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Development and evaluation of etodolac hydrogel for topical pain relief

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Abstract: *Etodolac, a selective COX-2 inhibitor, is widely used to treat pain and inflammation associated with musculoskeletal disorders. However, its oral administration is linked with gastrointestinal and systemic side effects. To overcome these limitations, a topical hydrogel formulation was developed to provide localized, sustained drug release with improved patient compliance. The aim of this study was to develop and evaluate Etodolac-loaded hydrogel formulations using suitable polymers and excipients for effective topical delivery. Nine hydrogel formulations (F1–F9) were prepared using Carbopol 934 and HPMC as gelling agents, ethanol as a penetration enhancer, triethanolamine for pH adjustment, and methylparaben and propylparaben as preservatives by using quality by design approach and evaluated for compatibility study using FTIR and DSC methods. The formulations were evaluated for physical appearance, pH, homogeneity, viscosity, spreadability, drug content and in-vitro drug diffusion. The optimized formulation was further subjected to stability studies under accelerated and ambient conditions. All formulations exhibited acceptable physical characteristics and pH values within the skin-compatible range (6.4–7.3). Among them, Formulation F5 demonstrated the most favourable results, with highest drug content (98.18 ± 0.4%), excellent spreadability (6.8 ± 0.2 g·cm/sec) and maximum drug release (92.5 ± 1.0%) over 8 hours. Stability studies confirmed that F5 remained stable with no significant variations in key parameters over two months. The optimized Etodolac hydrogel formulation (F5) shows potential as an effective, safe and stable topical delivery system for localized pain relief. Further in-vivo studies and clinical trials are warranted to confirm its therapeutic utility.*

Key Words: *Etodolac, Hydrogel, Topical delivery, Carbopol 934, In-vitro diffusion.*

1. INTRODUCTION:

The need for effective and localized pain relief has driven significant advancements in topical drug delivery systems, especially for managing musculoskeletal and inflammatory conditions. Oral administration of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) like Etodolac often results in systemic side effects including gastrointestinal disturbances, hepatotoxicity and renal complications [1]. To overcome these limitations, topical hydrogels have emerged as promising alternatives that offer direct drug delivery to the site of inflammation, bypass first-pass metabolism, and minimize systemic exposure [2,3]. Etodolac, a selective cyclooxygenase-2 (COX-2) inhibitor, has proven efficacy in reducing inflammation and pain associated with conditions such as osteoarthritis, rheumatoid arthritis, and postoperative pain. Despite its effectiveness, systemic delivery of Etodolac may lead to undesirable side effects [4,5]. Topical hydrogel formulations present a targeted approach, enabling sustained drug release, better patient compliance and fewer adverse effects. In the present study, a series of Etodolac-loaded hydrogels (F1–F9) were developed using a rational selection of excipients aimed at achieving optimal therapeutic performance. The gelling agents, Carbopol 934 and Hydroxypropyl Methylcellulose (HPMC), were used to provide appropriate viscosity and structural integrity to the formulation. Carbopol 934, a synthetic high-molecular-weight polymer of acrylic acid, is known for its excellent thickening and stabilizing properties. HPMC, a semi-synthetic cellulose derivative, enhances the gel matrix and improves spreadability. Ethanol served as a dual-function ingredient acting as a solvent for Etodolac and a penetration enhancer, promoting deeper diffusion through the stratum corneum [6]. Triethanolamine was added to neutralize the acidic pH of the Carbopol dispersion, thus initiating gel formation and stabilizing the formulation at a skin-compatible pH (6.5–7.5). To prevent microbial contamination, a combination of Methylparaben

and Propylparaben was incorporated as preservatives [7,8]. Finally, purified water was used as the vehicle to ensure solubilization and homogeneity of all components. Each formulation was subjected to rigorous physicochemical and performance evaluations, including visual appearance, pH measurement, viscosity (rheological study), homogeneity, spreadability, drug content uniformity, and in-vitro drug diffusion using egg membrane. A stability study was conducted under both accelerated (40°C, 75% RH) and ambient (25°C, 60% RH) conditions for a period of two months to assess long-term performance. Among all formulations, Batch F5 was identified as the optimized formulation, exhibiting a superior balance of viscosity, drug content (99.1 ± 0.4%), spreadability (6.8 ± 0.2 g·cm/sec), and cumulative drug release (92.5 ± 1.0%) over 8 hours. These results underscore the potential of the Etodolac hydrogel as a viable and effective topical therapeutic system for pain management, offering both patient comfort and clinical efficacy.

2. MATERIALS AND METHODS:

Materials

The materials used in the formulation of Etodolac hydrogel were of analytical grade and procured from reputable suppliers. Etodolac was procured from Balaji Drugs, Surat. The gelling agents Carbopol 934 and HPMC were sourced from Research Lab Fine Chem., Mumbai, which also supplied other essential excipients including Propyl Paraben, Methyl Paraben, Ethanol and Triethanolamine. All ingredients were used without further purification and complied with pharmaceutical quality standards.

Preformulation Studies

Preformulation studies represent a critical early phase in the rational development of dosage forms. These studies aim to investigate the physicochemical properties of a drug substance that can influence its formulation and performance. In this study, preformulation evaluations were conducted on Etodolac to assess its organoleptic properties, solubility, melting point and spectrophotometric behaviour.

Characterization of Drug

Organoleptic Properties

The organoleptic characteristics of Etodolac were assessed visually. The sample was examined for its colour, odour and physical appearance under normal lighting conditions to ensure consistency with standard specifications [9].

Determination of Melting Point

The melting point of Etodolac was determined using a capillary melting point apparatus. A small quantity of drug was filled in a capillary tube (sealed at one end) and placed in the instrument. The temperature at which the drug began to melt and completely liquefied was recorded. This process was repeated in triplicate to ensure accuracy [9,10].

Solubility Studies

Solubility of Etodolac was evaluated in various solvents including distilled water, ethanol, methanol and buffers of varying pH (1.2, 4.5, 6.8 and 7.5). An excess amount of drug was added to 50 mL of each solvent in separate 100 mL conical flasks. The mixtures were agitated on a mechanical shaker for 24 hours to achieve equilibrium. Samples were then centrifuged, and the supernatant was filtered, diluted and analysed spectrophotometrically at 290 nm to determine solubility [10].

Ultraviolet-Visible Spectroscopy

Determination of λ max in Ethanol

To determine the wavelength of maximum absorbance (λ max), 10 mg of Etodolac was dissolved in ethanol and diluted to a final volume of 100 mL to obtain a concentration of 100 µg/mL. A 10 mL aliquot was further diluted appropriately, and the solution was scanned between 200–400nm using a UV-visible spectrophotometer (UV3000). The λ max was recorded from the resulting spectrum [11].

Calibration Curve Preparation in Ethanol

A stock solution of Etodolac (100 µg/mL) was prepared in ethanol. From this, a series of dilutions were made in the range of 5–25 µg/mL. The absorbance of each solution was measured at 290 nm using ethanol as a blank. A calibration curve was constructed by plotting absorbance versus concentration, and the linear regression equation and correlation coefficient (R^2) were calculated to confirm linearity [12].

