-inflammatory drug used in the treatment of rheumatoid-arthritis with half-life 4-6 hours. The present study is aimed at reducing gastro-intestinal related toxicities associated with oral administration of Etodolac, and also to improve drug release, permeation, selective absorption of drug at site of action and for enhancing stability. In this study, the effect of various gelling agents and penetration enhancers are also aimed to be studied. Two gelling agents used are carbopol and HPMC. Physical evaluation and rheological studies were done to determine the best gelling agent for preparation of emulgel and it was found that carbopol was a better gelling agent. Hence, further studies to find out the effect of penetration enhancer was done using carbopol as gelling agent. Two penetration enhancers used are propylene glycol and oleic acid. Optimization studies have been done by Design Expert software using Box-Behnken design. 17 formulations were prepared. All the formulations were evaluated for physical appearance, viscosity, pH, spreadability, extrudability, drug content and *in vitro* drug release. All the formulations showed results within acceptable range. The optimized formulation F4 showed drug release 95.4% and spreadability 30g.cm/sec. Kinetic studies, stability and skin-irritation studies were conducted on the optimized formulation. Mechanism of drug release was found to be zero-order and non-fickian super case-II transport. The stability and skin-irritation studies of optimized formulation confirmed that the formulation was stable and safe for use in animals.

**KEYWORDS:** Emulgels, etodolac, anti-inflammatory, carbopol, HPMC, optimization.

## INTRODUCTION

Topical formulations of non-steroidal anti-inflammatory drugs have been used and studied as an alternative to oral forms used in the treatment of arthritis. Emulgels are emulsions, either oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. Emulgel is a novel drug delivery system having characteristics of dual control release, i.e., emulsion as well as gel. Emulgels have advantage over other topical dosages in delivery of hydrophobic drugs.[1]

Etodolac is a highly lipophilic anti-inflammatory drug used in rheumatoid arthritis. It is a BCS class II drug with poor water solubility and high permeability. It is having less bioavailability and biological half-life of 4-6 hours.[2]

The present study is aimed at reducing the gastro-intestinal related toxicities associated with oral administration of acidic drugs, also to improve the drug release, permeation, selective absorption of drug at site of action and for enhancing the stability. Different topical dosage forms of etodolac such as gels are available in market, but emulgel is said to have more drug release and stability. Etodolac is an acidic drug having poor bioavailability and short half-life .This particular study is being aimed to reduce the gastro-intestinal side effects of Etodolac. So it is aimed to be formulated as an emulgel. In this study the effect of various gelling agents and penetration enhancers are also aimed to be studied so as to improve the drug release, penetration and absorption of the drug at the site of action, thereby enhancing its stability.

## 1. MATERIAL AND METHODS

### 1.1. Chemicals used

Etodolac (Yarrow Chem Products, Mumbai), Carbopol (Loba Chemie, Mumbai), HPMC (Loba Chemie, Mumbai), Liquid paraffin (Spectrum Reagents and Chemicals, Cochin), Span 20 (Burgoyne Burdidges & Co, Mumbai), Tween 20 (Burgoyne Burdidges & Co, Mumbai), Propylene glycol (Spectrum Reagents and Chemicals, Cochin), Oleic acid (Finar reagents, Ahmedabad), Methyl paraben (Loba Chemie, Mumbai), Triethanolamine (Spectrum Reagents and Chemicals, Cochin).

### 1.2. Instruments used

Double beam UV Spectrophotometer (Systronics, UV-VIS Spectrophotometer117, Ahmedabad), FT-IR (Jasco model FT/IR 4100), Digital pH meter (Roy instruments, Varanasi), Brookfield viscometer (LVDV Prime-1, Brookfield Engineering Laboratory, USA).

### 1.3. Formulation of Etodolac emulgel

- **Preparation of gel**

The gel is prepared by dispersing the gelling agents, *ie*.,carbopol and HPMC separately in purified water with continuous stirring. Then the pH was adjusted to 6-6.5 using triethanolamine.

- **Preparation of emulsion**

The oil phase of emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl paraben was dissolved in penetration enhancer, *ie*., propylene glycol or oleic acid and ETD was dissolved in ethanol separately, and both solutions were added to the aqueous phase. The oily and aqueous phases were separately heated between 70° to 80°C. The oily phase was then added to the aqueous phase with continuous stirring followed by cooling to room temperature.

- **Preparation of emulgel**

The emulgel was obtained by mixing gel and emulsion in ratio 1:1.[3]

Four formulations with different gelling agents *ie*, carbopol and HPMC were prepared.

**Table 1: Formulation of Etodolac emulgel - Effect of gelling agent.**

| Sl No. | Ingredients (in g / ml) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| 1 | Etodolac | 1.0 | 1.0 | 1.0 | 1.0 |
| 2 | Carbopol | 1.5 | 3.0 | ---- | ---- |
| 3 | HPMC | ---- | ---- | 1.5 | 3.0 |
| 4 | Ethanol | 2.5 | 2.5 | 2.5 | 2.5 |
| 5 | Liquid Paraffin | 7.5 | 7.5 | 7.5 | 7.5 |
| 6 | Span 20 | 1.5 | 1.5 | 1.5 | 1.5 |
| 7 | Tween 20 | 1.0 | 1.0 | 1.0 | 1.0 |
| 8 | Propylene glycol | 5.0 | 5.0 | 5.0 | 5.0 |
| 9 | Methyl paraben (mg) | 0.3 | 0.3 | 0.3 | 0.3 |
| 10 | Triethanolamine | 1.0 | 1.0 | 1.0 | 1.0 |
| 11 | Purified water q.s. | 100.0 | 100.0 | 100.0 | 100.0 |

This formulation design is used as a preliminary step to find out which gelling agent should be used for further studies to prepare emulgel and to find out the effect of different penetration enhancers.

