

FORMULATION, OPTIMIZATION AND ESTIMATION OF CELECOXIB TOPICAL
EMULGEL

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ABSTRACT

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is widely used for chronic inflammatory disorders such as rheumatoid arthritis and osteoarthritis. However, its clinical utility via oral administration is restricted by negligible aqueous solubility, extensive first-pass hepatic metabolism by CYP2C9, and adverse gastrointestinal, renal, and cardiovascular effects. The objective of the present investigation was to formulate, optimize, and characterize a stable celecoxib topical emulgel to achieve sustained localized anti-inflammatory action, enhance cutaneous permeability, and minimize systemic exposure. A 2^3 factorial design was implemented to optimize the formulation parameters by evaluating three independent variables: gelling agent type (Carbopol 934 vs. HPMC), concentration of liquid paraffin (5.0% vs. 7.5% w/w), and emulsifier blend concentration (Tween 20 / Span 20 at 1.5% vs. 2.5% w/w). Preformulation screening included organoleptic testing, UV spectrophotometric calibration, equilibrium solubility profiling across multiple solvents, and forced degradation studies under stress conditions. Drug-excipient compatibility was investigated using Attenuated Total Reflectance Fourier-Transform Infrared (ATR-FTIR) spectroscopy and Differential Scanning Calorimetry (DSC). Formulations (F1–F8) were evaluated for physical appearance, pH, rheological behavior, spreadability, drug content uniformity, in vitro drug release via vertical Franz diffusion cells across synthetic dialysis membranes, mathematical release kinetics, ex-vivo permeation through excised porcine skin, and accelerated stability according to ICH Q1A(R2) guidelines. Preformulation confirmed drug purity with a melting endotherm at 161.8 °C and λ_{max} of 252 nm. FTIR and DSC studies demonstrated the preservation of characteristic functional peaks (3336 cm^{-1} N–H stretch, 1348 cm^{-1} SO₂ stretch) without chemical degradation. All eight batches exhibited skin-compatible pH (6.18 $\pm$ 0.04 to 6.42 $\pm$ 0.04), viscosity ranging between 21,450 $\pm$ 120 and 29,580 $\pm$ 180 cP, spreadability between 17.6 $\pm$ 0.30 and 24.6 $\pm$ 0.42 g·cm/s, and drug content between 97.42 $\pm$ 0.64% and 99.48 $\pm$ 0.29%. Formulation F6 (2.5% HPMC, 5% liquid paraffin, 2.5% surfactant) was identified as the optimal batch, demonstrating superior spreadability (22.4 $\pm$ 0.34 g·cm/s), desirable viscosity (24,120 $\pm$ 145 cP), and highest sustained in vitro cumulative drug release of 93.2 $\pm$ 1.2% over 36 hours compared to the standard formulation (45%). Release kinetics best fitted the Higuchi diffusion model ($R^2=0.996$), confirming diffusion-controlled drug release. Ex-vivo permeation revealed a cumulative transdermal delivery of 75.6 $\pm$ 1.9% (4267 $\pm$ 107 $\mu\text{g}/\text{cm}^2$) and cutaneous retention of 12.8 $\pm$ 1.1%. Accelerated stability studies (40 $\pm$ 2 °C / 75 $\pm$ 5% RH for 3 months) showed no significant degradation or physicochemical alterations ($p>0.05$). The developed celecoxib emulgel (F6) provides controlled release, high skin permeation, and excellent physical stability, making it an effective alternative to conventional oral celecoxib delivery.

KEYWORDS: Topical Emulgel, 2^3 Factorial Design, Skin Permeation, Higuchi Kinetics, Anti-inflammatory, Carbopol 934, HPMC.**1. INTRODUCTION**

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, represents a significant advancement in non-steroidal anti-inflammatory drug (NSAID) therapy,

offering potent anti-inflammatory and analgesic effects with reduced gastrointestinal toxicity compared to non-selective NSAIDs. It is commonly recommended for the treatment of rheumatoid arthritis, osteoarthritis, and

many other inflammatory conditions due to its pain-relieving and anti-inflammatory properties. Nonetheless, oral intake of celecoxib may lead to undesirable systemic side effects, especially gastrointestinal discomfort, cardiovascular risks, and renal complications. These constraints have prompted investigators to examine localized medication delivery devices that can target inflammation directly while reducing systemic exposure.^[1]