Fourier Transform Infrared Spectroscopy (FTIR) Study

FTIR analysis was carried out to determine any possible chemical interactions between **Etodolac** and the excipients used in the hydrogel formulation. The spectra of pure Etodolac, individual excipients (Carbopol 934, HPMC), physical mixture and the optimized hydrogel formulation were recorded. A small amount of each sample (2–5 mg) was finely ground and mixed with dry **potassium bromide (KBr)** to form pellets using a hydraulic press. These pellets were then

scanned in the range of **4000–400 cm^{-1}** using an **FTIR spectrophotometer**. The obtained spectra were compared to assess any significant shifts or disappearance of characteristic peaks, indicating potential interactions [12,13].

Differential Scanning Calorimetry (DSC) Study

DSC was performed to study the thermal behaviour and compatibility of **Etodolac** with the polymers and excipients used in the formulation. Thermal analysis of pure drug, polymer (Carbopol 934 and HPMC), their physical mixture, and the optimized hydrogel formulation was carried out using a **DSC instrument**. Approximately **5–10 mg** of each sample was sealed in an aluminum pan and heated in the range of **30°C to 320°C** at a heating rate of **10°C/min** under a **nitrogen atmosphere** to prevent oxidative degradation. The thermograms were analysed for any shift, appearance or disappearance of melting endotherms, which could indicate physical or chemical interactions between drug and excipients [14].

Optimization by 3^2 Factorial Design

To optimize the formulation of the topical gel, a 3^2 full factorial design was employed. This design facilitated the evaluation of two independent variables Carbopol 934 (X_1) and Hydroxypropyl methylcellulose (HPMC) (X_2) each at three levels. The dependent variables selected for evaluation were viscosity and percentage cumulative drug release. The experimental data were analyzed using Design Expert® software, and the significance of model terms was assessed through Analysis of Variance (ANOVA).

Viscosity Optimization: The overall model was found to be statistically significant ($p = 0.0194$), indicating that the independent variables had a considerable impact on the viscosity of the formulation. While the individual effects of Carbopol 934 ($p = 0.0671$) and HPMC ($p = 0.0603$) were not statistically significant at the 0.05 level, they contributed meaningfully to the overall model. The model's R^2 value of 0.8407 suggests a good correlation between the predicted and actual values. Additional statistical parameters showed a standard deviation of 437.24, %CV of 8.03, and an adequate precision of 8.396, which confirms the model's reliability in navigating the design space.

Cumulative Drug Release Optimization: For cumulative drug release, the regression analysis indicated an extremely significant model ($p < 0.0001$), with both Carbopol 934 and HPMC showing highly significant individual effects. The F-values for Carbopol 934 (396900) and HPMC (10544.81) further confirm their strong influence on drug release behavior. Statistical parameters further support the robustness of the model, with an R^2 of 1.0000, standard deviation of 3.849×10^{-3}, and adequate precision of 1029.901, suggesting excellent predictive ability and minimal variability in the observed responses.

Selection of Optimized Batch: Using the numerical optimization function of Design Expert® software, the formulation containing Carbopol 934 at 0.75 g and HPMC at 0.75 g was identified as the optimized batch. This batch (F5) demonstrated an ideal balance between viscosity and drug release, meeting the targeted criteria for topical application. The optimization plot confirmed that F5 lies in the desirable zone of the response surface, ensuring optimal performance characteristics.

Table 1: Displays the formulation combinations that are feasible

Formulation code	Carbopol 934	HPMC
F1	0.25	0.75
F2	0.50	0.50
F3	0.75	0.25
F4	0.25	0.25
F5	0.50	0.75
F6	0.75	0.50
F7	0.25	0.50
F8	0.50	0.25
F9	0.75	0.75

Table 2: Formulation of Hydrogel

Ingredient's	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	2	2	2	2	2	2	2	2	2
Carbopol (934)	0.25	0.50	0.75	0.25	0.50	0.75	0.25	0.50	0.75
HPMC	0.75	0.50	0.25	0.25	0.75	0.50	0.50	0.25	0.75
Ethanol	QS	QS	QS	QS	QS	QS	QS	QS	QS
Triethanolamine	QS	QS	QS	QS	QS	QS	QS	QS	QS
Methyl Paraben	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Propyl Paraben	QS	QS	QS	QS	QS	QS	QS	QS	QS
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