Design Expert Stat Ease Software was used to design formulations. Seventeen formulations with different penetration enhancers *ie*, propylene glycol and oleic acid were suggested by the software. The formulation is shown in table 2:

**Table 2: Formulation of Etodolac emulgel - Effect of penetration enhancer.**

| INGREDIENTS (in g or ml) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 | F17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Etodolac | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Carbopol 940 | 1.5 | 3.0 | 1.5 | 3.0 | 1.5 | 3.0 | 1.5 | 3.0 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 |
| Ethanol | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Liquid Paraffin | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Span 20 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Tween 20 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Propylene glycol | ---- | ---- | 5.0 | 5.0 | 2.5 | 2.5 | 2.5 | 2.5 | ---- | 5.0 | ---- | 5.0 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Oleic acid | 2.5 | 2.5 | 2.5 | 2.5 | ---- | ---- | 5.0 | 5.0 | ---- | ---- | 5.0 | 5.0 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Methyl paraben (mg) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Triethanolamine | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Purified water q.s. | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

### 1.4. Analytical Methods

#### 1.4.1. Determination of UV λ max

Dissolve accurately weighed 100mg of Etodolac in 100ml of phosphate buffer pH 7.4 in 100ml standard flask to get 1mg/ml from the stock solution of Etodolac, 1ml is pipetted out and diluted to 100ml with ethanol to get 10µg/ml. The absorption maximum of standard solution of Etodolac is determined by scanning the

resulting stock solution in UV spectrometer at 200 - 400 nm. The absorption maxima obtained is compared with reference standard for the value.

#### 1.4.2. Preparation of Standard Calibration Curve of Etodolac

10 mg of Etodolac was accurately weighed and taken in 100 ml clean and dry volumetric flask containing 80 ml of solvent and then the solution was made upto the mark using the solvent. This is considered as standard solution (100µg/ml). 1 ml of stock solution was pipetted out and made upto 10 ml to get a concentration 10µg/ml, treated as working standard. The stock solution of Etodolac was subsequently diluted to a series of dilutions containing 2, 4, 6, 8 and 10 µg/ml of solution using 0.2M phosphate buffer of pH 7.4. The absorbance of these solutions was measured in UV-visible spectrophotometer at 228 nm against some dilution as blank. A calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.[4]

### 1.5. Preformulation studies

#### 1.5.1. Solubility Studies

Solubility of etodolac was observed in different solvents such as distilled water, 95% ethanol, 0.1N sodium hydroxide solution, 0.1N hydrochloric acid solution and phosphate buffer pH 7.4.[5]

#### 1.5.2. Identification of melting point

Melting point of drug was determined using Melting point apparatus and compared with official monograph.[6]

#### 1.5.3. Organoleptic Properties

Physical appearance of drug was observed and compared with official monograph.[6]

#### 1.5.4. Partition coefficient (Kp)

The partition coefficient of drug was determined by shaking equal volumes of organic phase (n-octanol) and the aqueous phase in a separating funnel. A drug solution of 1 mg/ml was prepared in phosphate buffer pH 7.4 and 50ml of this solution was taken in a separating funnel and shaken with an equal volume of n-octanol for 10 minutes and allowed to stand for 24 hours with intermittent shaking. Then, the concentration of etodolac in aqueous phase was determined by using a UV spectrophotometer at 228 nm to get partition coefficient value. [5]

The partition coefficient (Kp) was calculated using the equation,

$$Kp = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

#### 1.5.5. Drug-excipient interaction studies

FT-IR spectra of pure drug, carbopol, HPMC and their physical mixtures were taken by KBr pellet technique between 600 – 4000 $cm^{-1}$. This is to ensure that there is no incompatibility between drug and gelling agents. Once spectra was recorded, the peaks of pure drug, gelling agents and physical mixtures of gelling agents and drug were compared for incompatibility.[7]

### 1.6. Evaluation of Etodolac Emulgels

#### 1.6.1. Physical Appearance

The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation.[3]

#### 1.6.2. Rheological Studies

Viscosity (in Cps) of prepared emulgel formulations were determined using Brookfield viscometer with spindle no. 63 at a speed of 50 rpm and this was repeated 3 times. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25º ± 1ºC) before the measurement was taken. Spindle was lowered perpendicular into the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.[3]

#### 1.6.3. pH determination

1g of emulgel was accurately weighed and dispersed in 100ml of distilled water and it is placed for 2 hours. The pH of dispersion was measured by using a digital pH meter. The measurement of pH of each formulations were done in triplicates and average values were calculated.[3]

#### 1.6.4. Spreadability

Spreadability of formulation was determined by using an apparatus designed and developed in laboratory especially for project. Two rectangular glass plates of same dimension were selected. 0.5g of sample was placed on one of the glass plate. Second plate was placed over the other one to sandwich sample between plates. A 20g weight was placed on top of upper plate to provide a uniform thin film of sample between the plates. Weight was removed; excess of emulgel sample was scrapped off from edges .The top plate was then subjected to pull by using string to which 50g weight was added. The time required by upper plate to travel a distance of 6cm and separate from lower plate was noted. This was repeated for 3 times. A shorter interval indicates better spreadability.[3]

$$Spreadablility = \frac{M.L}{T}$$

*M = weight tied to the upper side; L = length of glass slide; T = time in seconds*

#### 1.6.5. Extrudability

The developed formulations were filled in collapsible metal tubes and crimped at one end. After removing the cap, tube is pressed to extrude the product from the tube.[3]

#### 1.6.6. Drug content determination

Drug content of emulgel was determined by dissolving an accurately weighed quantity of 1g of emulgel in 100ml solution of phosphate buffer pH 7.4. 2ml of this solution was diluted to 10ml with buffer solutions. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer and analyzed for drug content at 228nm. Drug content was determined from standard curve of Etodolac.[3]

#### 1.6.7. *In vitro* drug release of Etodolac Emulgel

Diffusion study of emulgel formulations were performed using Franz-diffusion cell. Cellophane membrane was used in Franz-diffusion cell. The cell was locally fabricated and volume of receptor compartment was 20ml. Phosphate buffer of pH 7.4 was used for *in vitro* release as receptor medium. The emulgel sample was applied on the membrane and then fixed in between donor and receptor compartment of quality diffusion cell. The receptor compartment contained phosphate buffer pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37º ± 0.5ºC by surrounding water in jacket and the medium was continuously stirred by magnetic stirrer at speed of 50 rpm. Aliquots, each of 1ml were withdrawn at hourly intervals and replaced by an equal volume of receptor medium for 12hrs. The aliquots were diluted to 10ml with receptor medium and analysed by UV spectrophotometer at 228 nm and % drug release was calculated.[3]