Topical drug administration is seen as a viable substitute for medications aimed at localized anti-inflammatory effects. Administering the medication topically circumvents hepatic first-pass metabolism and diminishes the occurrence of adverse effects linked to oral treatment. The primary obstacle in the topical administration of celecoxib is its inadequate aqueous solubility and restricted skin permeability. Due to celecoxib's lipophilicity, traditional hydrogels fail to solubilize it efficiently, and conventional semisolids might not ensure sufficient transdermal delivery.^[2]

To address these constraints, emulgels have emerged as an effective topical formulation. An emulgel merges the benefits of emulsions and gels, rendering it particularly appropriate for hydrophobic pharmaceuticals. The emulsion phase facilitates drug solubilization, while the gel base enhances uniformity, spreadability, stability, and

patient compliance. Emulgels are non-greasy, cosmetically appealing, and easy to apply, enhancing adherence in chronic therapy.^[3]

2. MATERIALS AND METHODS

2.1 Materials and Equipment

- **Materials:** Celecoxib, Carbopol 934, Light Liquid Paraffin (LLP), Span 20, Tween 20, Propylene Glycol (PG), Ethanol, Triethanolamine, Methylparaben, and Propylparaben.
- **Equipment:** Magnetic stirrer with hot plate, UV-Visible Spectrophotometer, Brookfield Viscometer, Anton Paar MCR 302s Rheometer, Digital pH meter, Franz diffusion cells.

2.2 Formulation Optimization using 2³ Factorial Design

A 2³ full factorial design was utilized to optimize the formulation parameters. The independent variables were:

1. X1: Gelling agent type (Carbopol 934 vs. HPMC)
2. X2: Liquid paraffin concentration (5.0% vs. 7.5% w/w)
3. X3: Emulsifier concentration (1.5% vs. 2.5% w/w)

The dependent variables evaluated were Viscosity (Y1), Spreadability (Y2), and Cumulative Drug Release at 36 h (Y3).

Table 1: Quantitative Composition of Celecoxib Emulgel Formulations (% w/w).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Celecoxib	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Carbopol 934	1.0	—	1.0	—	1.0	—	1.0	—
HPMC	—	2.5	—	2.5	—	2.5	—	2.5
Light Liquid Paraffin	5.0	5.0	7.5	7.5	5.0	5.0	7.5	7.5
Tween 20	0.6	0.6	0.6	0.6	1.0	1.0	1.0	1.0
Span 20	0.9	0.9	0.9	0.9	1.5	1.5	1.5	1.5
Propylene Glycol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methylparaben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified Water (q.s. to)	100	100	100	100	100	100	100	100

2.3 Preparation of Celecoxib Emulgel

- **Gel Base:** Carbopol gels (F1, F3, F5, F7) were prepared by hydrating Carbopol 934 in water and neutralizing with triethanolamine. HPMC gels (F2, F4, F6, F8) were dispersed in hot water (80 °C) and cooled overnight.
- **Emulsion Phase:** Span 20 was dissolved in light liquid paraffin (oil phase). Tween 20 was dissolved in water. Celecoxib, methylparaben, and propylparaben were solubilized in ethanol and propylene glycol, then incorporated into the aqueous phase.
- **Mixing:** Both phases were heated to 70–80 °C, and the oil phase was added dropwise to the aqueous phase with continuous stirring. The resulting

emulsion was blended with the gel base in a 1: 1 ratio.

2.4 Ex-Vivo Skin Permeation

Freshly excised porcine ear skin was obtained from a registered abattoir. According to CPCSEA guidelines, abattoir byproducts do not require specific IAEC approval for ex-vivo studies. The skin was mounted in Franz cells. Parameters calculated included steady-state flux (J_{ss}), permeability coefficient (K_p), and skin retention.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

Table 2: Calibration Curve of Celecoxib in Methanol ($\lambda_{\max}=252$ nm).