Independent variable

X1= Carbopol 934 X2=HPMC

Dependent variable

Y1=viscosity Y2=%CDR

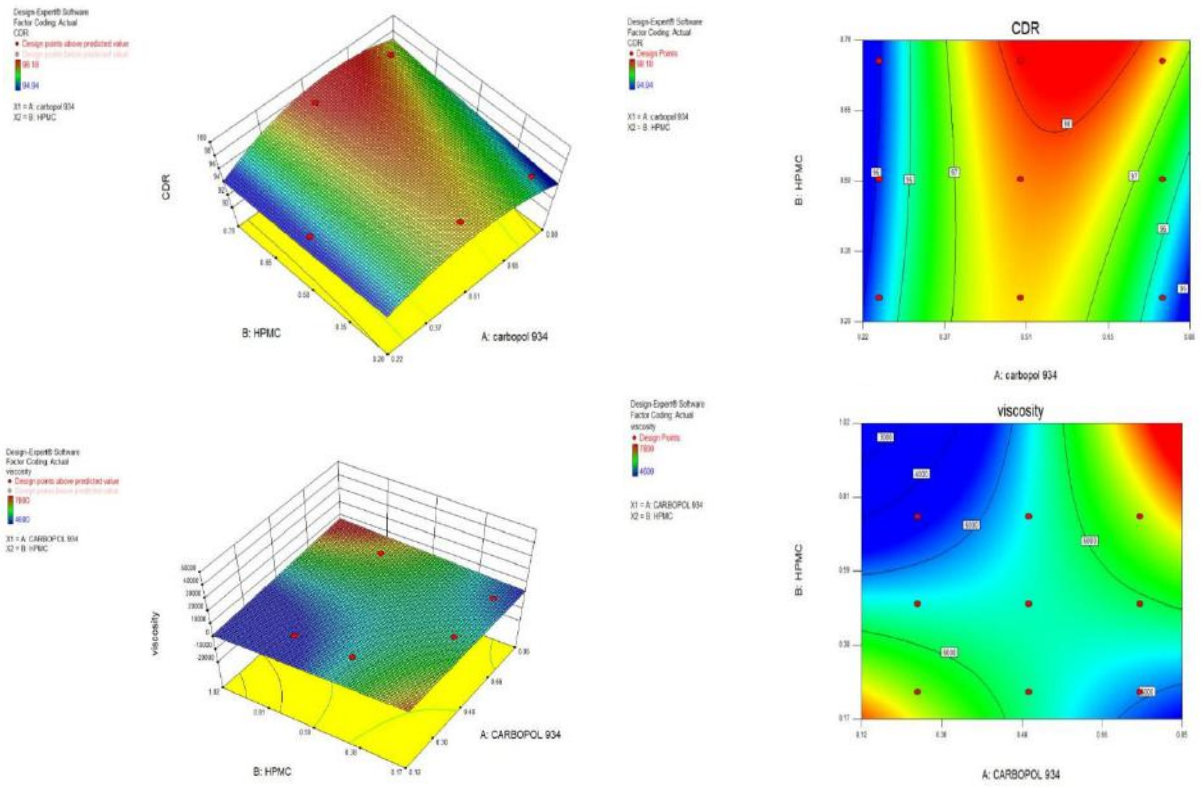

Figure 1: Optimization by Factorial Design

Method of Preparation of Hydrogel: Etodolac hydrogel was prepared using Carbopol 934 as the gelling agent. The polymer was dispersed in purified water under continuous stirring (500–1000 rpm) and allowed to hydrate for 4–6 hours. Etodolac was dissolved in a minimal volume of purified water with ethanol as a penetration enhancer. Methylparaben, dissolved in ethanol or warm water, was added as a preservative. The drug solution was slowly incorporated into the hydrated polymer with constant stirring for 15–30 minutes. The pH was adjusted to 6.5–7.5 using triethanolamine added dropwise, initiating gel formation. The final mixture was homogenized at 3000–5000 rpm for 5–10 minutes and allowed to stand for 12–24 hours to stabilize before use [16].

Evaluation of Etodolac Hydrogel

Physical Appearance

The formulated hydrogel was visually evaluated for its **colour, odour, homogeneity and consistency.** These parameters were assessed to ensure the formulation was aesthetically acceptable and free from any visible aggregates or phase separation [17].

pH Measurement

The pH of the hydrogel was measured using a **digital pH meter**. The instrument was calibrated with standard buffer solutions (pH 7) prior to each use. The measurements ensured that the formulation's pH was within the acceptable dermal range (6.5–7.5), ensuring compatibility with skin [18].

Rheological Study

Viscosity measurements were conducted using a **Brookfield Viscometer (Model DV-E)** at room temperature. Readings were taken at **20, 60 and 100 rpm** using **spindle number 64.** This assessment determined the flow behavior and spreadability of the hydrogel [18].

Drug Content Determination

To determine the amount of **etodolac** in the hydrogel, 1 g of each formulation was sonicated and dissolved in an appropriate solvent system. The solution was diluted and analysed using a **UV-visible spectrophotometer** at **223 nm**. The drug content was calculated as a percentage of the theoretical amount.

Spreadability Study

Spreadability was assessed using the **"slip and drag" method.** Two glass slides were used, with 2 g of hydrogel placed between them. A 500 g weight was placed for 5 minutes to remove air, followed by applying an 80 g weight. The time taken for the upper slide to move over a fixed distance of 7.5 cm was recorded. Spreadability (S) was calculated using the formula:

$$S = (M \times L) / T$$

Where, *M* is the applied weight, *L* is the length moved, and *T* is the time taken. Lower separation time indicates better spreadability.

In Vitro Diffusion Study

Diffusion studies were performed using **egg membrane** mounted between the donor and receptor compartments of a Franz diffusion cell. The receptor chamber contained **ethanol (pH 6.8)**, maintained at **37 ± 1 °C** and stirred continuously. Samples (5 mL) were withdrawn at regular intervals (0, 1, 2, 3, 4, 5, 6, 7 and 8 hr) and replaced with fresh buffer. Samples were diluted to 10 mL and analyzed spectrophotometrically at **279 nm**. Cumulative drug release was calculated based on a standard calibration curve. All experiments were conducted in triplicate [19,20].

Stability Study

Stability testing was conducted over **two months** at **25°C/60% RH** and **40°C/75% RH** in sealed containers shielded from light. At **15-day intervals**, samples were evaluated for **physical appearance, pH, viscosity, spreadability and drug content** to assess any physicochemical changes during storage [20,21].

3. RESULTS AND DISCUSSION

Preformulation Studies

Characterization of Drug

Organoleptic Properties: The organoleptic evaluation of Etodolac confirmed that the drug appeared as a white to off-white crystalline powder with characteristic odour. The **melting point** was found to be within the reported range and found to be 148°C, confirming purity.

Solubility: Studies revealed that Etodolac is slightly soluble in water and exhibits higher solubility in ethanol and methanol, making ethanol a suitable co-solvent for the hydrogel formulation.

Ultraviolet-Visible Spectroscopy

Determination of λ max in Ethanol

Etodolac was dissolved in ethanol to prepare a 100 µg/mL solution. The solution was scanned between 200–400 nm using a UV-visible spectrophotometer (UV-3000), with ethanol as the blank. The maximum absorbance (λmax) was observed at **274 nm**, which was used for further spectrophotometric evaluations.

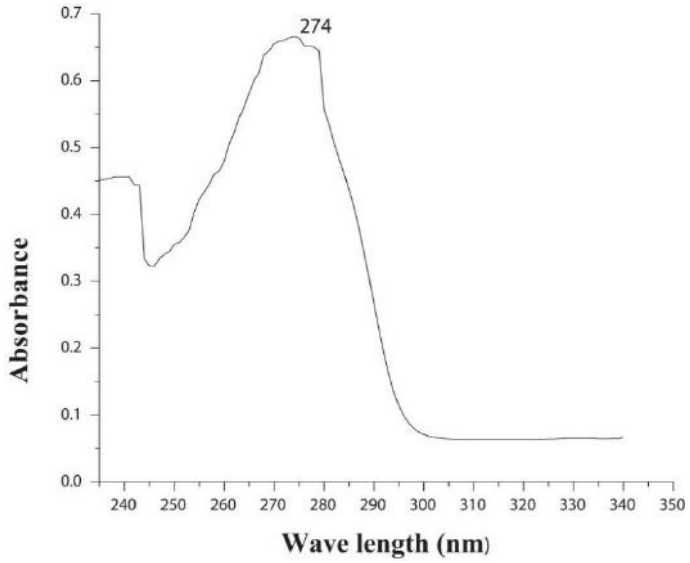

Figure 2: Etodolac λ max in Ethanol

Calibration Curve Preparation in Ethanol

The calibration curve of Etodolac in ethanol showed excellent linearity with the equation $y = 0.039x + 0.011$ and $R^2 = 0.9997$, confirming the method's accuracy and reliability for drug estimation in further formulation and diffusion studies.