#### 1.6.8. Optimization by Design Expert Stat Ease Software

Statistical design of experiments, a computer-aided optimization technique, was used to identify critical factors, their interactions and ideal process conditions that accomplish the targeted response. The best formulation was determined using Design Expert Stat Ease Software. Box-Behnken design was used for the optimization. In the study, carbopol, propylene glycol and oleic acid were selected as the three factors and spreadability and *in vitro* drug release were considered as the two responses. Hence, seventeen experimental trials were done. Countour plots were drawn and optimum formulation was selected by optimization criteria. The emulgel with high penetration and drug release was fixed as QTPP(Quality Target Product Profile), spreadability and *in vitro* drug release data were set as the CQA (Critical Quality Attribute) and carbopol, propylene glycol and oleic acid were selected as the CMA (Critical Material Attribute).[8]

#### 1.6.9. Drug release kinetics

Cumulative drug release study of the optimized formulation, F4 was fitted into models representing zero order, first order, Higuchi's plot and Korsmeyer-peppas plot respectively.[3]

#### 1.6.10. Stability Studies

From the prepared etodolac emulgels, optimized formulation with highest *in vitro* drug release pattern and drug content was packed in aluminium collapsible tubes (5g) and subjected to stability studies. This study was carried out at temperature and humidity conditions as per ICH guidelines and the tests were carried out in a stability chamber. The temperature and humidity conditions used were, 40ºC ± 2ºC at 75% ± 5% RH; 25ºC ± 2ºC at 60% ± 5% RH; 5ºC ± 3ºC.

Samples were withdrawn at 0 day and 30 day time intervals for a period of 3 months and evaluated for physical appearance, pH, drug content and *in vitro* drug release.[3]

#### 1.6.11. Skin irritation Studies

The protocol for skin irritation studies for optimized formulation was presented before the Institutional Animal Ethics Committee (IAEC) and was approved with approval no – **CCPS/ IAEC/ 2021/01**. The rats (n=18) were randomly divided into three equal groups for application of marketed formulation containing Etodolac, blank formulation and optimized emulgel containing Etodolac. Hairs were removed by hair removal cream from an area ($2cm^2$) on the dorsal side of the albino rats to make a hairless area. A blank formulation without the drug Etodolac was applied on the rats of Group I (n=6). The marketed formulation containing Etodolac was applied on the rats of Group II (n=6). The optimized formulation containing Etodolac was applied on the rats of Group III (n = 6) for assessing any kind of irritation at specified sites. Formulation was removed after 24 hours and skin was examined for any sign of erythema/ oedema/ any other skin changes. Skin irritation is evaluated in 1$^{st}$, 24$^{th}$ and 48$^{th}$ hour after patch removal. The skin irritation were studied for a period of 14 days and noted.[9]

**Table 3: Score rating for skin irritation study.**

| S. No. | Score | Rating |
|---|---|---|
| 1 | 0 | Nil |
| 2 | 0 – 2 | Mild |
| 3 | 2 – 4 | Moderate |
| 4 | 4 – 6 | Severe |
| 5 | 6 and above | Very severe |

## 3. RESULTS AND DISCUSSION

### 3.1. Analytical method

#### 3.1.1. Determination of UV λ max

The pure drug of etodolac was scanned by UV spectroscopy and λmax was found to be 228 nm.

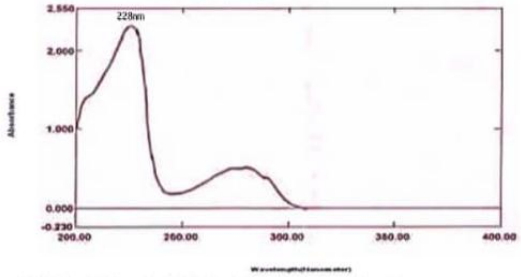


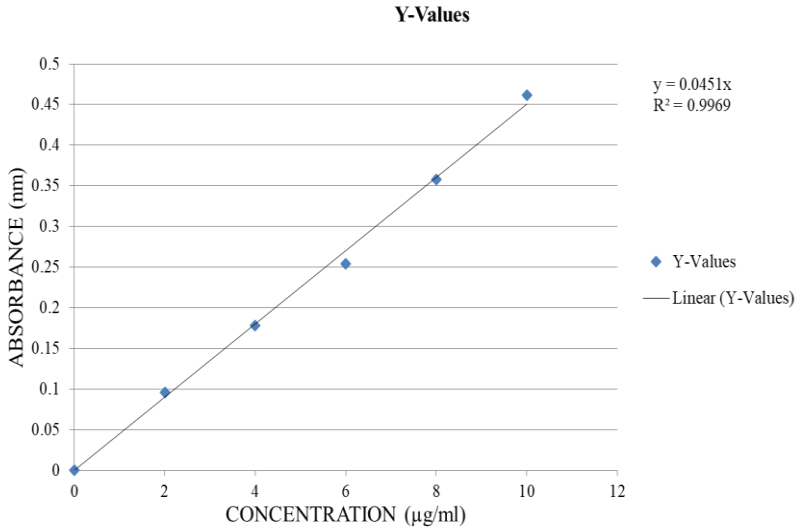

**Fig. 1: UV spectrum of Etodolac in phosphate buffer pH 7.4.**

### 3.1.2. Calibration curve of Etodolac

**Table 4: Absorbance values for Etodolac.**

| Concentration (µg/ml) | Absorbance (at 228nm) ± SD |
|---|---|
| 0 | 0 ± 0.03 |
| 2 | 0.096 ± 0.01 |
| 4 | 0.178 ±0.04 |
| 6 | 0.254 ±0.02 |
| 8 | 0.358 ±0.03 |
| 10 | 0.462 ±0.01 |

**Standard calibration curve of Etodolac**




*All values are expressed as a mean of ± SD, n = 3*

**Fig. 2: Standard calibration curve of Etodolac in phosphate buffer pH 7.4 at 228nm.**

The drug was scanned in UV region (200-400 nm) by preparing 1mg/ml solution using phosphate buffer pH 7.4 to find out wavelength of maximum absorption (λ max). The λmax was found to be 228 nm. So the standard calibration curve of Etodolac was developed at this wavelength. Standard calibration curve of Etodolac was determined in phosphate buffer pH 7.4 by plotting absorbance against concentration at 228 nm. The calculation of drug content, *in vitro* release and stability studies are based on this calibration curve.

### 3.2. Preformulation studies

### 3.2.1. Solubility profile

Solubility of drug in different solvents were carried out as shown in table:

**Table 5: Solubility of Etodolac.**

| Medium | Solubility |
|---|---|
| Water | Insoluble |
| Ethanol | Soluble |
| 0.1N HCl | Insoluble |
| 0.1N NaOH | Soluble |
| Phosphate buffer pH 7.4 | Soluble |

### 3.2.2. Determination of Melting Point

Melting point was carried out using melting point apparatus. Temperature was noted at which drug changes to liquid and it was found to be 145 ± 1ºC.