S. No.	Concentration ($\mu\text{g/mL}$)	Absorbance (Mean $\pm$ SD, $n=3$)
1	4	0.194
2	8	0.381
3	12	0.571
4	16	0.758
5	20	0.948

Regression Equation: $y=0.0469x+0.0057$ ($R^2=0.9998$).

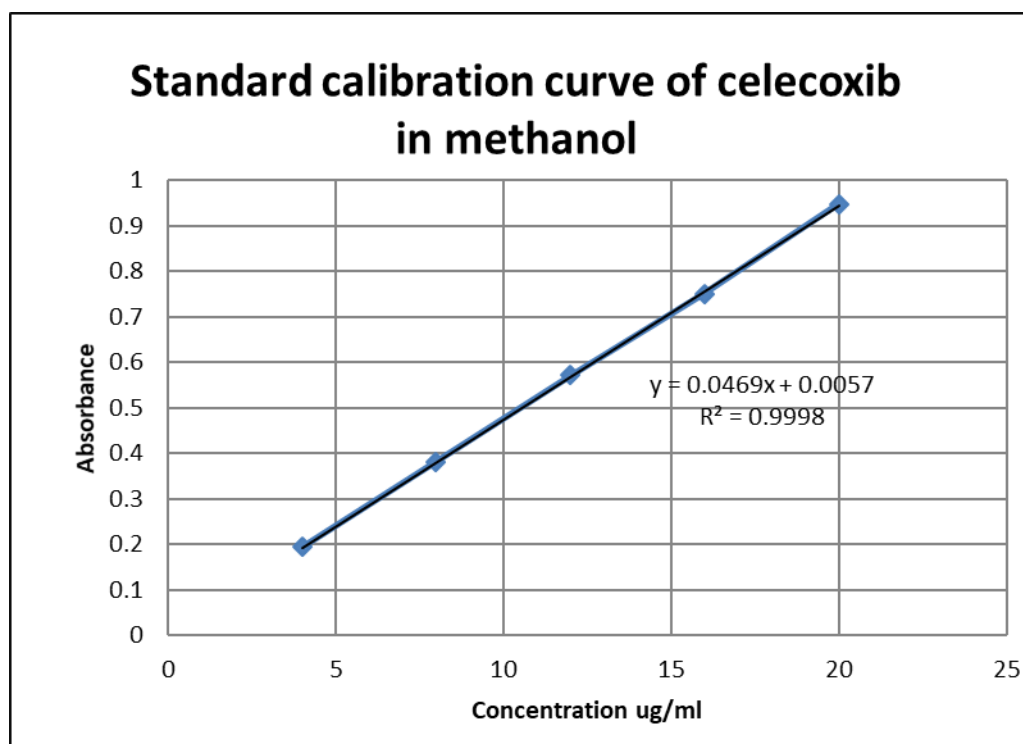


Figure 3.1: Calibration curve of Celecoxibin methanol.

The regression equation obtained was:

$$y = 0.0469x + 0.0057$$

where: y = absorbance at 252 nm

x = concentration of celecoxib in $\mu\text{g/mL}$

The correlation coefficient was:

$$R^2 = 0.9998$$

Table 3: Calibration Curve in PBS pH 7.4 : Ethanol (70: 30 v/v) ($\lambda=254$ nm).

S. No.	Concentration ($\mu\text{g/mL}$)	Absorbance (Mean $\pm$ SD, $n=3$)
1	4	0.192
2	8	0.380
3	12	0.569
4	16	0.758
5	20	0.945

Regression Equation: $y=0.0464x+0.0096$ ($R^2=0.9997$).