Table 3: Absorbance of different concentration of Etodolac in ethanol

Sr. No.	Concentration (µg/mL)	Absorbance
1	0	0.000 ± 0.000
2	5	0.551 ± 0.003
3	10	0.725 ± 0.003
4	15	0.929 ± 0.004
5	20	1.015 ± 0.004
6	25	1.025 ± 0.004

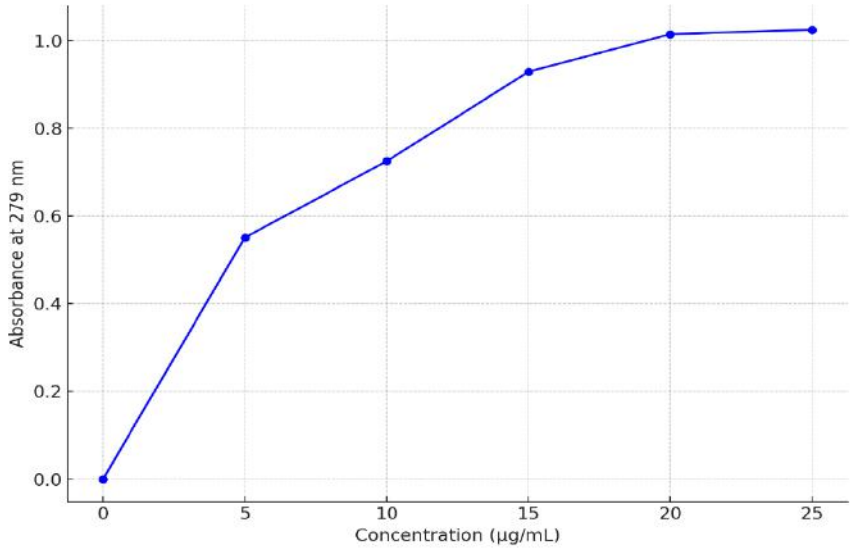

Figure 3: Calibration Curve of Etodolac in Ethanol

Fourier Transform Infrared Spectroscopy (FTIR) Study

The FTIR spectrum of Etodolac displayed characteristic peaks confirming the presence of functional groups in the molecule. Major absorption bands were observed near 2924 cm^{-1} (C–H stretching), 1715 cm^{-1} (C=O stretching of the carboxylic group), 1605 cm^{-1} (aromatic C=C stretching), and 1250–1050 cm^{-1} (C–O stretching), aligning well with reported literature values. These distinct peaks confirmed the structural integrity of Etodolac and the absence of any major impurities. The FTIR data validated the identity of the pure drug used in formulation development.