### 3.2.3. Physical Appearance

Etodolac is white crystalline powder and is odourless.

### 3.2.4. Partition Coefficient

The partition coefficient of etodolac in n-octanol phosphate buffer system was found to be 2.5 ± 0.001.

### 3.2.5. Identification and Compatibility by FTIR studies

FTIR studies were conducted in pure etodolac, carbopol, HPMC and their physical mixture. The FTIR spectrum is shown below:

**Table 6: FTIR peaks of Etodolac.**

| Peaks ($cm^{-1}$) | Groups |
|---|---|
| 3344.41 | N-H stretching |
| 3075.47 | C-H stretching |
| 1451.05 | C-C stretching |
| 1206.54 | C-O stretching |
| 960.59 | C-O stretching |

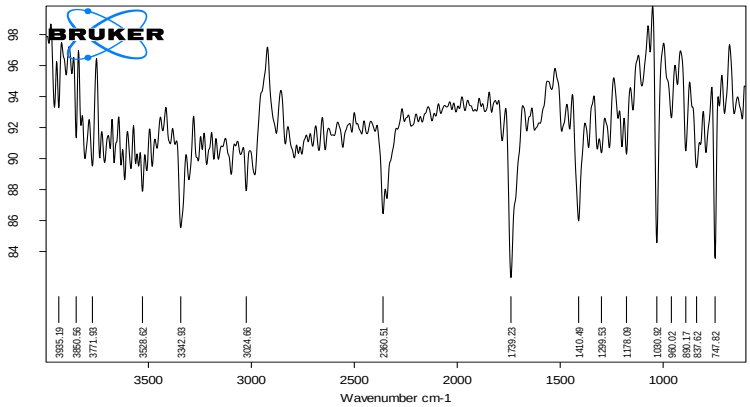



**Fig. 3: FTIR spectrum of Etodolac.**

**Table 7: FTIR peaks of physical mixture (Etodolac + Carbopol).**

| Peaks ($cm^{-1}$) | Groups |
|---|---|
| 3441.12 | N-H stretching |
| 2924.18 | C-H stretching |
| 1498.12 | C-C stretching |
| 1183.14 | C-O stretching |
| 990.32 | C-H bending |

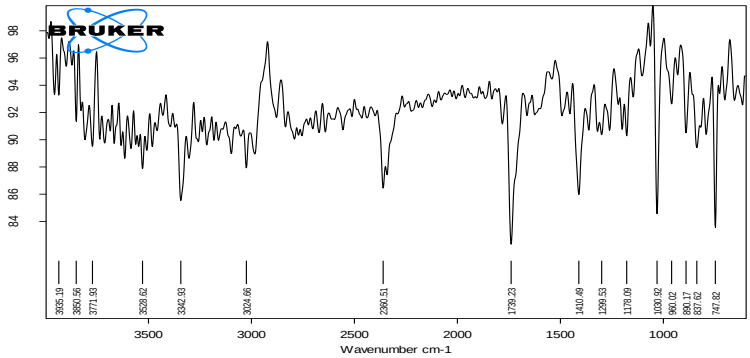



**Fig. 4 : FTIR spectrum of physical mixture (Etodolac+Carbopol).**

**Table 8: FTIR peaks of physical mixture (Etodolac + HPMC).**

| Peaks ($cm^{-1}$) | Groups |
|---|---|
| 3382.56 | N-H stretching |
| 3012.36 | C-H stretching |
| 1462.55 | C-C stretching |
| 1192.24 | C-O stretching |
| 974.98 | C-H bending |

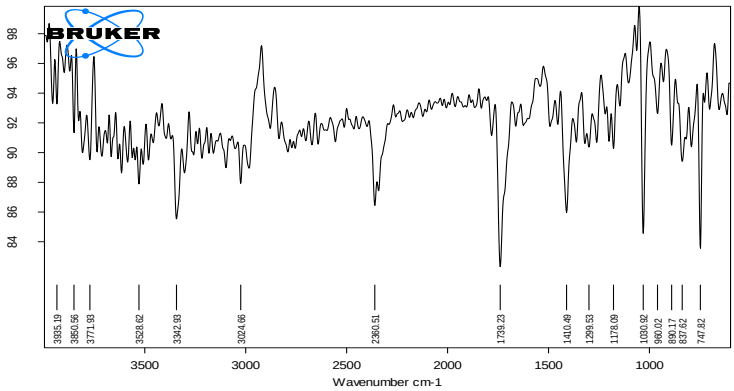



**Fig. 5: FTIR spectrum of physical mixture (Etodolac + HPMC).**

Drug identification is done by performing melting point determination and FT-IR studies. From the result, the melting point of drug was found to be 145ºC which complies with the official standard indicating the purity of sample. During FT-IR studies, the peak of Etodolac was obtained at 3344.41 $cm^{-1}$, 3075.47 cm-$^{1}$, 1451.05 $cm^{-1}$, 1206.54 $cm^{-1}$, 960.59 $cm^{-1}$. There is no significant change in the peak of the pure drug in the FTIR spectrum of physical mixture of pure drug with the gelling agents, ie., carbopol and HPMC. It indicates that there is no chemical interaction between the drug and the gelling agents. This shows that Etodolac was compatible with both the gelling agents.

### 3.3. Evaluation of formulated emulgels

#### 3.3.1. Physical Evaluation

**Table 9: Physical evaluation of formulations-Effect of gelling agents on the formulation design.**

| Formulation code | Colour | Homogeneity | Consistency | Phase separation |
|---|---|---|---|---|
| T1 | White | Excellent | Excellent | No Phase Separation |
| T2 | White | Excellent | Excellent | No Phase Separation |
| T3 | Off-white | Poor | Poor | Phase Separation |
| T4 | Off-white | Poor | Poor | Phase Separation |

The emulgels prepared using carbopol as gelling agent were white in colour having excellent consistency and homogeneity in appearance and had no phase separation. The emulgels formulated using HPMC as gelling agent was off-white in colour and had poor homogeneity and consistency. They also showed phase separation.