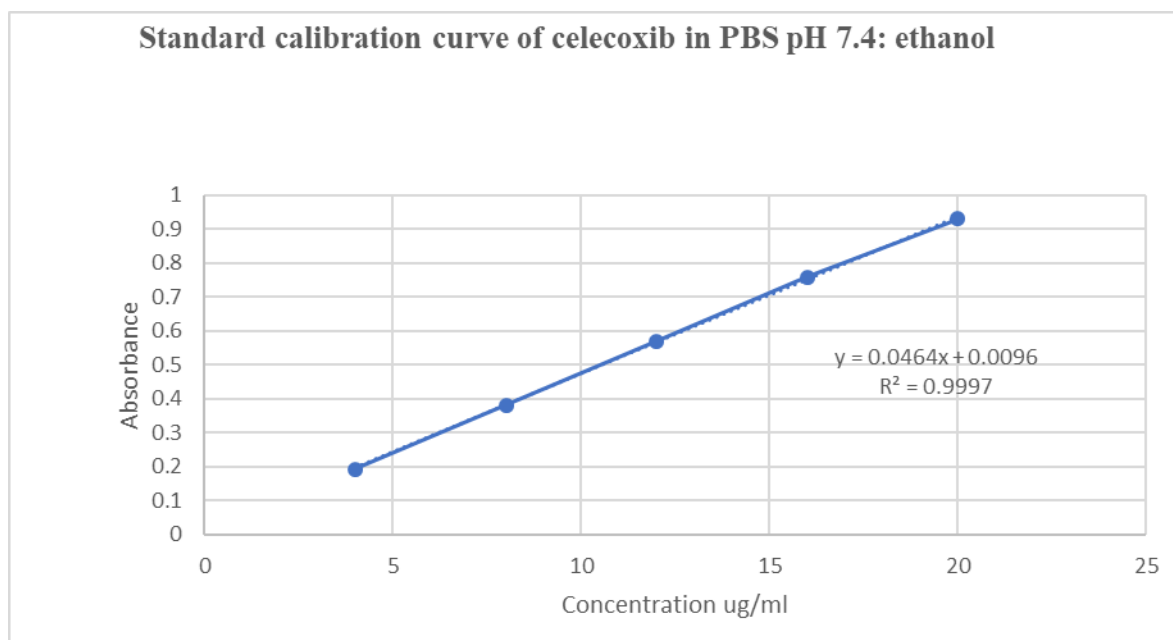


Figure 3.2: Calibration curve of celecoxib in phosphate buffer saline pH 7.4: ethanol (70: 30)

Regression Equation

$$Y = 0.0464X + 0.0096$$

Table 4: Equilibrium Solubility of Celecoxib in Different Solvents.

Solvent	Solubility (mg/mL)	Classification (USP/IP)
Purified Water	0.006±0.001	Practically insoluble
Phosphate Buffer pH 6.8	0.021±0.003	Very slightly soluble
Phosphate Buffer pH 7.4	0.034±0.002	Very slightly soluble
Methanol	19.86±0.35	Freely soluble
Ethanol	12.74±0.28	Sparingly soluble
Propylene Glycol	38.52±0.47	Soluble
PEG 400	54.68±0.52	Freely soluble

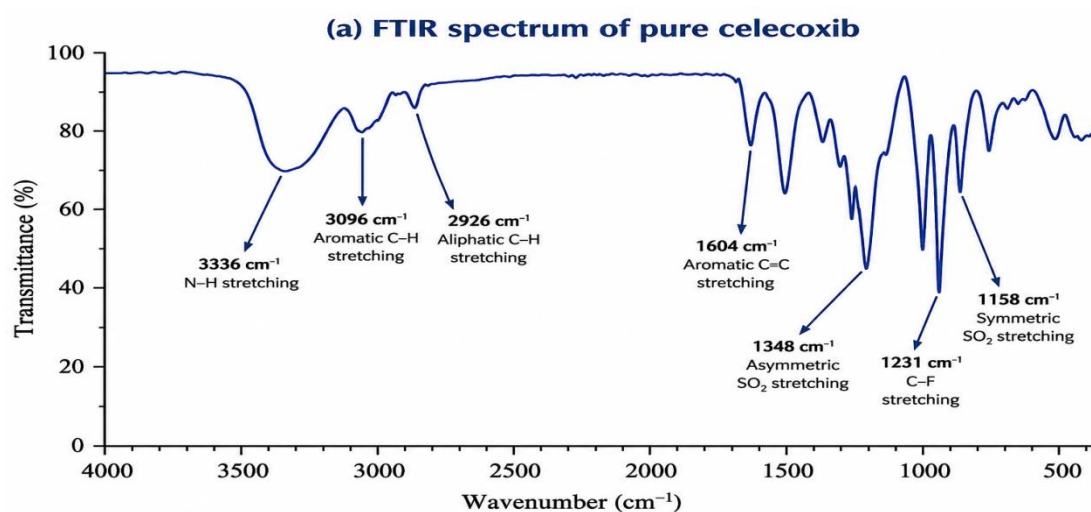


Figure 3.3: FTIR Spectra of Celecoxib.