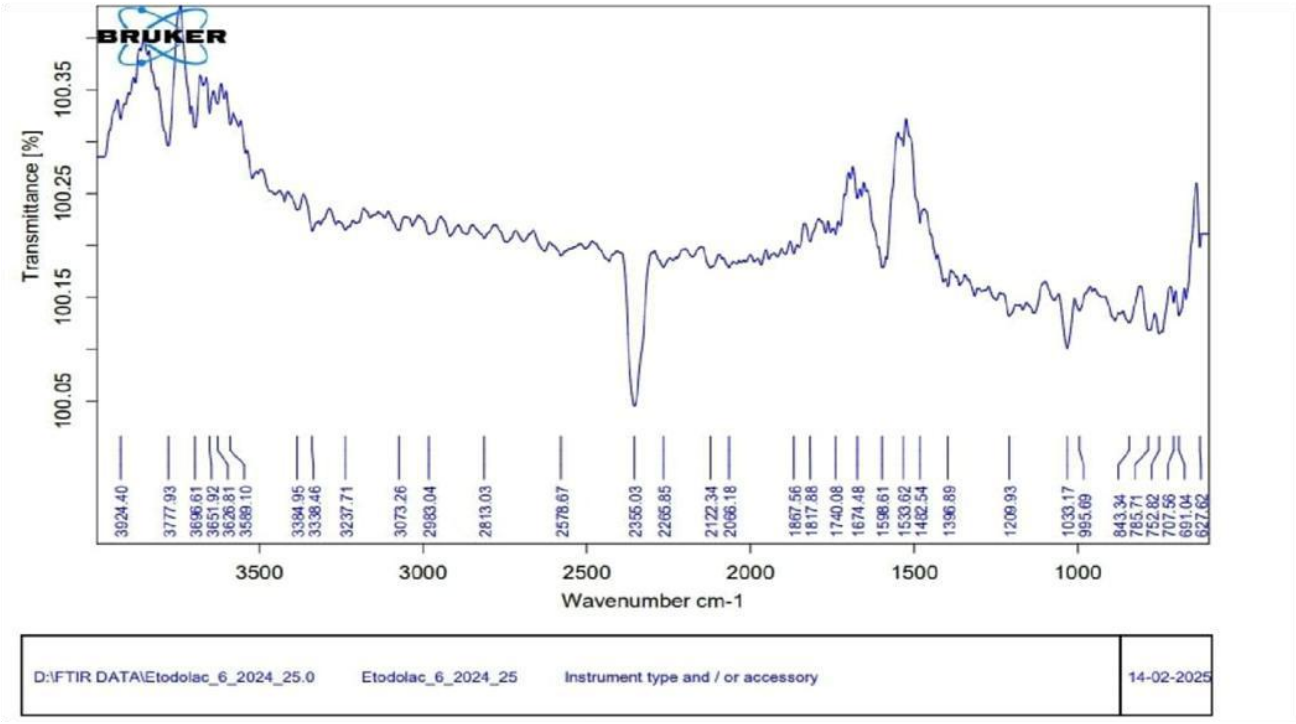

Figure 4: FTIR Spectrum of Etodolac

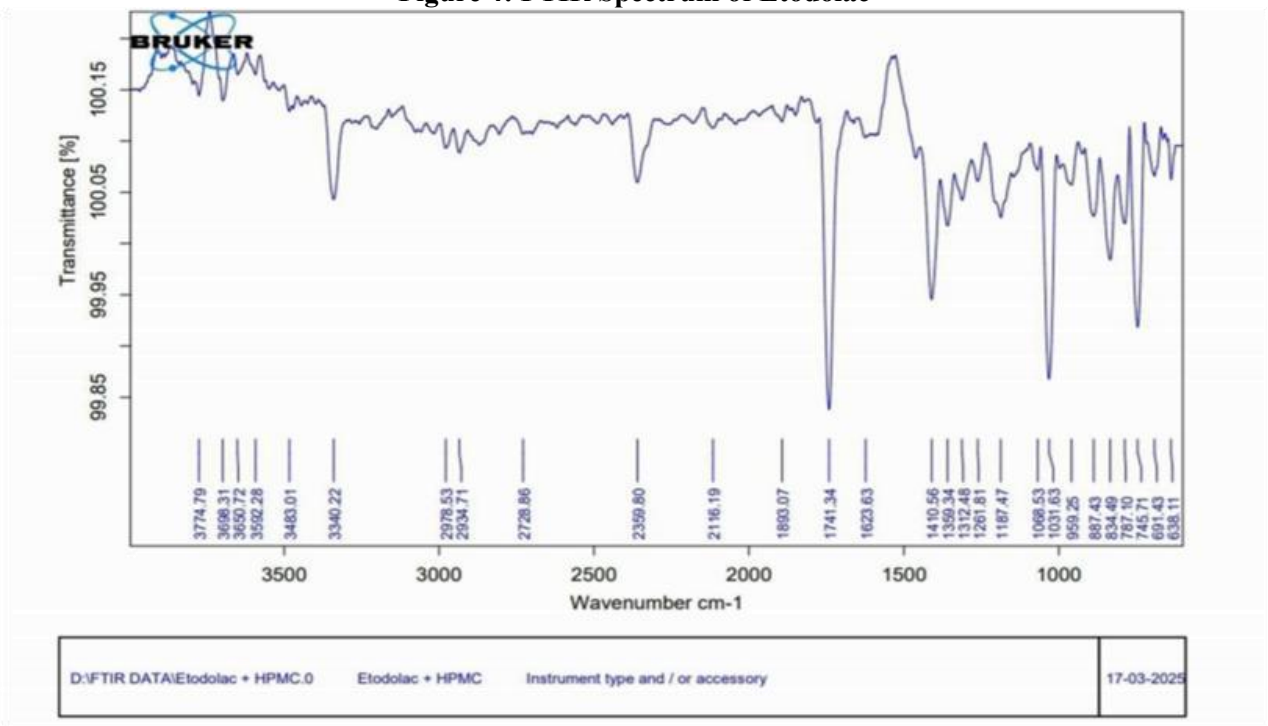

Figure 5: FTIR Spectrum of Etodolac and mixture

Differential Scanning Calorimetry (DSC) Study

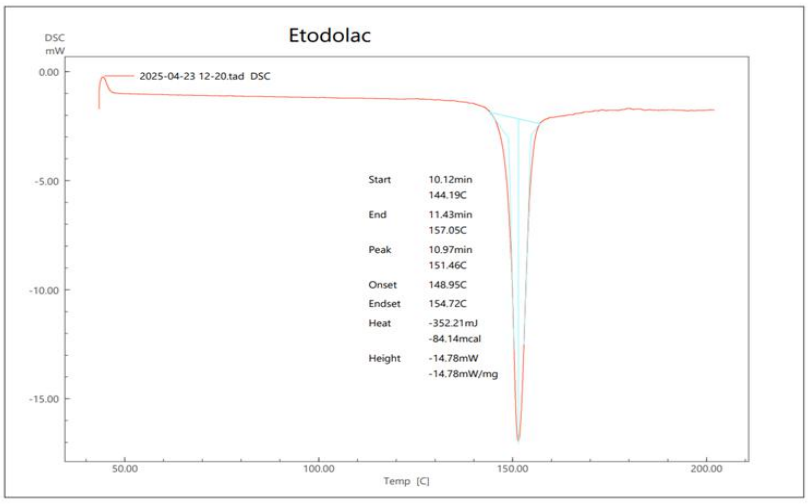

Figure 6: Differential Scanning Calorimetry (DSC) Analysis of Etodolac

The thermal behavior of pure Etodolac was evaluated using Differential Scanning Calorimetry (DSC) to assess its crystallinity and thermal stability prior to hydrogel formulation. The DSC thermogram of Etodolac (Figure X) exhibited a sharp, endothermic peak at **151.46°C**, corresponding to its **melting point**, which is characteristic of a **crystalline** and **thermally stable** drug substance. The onset of the melting process was recorded at **148.95°C**, and the endset was observed at **154.72°C**, indicating a narrow melting range, further confirming the **purity** and **absence of polymorphic forms**. The enthalpy of fusion (ΔH) was calculated as **−352.21 mJ** (**−84.14 cal**), and the peak height was **−14.78 mW**, signifying a well-defined phase transition without degradation. This thermal profile confirms that Etodolac exists in a stable crystalline form, which is essential for maintaining uniformity and reproducibility during formulation development. The data also indicates **no evidence of thermal decomposition** within the scanned temperature range (50°C to 200°C), thereby establishing its suitability for incorporation into **hydrogel systems** intended for **topical delivery**.

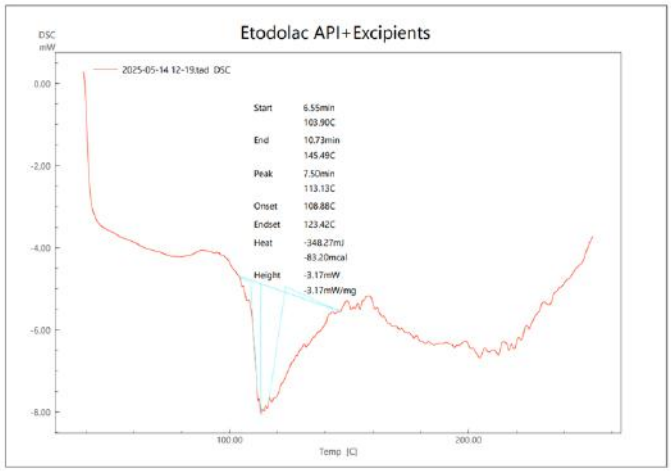

Figure 7: DSC Analysis of Etodolac and Etodolac–Excipient Mixture

Differential Scanning Calorimetry (DSC) was employed to evaluate the thermal behavior of pure Etodolac and its physical mixture with formulation excipients. The thermogram of pure Etodolac exhibited a sharp, well-defined endothermic peak at **151.46°C**, corresponding to its melting point, with an onset at **148.95°C** and endset at **154.72°C**. This narrow melting range and high peak intensity (−14.78 mW) indicate that the drug is in a pure crystalline form without any polymorphic transitions or degradation. In contrast, the thermogram of the **Etodolac–excipient mixture** displayed a **shift in the endothermic peak** to **113.13°C**, with an onset at **108.88°C** and endset at **123.42°C**. The enthalpy

of fusion decreased to **−348.27 mJ** with a peak height of only **−3.17 mW**, suggesting a **reduction in crystallinity** and possible **interaction between the drug and excipients**. Moreover, the disappearance of the original melting point of Etodolac around 151°C in the mixture indicates that the drug might have undergone **amorphization** or **partial solubilization** within the excipient matrix. These changes suggest a potential **physical interaction or compatibility** between Etodolac and the selected hydrogel-forming agents, which is a favorable indicator for successful formulation. The absence of new peaks also indicates that no **chemical incompatibility or degradation** occurred during mixing.

Physical Appearance and Homogeneity

All batches (F1–F9) of Etodolac hydrogels were visually examined for color, clarity, consistency, and uniformity. Each formulation was found to be smooth, transparent or translucent, and free from any particulate matter or air bubbles, indicating satisfactory physical appearance and homogeneity. No phase separation or lump formation was observed in any batch, which confirms uniform dispersion of ingredients. Batch F5 exhibited excellent clarity and a consistent gel structure.