**Table 10: Physical evaluation of formulations- Effect of penetration enhancers on the formulation design.**

| Formulation code | Colour | Homogeneity | Consistency | Phase separation |
|---|---|---|---|---|
| F1 | White | Excellent | Excellent | No |
| F2 | White | Excellent | Excellent | No |
| F3 | White | Excellent | Excellent | No |
| F4 | White | Excellent | Excellent | No |
| F5 | White | Excellent | Excellent | No |
| F6 | White | Excellent | Excellent | No |
| F7 | White | Excellent | Excellent | No |
| F8 | White | Excellent | Excellent | No |
| F9 | White | Excellent | Excellent | No |
| F10 | White | Excellent | Excellent | No |
| F11 | White | Excellent | Excellent | No |
| F12 | White | Excellent | Excellent | No |
| F13 | White | Excellent | Excellent | No |
| F14 | White | Excellent | Excellent | No |
| F15 | White | Excellent | Excellent | No |
| F16 | White | Excellent | Excellent | No |
| F17 | White | Excellent | Excellent | No |

All the prepared emulgel formulations were white in colour having excellent consistency and homogeneity in appearance and had no phase separation.

#### 3.3.2. Rheological studies

Rheological studies were conducted on formulation.

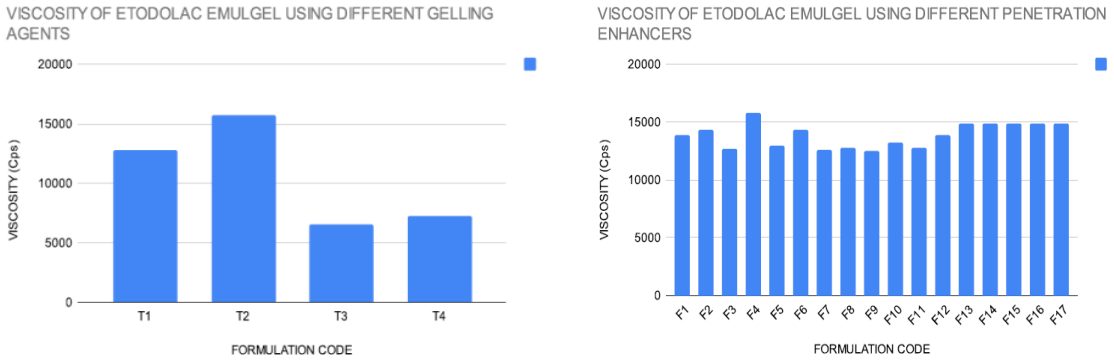



**Fig. 6: Viscosity of formulations using different (a) gelling agents (b) penetration enhancers.**

- **Effect of gelling agents**

The rheological behaviour of all formulated emulgels were studied using Brookfield viscometer at a speed of 50 rpm and spindle no. 63 was used. The viscosity of emulgels prepared using carbopol as gelling agent were found to be in the range of 12,000- 21,000 Cps. The emulgels prepared using HPMC as gelling agent had lesser viscosity when compared to the formulations prepared using carbopol as gelling agent. Hence, further evaluation studies were done on formulations prepared using carbopol as gelling agent.

- **Effect of penetration enhancers**

The rheological behavior of all formulated emulgels was studied using Brookfield viscometer at a speed of 50rpm and spindle no. 63 was used. The viscosity of all the emulgel formulations were found to be in the range of 12,000- 21,000 Cps.

### 3.3.3. pH determination

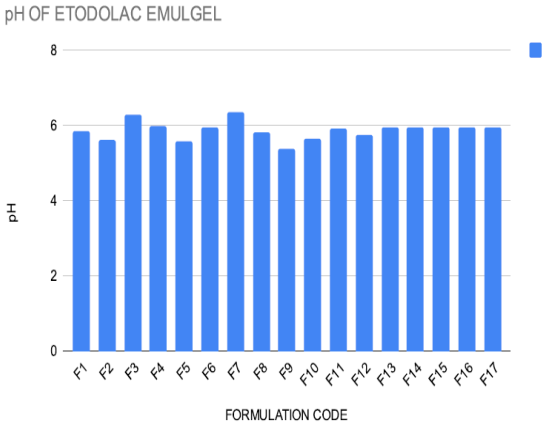



**Fig. 7: pH of formulations.**

The pH values of all prepared formulations ranged 5.5-6.5 which lies within normal pH range of skin and was considered acceptable to avoid any irritation upon application to the skin.

### 3.3.4. Spreadability studies

The spreadability of formulations were studied using apparatus fabricated in our laboratory:

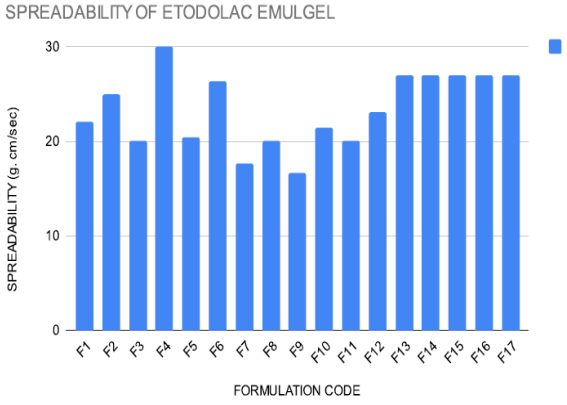



**Fig. 8: Spreadabilty of formulations.**

Spreadability of formulations were in range of 16-30 g.cm/sec, indicating good spreadability.

### 3.3.5. Extrudability studies

The extrudability of the formulations were studied and the results are shown below:

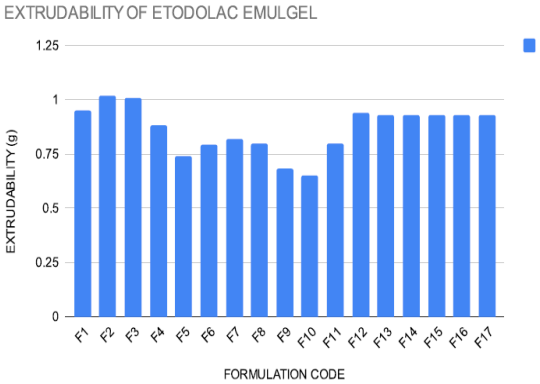



**Fig. 9: Extrudability of formulations.**

The extrusion of emulgel from tube is important during its application. Emulgel with high consistency may not extrude from tube where as less viscous emulgel may flow quickly and hence suitable consistency is required to extrude emulgel from the tube. Extrudability of emulgel was found to be good.