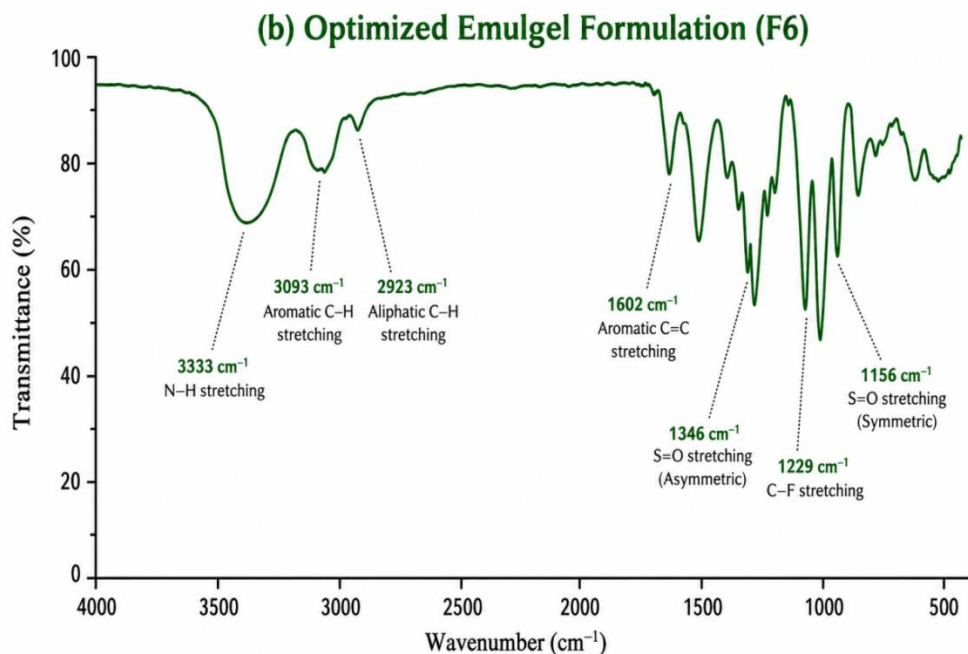


Figure 3.4: FTIR Spectra of formulation.

Table 5: Forced Degradation Profiling of Celecoxib.

Stress Condition	Drug Recovered (%)	Drug Degraded (%)
Control	100.00 $\pm$ 0.00	0.00
Acid Hydrolysis (0.1 M HCl)	95.42 $\pm$ 0.54	4.58
Alkaline Hydrolysis (0.1 M NaOH)	91.63 $\pm$ 0.63	8.37
Oxidative (3% H ₂ O ₂)	88.76 $\pm$ 0.71	11.24
Thermal (60 °C)	97.28 $\pm$ 0.41	2.72
Photolytic (UV Radiation)	96.64 $\pm$ 0.45	3.36