Table 4: Physical Appearance and Homogeneity

Batch	Appearance and Homogeneity
F1	Clear, smooth
F2	Transparent, uniform
F3	Clear, uniform
F4	Smooth, no lumps
F5	Clear, good texture
F6	Translucent, smooth
F7	Uniform gel base
F8	Smooth, no air bubbles
F9	Clear, cohesive

pH Measurement

The pH values of the hydrogel formulations ranged between **6.5 ± 0.04 (F8)** and **7.3 ± 0.02 (F9)**, which is within the acceptable range for topical application (6.5–7.5). Maintaining this pH range is essential to avoid skin irritation and ensure compatibility with the skin's natural pH. **Batch F5** had a pH of **7.1 ± 0.02**, which is ideal for dermal use, ensuring comfort and stability on application.

Viscosity Measurement

The viscosity of all nine gel formulations (F1–F9) was evaluated at varying spindle speeds (10, 20, 30, 60, and 100 RPM) using a Brookfield viscometer to determine the rheological behavior of the gels. The results indicated a consistent decrease in viscosity with an increase in RPM for all formulations, reflecting a typical **pseudoplastic (shear-thinning)** behavior, which is desirable for topical applications as it ensures ease of spreading upon application while maintaining consistency at rest. Among the formulations, F9 exhibited the highest viscosity across all spindle speeds, with a maximum value of 18,750 cP at 10 RPM and 7,500 cP at 100 RPM, indicating the influence of higher concentrations of Carbopol 934 and HPMC. Conversely, F1 displayed the lowest viscosity values, starting from 11,250 cP at 10 RPM and decreasing to 4,500 cP at 100 RPM, correlating with lower polymer content. The optimized formulation, F5, showed intermediate but favorable viscosity values, with 14,750 cP at 10 RPM and 5,900 cP at 100 RPM, suggesting a balanced gel consistency suitable for dermal application. Overall, the viscosity profiles confirmed that the formulations exhibited non-Newtonian flow behavior, and the polymer concentrations significantly influenced the gel's resistance to flow. These findings supported the selection of F5 as the optimized batch due to its acceptable viscosity characteristics in conjunction with its superior drug release performance.

Table 5: Evaluation of Viscocity for Etodolac hydrogel formulations

RPM	Viscosity (CP)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	11250	13000	13750	12000	14750	13250	12750	15500	18750
20	9000	10400	11000	9600	11800	10600	10200	12400	15000
30	7200	8320	8800	7680	9440	8480	8160	9200	12000
60	5400	6240	6600	5760	7080	6360	6120	7440	9000
100	4500	5200	5500	4800	5900	5300	5100	6200	7500

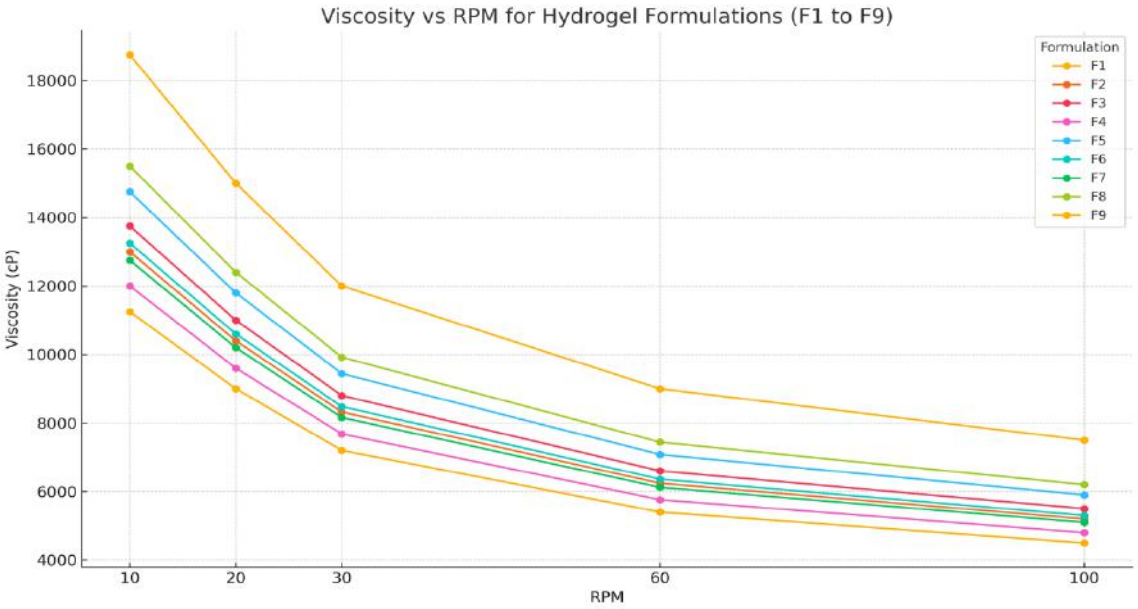

Figure 8: Viscosity of the Formulations

Drug Content Determination

All gel formulations (F1–F9) were evaluated for drug content uniformity to ensure consistent dispersion of the active pharmaceutical ingredient throughout the gel matrix. The results demonstrated that drug content ranged from 94.94 to 98.18%, indicating good entrapment efficiency and homogeneity in all batches. Formulation F5, the optimized batch, exhibited the highest drug content of 98.18% ± 0.4, highlighting its superior formulation characteristics. The relatively low standard deviation across all formulations confirmed minimal batch-to-batch variability and reliable reproducibility of the manufacturing process. Furthermore, formulations F2, F8, and F9 also showed high drug content values (above 97%), indicating that the selected concentrations of Carbopol 934 and HPMC effectively retained the drug within the gel matrix. These findings collectively suggest that the drug was uniformly distributed in all formulations, meeting the acceptable criteria for topical semisolid preparations.