### 3.3.6. Drug content determination

Drug content of formulated emulgels were determined by UV spectrophotometer at λ max 228 nm and the results of drug content of each formulation was given in the table below:

**Table 11: Drug content of formulations.**

| FORMULATION CODE | DRUG CONTENT (%) |
|---|---|
| F1 | 89.32 ± 0.169 |
| F2 | 86.3 ± 0.324 |
| F3 | 85.79 ± 0.69 |
| **F4** | **91.2 ± 0.784** |
| F5 | 90.4 ± 0.45 |
| F6 | 83.4 ± 0.369 |
| F7 | 80.65 ± 0.423 |
| F8 | 81.6 ± 0.965 |
| F9 | 79.36 ± 0.147 |
| F10 | 84.6 ± 0.025 |
| F11 | 85.4 ± 0.014 |
| F12 | 84.9 ± 0.365 |
| F13 | 85.3 ± 0.95 |
| F14 | 85.3 ± 0.95 |
| F15 | 85.3 ± 0.95 |
| F16 | 85.3 ± 0.95 |
| F17 | 85.3 ± 0.95 |

*All values are expressed as a mean of ± SD, n = 3*

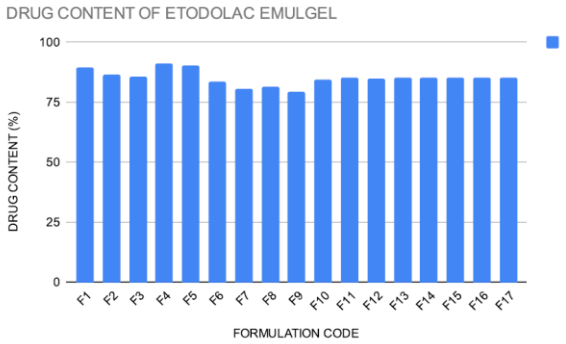



**Fig. 10: Drug content of formulations.**

Drug content of formulated emulgel was estimated by UV spectrophotometer at λmax 228 nm and the drug content was calculated from calibration curve. Among all the 17 formulations, F4 showed greater drug content, *ie.*, 91.2%.

### 3.3.7. In vitro drug release studies

*In vitro* drug release of formulations were determined using Franz-diffusion cell fabricated in our laboratory and the results are given below:

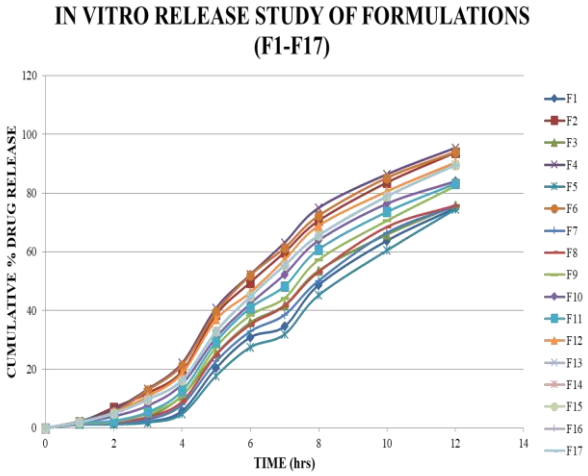



**Fig. 11: *In vitro* drug release of formulation.**

The *in vitro* drug release of all the 17 formulations were determined using Franz diffusion cell. Among all the formulations, F4 showed greater *in vitro* drug release (95.4%) than all other formulations.

### 3.3.8. Optimization by Design Expert Software

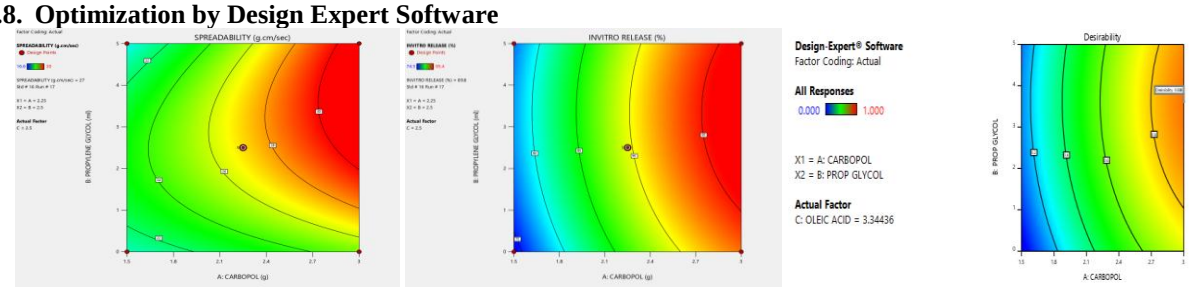



**Fig. 12: Countour plot showing the effect of carbopol and propylene glycol on (a) spreadability (b) *in vitro* drug release (c) desirability**

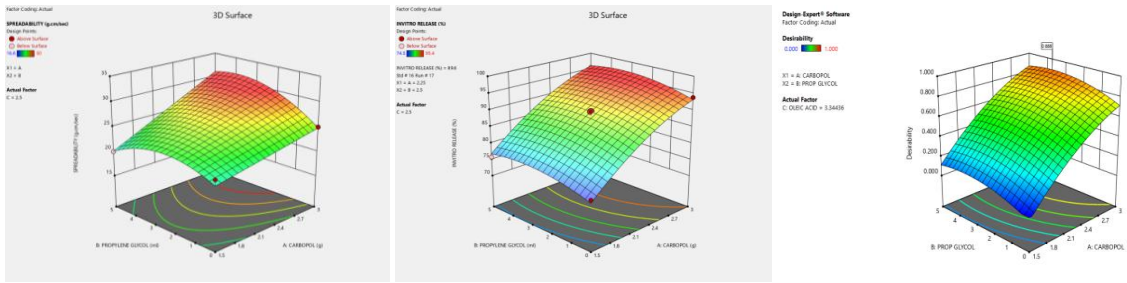



**Fig. 13: 3-D surface response plot showing the effect of carbopol and propylene glycol on (a) spreadability (b) *in vitro* drug release (c) desirability.**

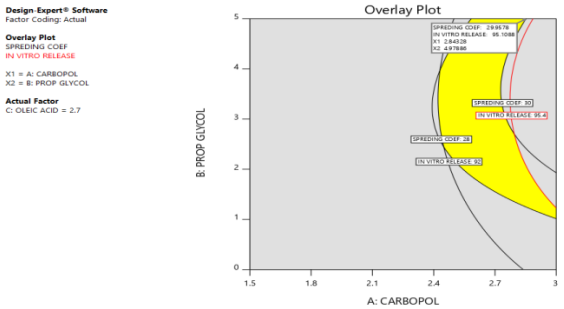



**Fig. 14: Overlay plot.**

Optimization was done by Design Expert Stat Ease Software version 13.0.7.0. 3 factors were selected for optimizing the formulation. The factors selected were carbopol, propylene glycol and oleic acid. Box-Behnken design was used for optimization. To determine the best formulation, 2 responses ie., spreadability and *in vitro* drug release were considered.17 formulations were suggested by the software. After the analysis of the optimized data, 10 solutions were obtained and one was selected by considering the spreadability and *in vitro* drug release of the formulation.