3.2 Differential Scanning Calorimetry (DSC)

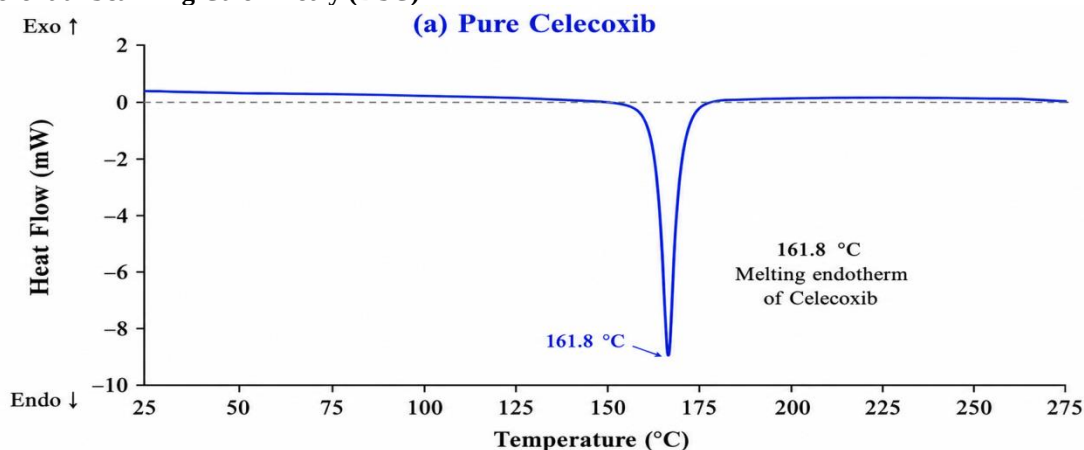


Figure 3.5: DSC thermogram of celecoxib.

3.3 Physicochemical Characterization of Formulations (F1–F8)

Table 6: Physicochemical Evaluation of Formulations F1–F8.

Formulation	Physical Appearance	pH	Viscosity (cP)	Spreadability ($\text{g}\cdot\text{cm/s}$)	Drug Content (%)
F1	White, smooth	6.24 $\pm$ 0.03	24,860 $\pm$ 135	20.8 $\pm$ 0.35	97.42 $\pm$ 0.64
F2	White, smooth	6.18 $\pm$ 0.04	21,450 $\pm$ 120	24.6 $\pm$ 0.42	98.05 $\pm$ 0.52
F3	Off-white, smooth	6.28 $\pm$ 0.02	26,380 $\pm$ 150	19.4 $\pm$ 0.31	98.62 $\pm$ 0.41
F4	Off-white, smooth	6.20 $\pm$ 0.03	22,680 $\pm$ 130	23.2 $\pm$ 0.37	98.84 $\pm$ 0.48
F5	White, smooth	6.36 $\pm$ 0.03	27,950 $\pm$ 160	18.5 $\pm$ 0.29	99.12 $\pm$ 0.37
F6	White, smooth	6.31 $\pm$ 0.02	24,120 $\pm$ 145	22.4 $\pm$ 0.34	99.36 $\pm$ 0.44

F7	Off-white, thick	6.42±0.04	29,580±180	17.6±0.30	99.48±0.29
F8	Off-white, thick	6.35±0.03	25,280±150	21.6±0.32	99.21±0.33

3.4 In Vitro Drug Release and Kinetics

The in vitro drug release of optimized formulation F6 was evaluated against a standard formulation (STD; plain

celecoxib gel without emulgel base). F6 showed sustained release reaching 93.2±1.2% at 36 h, while STD reached only 45.0±2.1%.

Table 7: Drug Release Kinetic Analysis of Optimized Batch F6.

Kinetic Model	Linear Regression Equation	Correlation Coefficient (R ²)	Release Mechanism
Zero-order	$y=3.0911x+10.761$	0.9030	Concentration-independent release
First-order	$y=0.0551x+0.9337$	0.5350	Concentration-dependent release
Higuchi	$y=0.0631x+0.1482$	0.9960	Matrix diffusion-controlled (Fickian)
Hixson-Crowell	$y=-0.0211x+3.8331$	0.1410	Erosion / dissolution rate-limited
Korsmeyer-Peppas	$y=0.9559x-0.7753$	0.6618	Non-Fickian transport