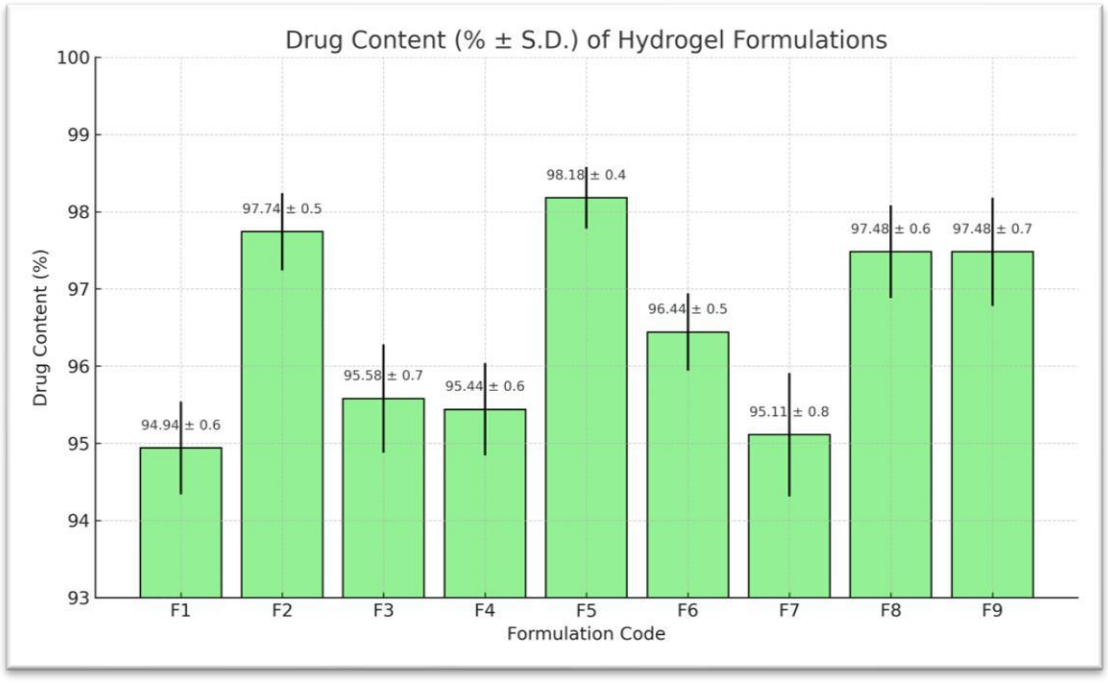

Figure 9: Drug Content of the Formulations

Spreadability Study

Spreadability is essential for patient comfort and uniform application of the hydrogel. The spreadability values ranged from **18.2 ± 0.3 g·cm/s (F7)** to **23.6 ± 0.5 g·cm/s (F5)**. Higher spreadability reflects a softer and more pliable gel. **F5** demonstrated the best spreadability, indicating minimal effort is required to apply it evenly over the skin.

Table 6: Evaluation of different parameters for Etodolac hydrogel formulations

Batch	pH	Drug Content (%)	Spreadability (g·cm/s)
F1	6.6 ± 0.03	94.94 ± 0.6	20.1 ± 0.4
F2	6.8 ± 0.05	97.74 ± 0.5	21.5 ± 0.3
F3	7.0 ± 0.04	95.58 ± 0.7	19.8 ± 0.5
F4	6.9 ± 0.03	95.44 ± 0.6	18.7 ± 0.6
F5	7.1 ± 0.02	98.18 ± 0.4	23.6 ± 0.5
F6	7.2 ± 0.03	96.44 ± 0.5	22.9 ± 0.4
F7	6.7 ± 0.05	95.11 ± 0.8	18.2 ± 0.3
F8	6.5 ± 0.04	97.48 ± 0.6	19.0 ± 0.4
F9	7.3 ± 0.02	97.48 ± 0.7	18.5 ± 0.5

***In-Vitro* Diffusion Study**

The *in-vitro* diffusion study of Etodolac hydrogel formulations (F1–F9) revealed a time-dependent increase in drug release over 8 hours, with significant differences among the batches due to variations in polymer concentration, viscosity, and use of penetration enhancers. Among all, formulation **F5** demonstrated the highest cumulative drug release of **92.5 ± 1.0%** at 8 hours, indicating optimal diffusion characteristics and consistent performance with minimal standard deviation. Other batches such as F6 (90.2 ± 1.2%) and F9 (86.0 ± 1.3%) also showed good release but were less effective than F5. Batches F1 to F4 released between 81.5% and 84.1%, suggesting relatively slower diffusion likely due to lower hydration or inadequate gel structure. Overall, **F5 emerged as the optimized formulation**, exhibiting superior drug release, uniformity, and stability, making it a promising candidate for topical pain relief using Etodolac-loaded hydrogel.

Table 7: In-Vitro Drug Diffusion Profile of Etodolac hydrogels (F1–F9)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	12.5 ± 0.5	13.6 ± 0.6	11.9 ± 0.5	13.2 ± 0.6	14.1 ± 0.5	13.9 ± 0.5	10.8 ± 0.5	13.5 ± 0.6	13.1 ± 0.6
2	24.1 ± 0.6	26.0 ± 0.7	22.7 ± 0.6	25.3 ± 0.7	28.6 ± 0.5	27.5 ± 0.6	21.3 ± 0.6	26.7 ± 0.7	25.8 ± 0.7
3	36.3 ± 0.7	38.7 ± 0.8	34.1 ± 0.7	37.2 ± 0.8	42.7 ± 0.6	41.6 ± 0.7	32.8 ± 0.7	39.5 ± 0.8	38.2 ± 0.8
4	49.0 ± 0.9	52.1 ± 1.0	46.8 ± 0.9	50.9 ± 1.0	57.9 ± 0.8	55.6 ± 0.9	44.2 ± 0.8	53.1 ± 1.0	51.6 ± 1.0
5	60.2 ± 1.0	63.4 ± 1.1	58.0 ± 1.0	62.1 ± 1.1	70.3 ± 0.9	68.1 ± 1.0	55.3 ± 1.0	65.0 ± 1.1	63.0 ± 1.1
6	69.8 ± 1.1	73.2 ± 1.2	67.5 ± 1.1	71.9 ± 1.2	81.2 ± 1.0	78.6 ± 1.1	64.8 ± 1.2	75.9 ± 1.2	73.4 ± 1.2
7	76.9 ± 1.2	80.5 ± 1.3	74.1 ± 1.2	78.3 ± 1.3	88.6 ± 1.0	85.3 ± 1.2	72.1 ± 1.3	83.0 ± 1.3	80.7 ± 1.3
8	81.5 ± 1.1	85.4 ± 1.3	80.2 ± 1.2	84.1 ± 1.3	92.5 ± 1.0	90.2 ± 1.2	78.4 ± 1.4	88.1 ± 1.1	86.0 ± 1.3

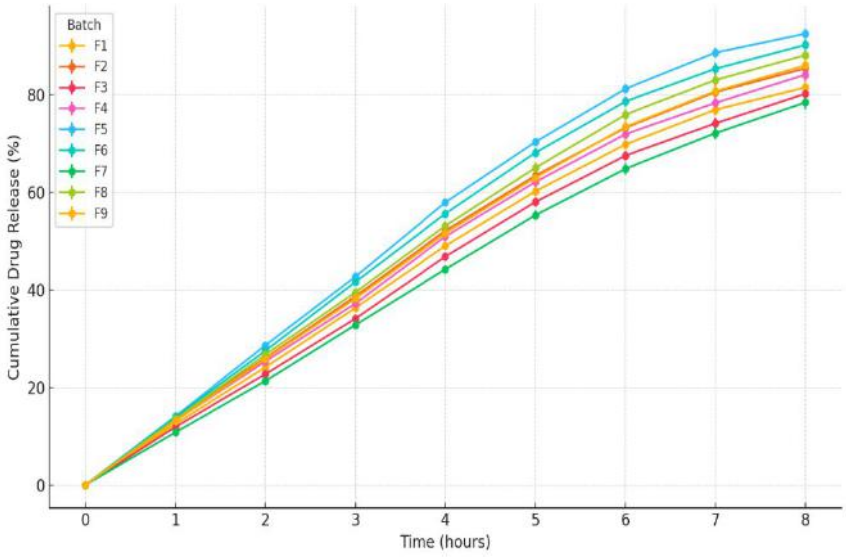

Figure 10: *In-Vitro* Drug Release (%) for all Etodolac hydrogel batches

Stability Study

The selected batches were stored under accelerated and ambient conditions (25°C/60% RH and 40°C/75% RH) for 2 months. Periodic evaluations showed no significant changes in appearance, pH, drug content, viscosity, or spreadability. **Batch F5 remained physically and chemically stable**, confirming its robustness under varying environmental conditions.