The batch with carbopol- 3g, propylene glycol- 5ml and oleic acid- 2.5ml with desirability 1 was found to be optimum. From this data, formulation F4 was selected as the optimized formulation having highest spreadability (30g.cm/sec) and *in vitro* drug release (95.4%).

Hence F4 was selected as optimized formulation.

**Fig. 15: Photograph of optimized formulation - F4.**

Out of 17 formulations prepared, the formulation F4 was found to be the optimized formulation. The data obtained from drug release profile was fitted into various models to determine the drug release kinetics and mechanism.

### 3.3.9. Drug release kinetics

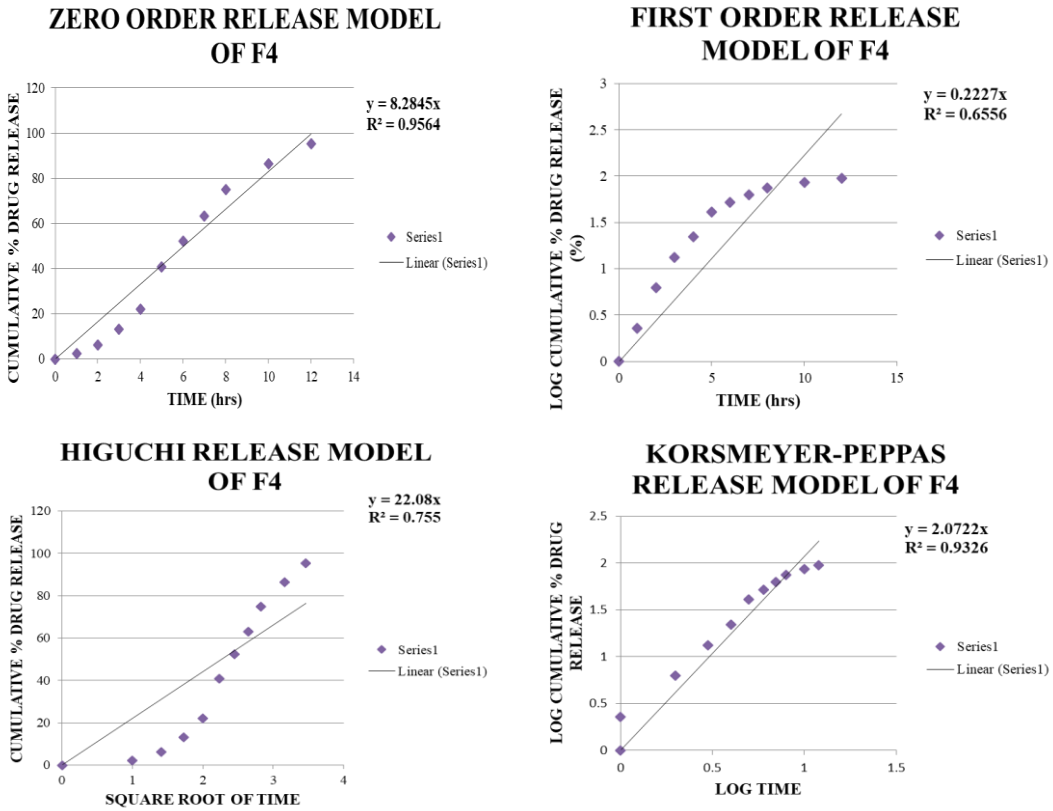



**Fig. 16: (a) Zero order release plot (b) First order release plot (c) Higuchi release plot (d) Korsmeyer-peppas plot.**

**Table 12: Drug release kinetics of optimized formulation - F4.**

| Formulation code | Zero order | First order | Higuchi | Korsmeyer-peppas | |
|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n |
| F4 | 0.9564 | 0.6556 | 0.755 | 0.9326 | 2.0722 |

In F4, correlation coefficient of zero order kinetics was found to be 0.9564, first order release kinetics was 0.6556 and Higuchi plot was found to0.755. Hence the formulation follows zero order kinetics. To confirm the exact mechanism of drug permeation from emulgel, data was fitted according to Korsmeyer-peppas plot. The value of slope of plot n gives indication of release mechanism when n=1, release is independent of time ie zero order. If n= 0.5, then release is fickian diffusion. If n=0.5 -1, diffusion is non-fickian and n>1 then it is super case transport. The 'n' exponent value of best batch was 2.0722. Hence it shows non-fickian super-case II transport mechanism.

### 3.3.10. Stability studies

**Table 13: Stability data of optimized formulation - F4.**

| FORMULATION CODE | STORAGE CONDITION | SAMPLING INTERVAL | APPEARANCE | pH | DRUG CONTENT (%) | IN VITRO DRUG RELEASE (%) |
|---|---|---|---|---|---|---|
| F4 | 40ºC ± 2ºC at 75% ± 5%RH | 0 day | White | 5.99 ± 0.25 | 91.2 ± 0.784 | 95.4 |
| | | 30 days | White | 5.99 ± 0.23 | 91.1 ± 0.764 | ----- |
| | | 60 days | White | 5.99 ± 0.23 | 90.8 ± 0.96 | ----- |
| | | 90 days | White | 5.99 ± 0.22 | 90.5 ± 0.854 | 94.1 |
| | 25ºC ± 2ºC at 60% ± 5% RH | 0 day | White | 5.99 ± 0.25 | 91.2 ± 0.784 | 95.4 |
| | | 30 days | White | 5.99 ± 0.25 | 91.2 ± 0.772 | ----- |
| | | 60 days | White | 5.99 ± 0.24 | 91.0 ± 0.74 | ----- |
| | | 90 days | White | 5.99 ± 0.23 | 90.9 ± 0.68 | 95.2 |
| | 5ºC ± 2ºC | 0 day | White | 5.99 ± 0.25 | 91.2 ± 0.784 | 95.4 |
| | | 30 days | White | 5.99 ± 0.25 | 91.0 ± 0.699 | ----- |
| | | 60 days | White | 5.99 ± 0.24 | 90.9 ± 0.657 | ----- |
| | | 90 days | White | 5.99 ± 0.24 | 90.8 ± 0.64 | 94.2 |

*All values are expressed as a mean of ± SD, n = 3*

From the prepared 17 formulations, the optimized formulation F4 was used for stability studies as per ICH Guidelines for 3 months. It showed that the prepared emulgel passed stability studies with no much significant changes in physical appearance, pH, drug content and *in vitro* drug release.