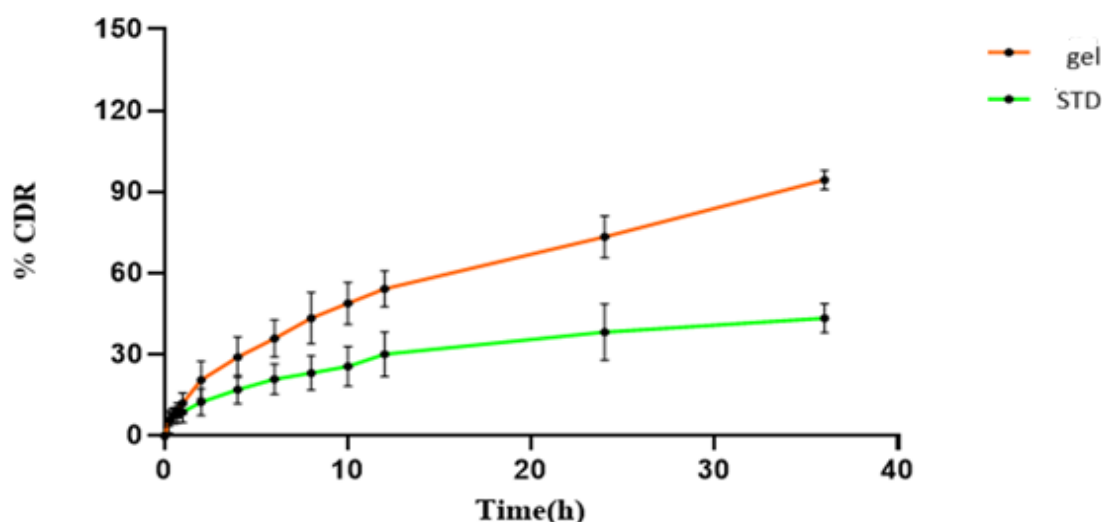


Figure 3.6: Percent cumulative drug release of emulgel and Standard formulation.

(STD). *Above data presented as Mean ± SD, n=6.

3.5 Ex-Vivo Skin Permeation Studies

Table 8: Ex-Vivo Skin Permeation Profile of Optimized Formulation F6.

Time (h)	Cumulative Permeation (%)	Cumulative Permeation (μg/cm ²)
0.5	2.8±0.3	158±17
1.0	4.7±0.4	265±23
2.0	8.9±0.5	502±29
4.0	15.8±0.8	892±45
6.0	22.4±0.9	1265±51
8.0	29.6±1.1	1672±62
10.0	36.8±1.2	2079±68
12.0	43.5±1.4	2457±79
24.0	61.8±1.7	3490±96
36.0	75.6±1.9	4267±107

Skin Retention: Celecoxib retained within the skin layers at 36 h was found to be 12.8±1.1% of the applied dose.

3.6 Accelerated Stability Study (ICH Q1A R2)

Table 9: Stability Study of Formulation F6 (40±2 °C / 75±5% RH).

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Smooth, homogeneous	No change	No change	No change
pH	6.31±0.02	6.30±0.03	6.29±0.02	6.28±0.03
Viscosity (cP)	24,120±145	23,980±152	23,890±161	23,760±168
Spreadability (g·cm/s)	22.4±0.34	22.3±0.31	22.2±0.36	22.1±0.33
Drug Content (%)	99.36±0.44	99.12±0.48	98.87±0.52	98.64±0.56
In-vitro Release (%)	93.2±1.2	92.8±1.3	92.4±1.4	91.9±1.5

4. CONCLUSION

In the present study, a stable celecoxib topical emulgel was successfully formulated and optimized using a 2³ factorial design. Preformulation, ATR-FTIR, and DSC analyses confirmed the purity of celecoxib and its chemical compatibility with Carbopol 934, HPMC, and the selected surfactant systems. Among all evaluated batches, formulation F6 (composed of 2.5% w/w HPMC, 5% w/w liquid paraffin, and 2.5% w/w Tween 20/Span 20 blend) demonstrated optimal physicochemical characteristics, including physiological skin pH (6.31±0.02), favorable spreadability (22.4±0.34 g·cm/s), and high drug content uniformity (99.36±0.44%). In vitro release exhibited a sustained release profile of 93.2±1.2% over 36 hours, best fitted by the Higuchi diffusion model ($R^2=0.996$), while ex-vivo studies demonstrated progressive transdermal permeation of 75.6±1.9% (4267±107 µg/cm²) across excised skin with 12.8±1.1% cutaneous retention. Accelerated stability studies for 3 months confirmed formulation integrity without significant degradation. Thus, the developed F6 emulgel represents a promising alternative to oral celecoxib for sustained, localized anti-inflammatory therapy with minimized systemic adverse effects.

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