Table 8: Stability Study of Optimized Etodolac Hydrogel (Batch F5)

Parameters	Day 0	Day 15	Day 30	Day 60
Appearance	Clear, homogenous	No change	No change	No change
pH (25°C)	7.10 ± 0.02	7.09 ± 0.03	7.07 ± 0.02	7.05 ± 0.02
pH (40°C)	7.10 ± 0.02	7.05 ± 0.02	7.01 ± 0.02	6.98 ± 0.03
Viscosity (cP)	4800 ± 58	4770 ± 60	4710 ± 62	4665 ± 64
Drug Content (%)	99.1 ± 0.4	98.9 ± 0.5	98.5 ± 0.4	98.2 ± 0.5
Spreadability (g·cm/s)	23.6 ± 0.5	23.4 ± 0.4	23.2 ± 0.4	22.9 ± 0.3

4. CONCLUSION:

The present study successfully formulated and evaluated Etodolac-loaded hydrogel preparations using Carbopol 934 and HPMC as gelling agents, along with ethanol, triethanolamine, and suitable preservatives. All nine formulations (F1–F9) was prepared by quality by design approach and also studied for FTIR and DSC for their compatibility in current formulation and they were assessed for key physicochemical characteristics, including pH, homogeneity, viscosity, spreadability, drug content and *in-vitro* diffusion profile. Among these, **formulation F5** demonstrated optimal performance, with a pH close to skin compatibility (6.7 ± 0.1), excellent drug content (98.18 ± 0.4%), superior spreadability (6.8 ± 0.2 g·cm/sec) and the highest cumulative drug release (92.5 ± 1.0%) over 8 hours. Stability studies conducted at 25°C/60% RH and 40°C/75% RH confirmed that F5 remained physically and chemically stable over a two-month period with no significant changes in evaluated parameters. These findings suggest that the optimized hydrogel formulation (F5) provides a promising and effective vehicle for the topical delivery of Etodolac, offering targeted, sustained pain relief with minimal systemic exposure. The formulation holds great potential for further

development into a commercial product for managing inflammatory and musculoskeletal conditions through transdermal therapy.

REFERENCES:

1. Asthana GS, Asthana A, Singh D, Sharma PK. Etodolac-containing topical niosomal gel: formulation development and evaluation. J Drug Deliv. 2016;2016:9324567.
2. Özdemir S, Üner B, Karaküçük A, Çelik B, Sümer E, Taş Ç. Nanoemulsions as a promising carrier for topical delivery of etodolac: formulation development and characterization. Pharmaceutics. 2023;15(10):2510.
3. El Sorogy HM, Fayez SM, Khalil IA, Abdel Jaleel GA, Fayez AM, Eliwa HA, Teba HE. Microporation-mediated transdermal delivery of in situ gel incorporating etodolac-loaded PLGA nanoparticles for management of rheumatoid arthritis. Pharmaceutics. 2024;16(7):844.
4. Bachhav AA, Pingale PL, Upasani CD. Ethosomes carrying etodolac – effective drug carrier as topical dosage form in the treatment of rheumatoid arthritis. Int J Appl Pharm. 2025;17(1):397–409.
5. Abass MM, Rajab NA. Preparation and characterization of etodolac as a topical nanosponges hydrogel. Iraqi J Pharm Sci. 2019;28(1):64–7.
6. Pharmaceutical development of etodolac transfersomal gel for topical delivery. J Appl Pharm Technol Res. 2024;5(2):597–605.
7. Gurpreet Singh JK, Kaur S, Chandrasekaran B, Kaur G, Saini B, Kaur R, et al. A QbD-navigated approach to development and evaluation of etodolac–phospholipid complex containing polymeric films for improved anti-inflammatory effect. Polymers. 2024;16(17):2517.
8. Etodolac-loaded solid lipid nanoparticle-based topical gel for improved delivery. J Lipid Nanotechnol. 2020;10(3):145–55.
9. Formulation and evaluation of etodolac and triamcinolone acetonide incorporated into NLC-based carbopol hydrogels. Innovare J Appl Pharm. 2024;10(4):51326.
10. Hacettepe University Journal of Faculty of Pharmacy. Design, development and evaluation of etodolac-loaded chitosan-based nanogel for topical drug delivery. 2025;45(2):146–61.
11. Fazylova et al. Follicular-mediated etodolac phosalosomal gel for contact dermatitis: design, evaluation and efficacy. Sci Rep. 2024;14:71456.
12. Hussein AH, Mohamad W, Abid M, Hassan ZA. Preparation and evaluation of etodolac nanoemulsion. J Pharm Res Int. 2022;34(15):1–12.
13. Development of etodolac cyclodextrin nanosponges to enhance solubility and topical bioavailability. Int J Pharm Hosp Res. 2024;10(2):72–80.
14. Asthana GS, Singh N, Sharma PK. Etodolac transfersomal film for transdermal delivery: preclinical evaluation. Int J Pharm Investig. 2024;14(3):125–34.
15. Patel K, Upadhyay TP, Vyas HA, Patel J, Upadhyay UM. Hydrogel thickened microemulsion for topical delivery of meloxicam: method development and evaluation. PharmaTutor. 2014;2(7):120–34.
16. Elkelish A, Elsayed MG, Abdel Razek A, et al. Etodolac nanoparticles in situ gel for transdermal rheumatoid arthritis therapy: pharmacokinetics and efficacy. Drug Deliv Transl Res. 2023;13(8):1650–60.
17. Tsai T, Chang T, Wang S. PLGA nanoparticle-loaded etodolac hydrogel for enhanced topical anti-inflammatory activity. Mater Sci Eng C. 2022;132:112481.
18. Mulla JAS, Karande BS. Microemulsion-based hydrogel formulation for topical drug delivery: review. Int J Pharm Pharm Res. 2017;9(2):124–59.
19. Gul U, Khan MI, Madni MA, Peltonen L. Olive oil- and clove oil-based nanoemulsion for topical delivery: in vitro and ex vivo evaluation. Pharm Dev Technol. 2022;27(2):449–58.
20. Landge VB, Jain SR, Hingane LD. Febuxostat nanoemulsion-based gel for gout: formulation and evaluation. Int J Pharm Res Appl. 2022;7(4):328–44.
21. Acharya SD, Tamane P, Khante S, Pokharkar V. Quality-by-design-based optimization of curcumin nanoemulsion: DoE and cytotoxicity studies. Indian J Pharm Educ Res. 2020;54(1):120–8.