### 3.3.11. Skin irritation studies

Skin irritation study on rats showed that after application of the optimized formulation there was no evidence of irritation (erythema and oedema). Hence, the optimized formulation F4 was found to be safe.

**Table 14: Formulations applied on animal skin.**

| Sl. No | Group | Name of the formulation administered | Number of animals |
|---|---|---|---|
| 1 | Group I | Blank formulation | 6 animals |
| 2 | Group II | Marketed formulation containing Etodolac | 6 animals |
| 3 | Group III | Optimized formulation of emulgel containing Etodolac | 6 animals |
| | | | |

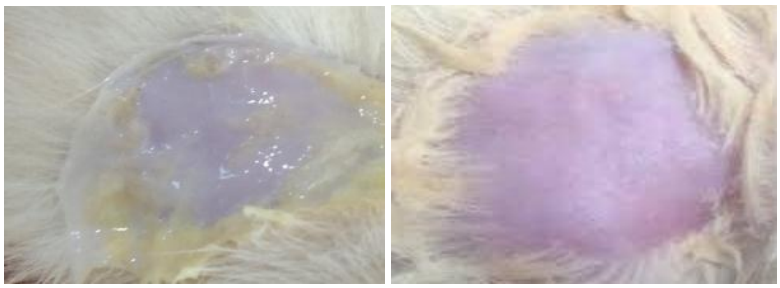


**Fig. 17: Photograph of skin irritation test on application of blank formulation on the first day and after 14 days.**

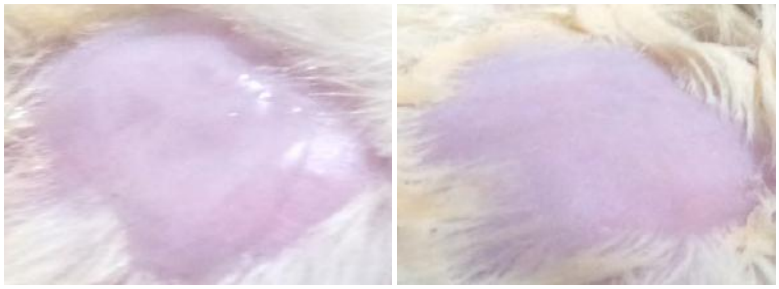


**Fig. 18: Photograph of skin irritation test on application of marketed formulation containing etodolac on the first day and after 14 days.**

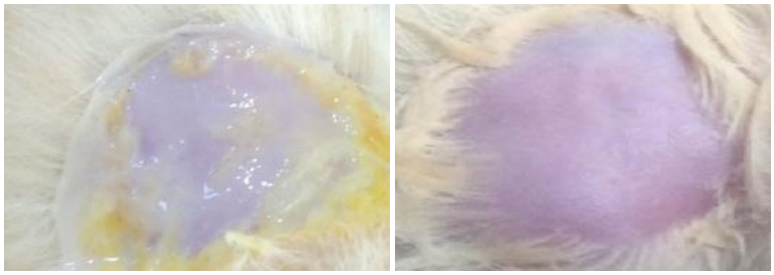


**Fig. 19: Photograph of skin irritation test on application of emulgel containing etodolac on the first day and after 14 days.**

**Table 15: Evaluation table for skin irritation study according to draize scoring method.**

| Group No. | Marketed formulation containing Etodolac | | Blank formulation | | Optimized formulation containing Etodolac | |
|---|---|---|---|---|---|---|
| | Erythema | Oedema | Erythema | Oedema | Erythema | Oedema |
| I | 0 | 0 | 0 | 0 | 0 | 0 |
| II | 0 | 0 | 0 | 0 | 0 | 0 |
| III | 0 | 0 | 0 | 0 | 0 | 0 |

*Erythema Scale : 0 – none; 1 – slight; 2 – well-defined; 3 – moderate; and 4 – scar formation*
*Oedema Scale : 0 – none; 1 – slight; 2 – well-defined; 3 – moderate; and 4 – severe.*

From the prepared 17 formulations, the optimized formulation F4 was used for skin irritation studies. It showed that after application of the optimized formulation, there was no evidence of irritation (erythema and oedema). Hence, the optimized formulation F4 was found to be safe.

## 4. CONCLUSION

Etodolac emulgels were successfully developed using carbopol and HPMC as gelling agent and propylene glycol and oleic acid as penetration enhancers with simple and feasible manufacuring process. The developed formulations were then characterized for their physical appearance, pH, viscosity, spreadability, extrudability, drug content, *in vitro* drug release, kinetic studies, stability and skin irritation studies. FT-IR studies for drug and excipients revealed that there is no incompatibility or interaction between drug and excipients. The optimum concentration of carbopol to prepare emulgel was found to be 3g. The optimum concentration of propylene glycol and oleic acid to prepare emulgel was found to be 5ml and 2.5ml respectively. Among all the formulations, F4 prepared using carbopol as gelling agent, propylene glycol and oleic acid in combination as penetration enhancer was found to show better result and hence selected as optimized formulation. The kinetic studies was better explained by zero order drug release and Korsmeyer-Peppas plot which indicated non-fickian super case-II transport. The stability studies indicated that the formulation remained stable as no significant changes occurred after 3 months storage. The skin irritation studies concluded that there were no irritant effects when the emulgel was applied to the rat skin. So the optimized formulation was found to be safe. If this process can be scaled up to manufacturing level, this will provide Etodolac emulgel with better bioavailability and cost effectiveness.

## 5. ACKNOWLEDGEMENT

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