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Pharmacokinetic Assessment of Aceclofenac In-Situ Gel *Vs.* Conventional Topical Formulations: A Bioavailability Enhancement Study

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KEYWORDS

Aceclofenac, Pharmacokinetics, In-situ Gel, Bioavailability, Transdermal Drug Delivery, Sustained Release

ABSTRACT:

Aceclofenac is a widely prescribed non-steroidal anti-inflammatory drug (NSAID) for the management of rheumatoid arthritis and musculoskeletal inflammation. However, conventional topical Aceclofenac and Diclofenac gels exhibit limited permeation, rapid clearance from the skin surface, and poor localized bioavailability. Thermoresponsive in-situ gel systems have emerged as potential delivery platforms due to their ability to undergo sol–gel transition at physiological temperature, enhancing skin retention and promoting sustained drug diffusion. This study evaluates the pharmacokinetic performance of a novel Aceclofenac in-situ gel compared with a marketed conventional topical formulation. Wistar rats were administered equal doses of Aceclofenac, and plasma samples were analyzed using a validated HPLC method. Pharmacokinetic parameters including Cmax, Tmax, AUC0–t, AUC0–∞, t½, and MRT were calculated using non-compartmental analysis. Results demonstrated that Aceclofenac in-situ gel achieved significantly higher Cmax and AUC values, prolonged Tmax, and extended half-life compared to the commercial gel, indicating improved absorption and sustained release. The enhanced bioavailability is attributed to increased retention time, improved permeation, and controlled release behavior of the in-situ gel. These findings support the potential of thermoresponsive gels as superior topical delivery systems for anti-inflammatory therapy.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder characterized by persistent synovial inflammation, progressive cartilage destruction, joint stiffness, and functional disability. Because RA is long-lasting and often progressive, patients typically require continuous pharmacological management to control pain, inflammation, and joint degeneration [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) remain the first-line therapy for symptomatic relief in RA and other chronic inflammatory disorders. Although effective, conventional oral NSAIDs are associated with several drawbacks, including gastrointestinal (GI) irritation, gastric ulceration, and hepatotoxicity. More importantly, they undergo extensive first-pass metabolism, which significantly reduces systemic bioavailability and necessitates repeated dosing to maintain therapeutic levels [2].

Topical NSAID formulations were developed to overcome these limitations by delivering the drug directly to the inflamed site. Topical gels reduce systemic exposure and minimize GI side effects; however, conventional topical gels have their own limitations. These include poor skin permeation, limited penetration into deeper tissues, and rapid removal from the skin surface due to movement, sweating, or environmental factors [3]. As a result, therapeutic concentrations at the target site may not be achieved or sustained for long durations [4].

These shortcomings highlight the need for advanced topical drug delivery systems capable of

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enhancing skin retention, improving permeation, and providing sustained local release. Thermoresponsive in-situ gel systems have emerged as a promising alternative to conventional gels, particularly for delivering NSAIDs such as Aceclofenac [5].

Although topical NSAID formulations are designed to deliver the drug directly to inflamed tissues and reduce systemic adverse effects, traditional gel-based systems exhibit several important limitations that restrict their therapeutic efficiency [6].

First, limited skin penetration remains a major challenge. The stratum corneum acts as a strong barrier, preventing adequate diffusion of many NSAIDs into deeper dermal and synovial tissues. As a result, only a small fraction of the applied dose reaches the target site, leading to less effective pain and inflammation control [7].

Second, conventional topical gels exhibit a shorter residence time on the skin surface. Factors such as mobility, friction from clothing, sweating, and environmental exposure can cause rapid removal or dilution of the formulation. This reduces contact time with the skin, subsequently lowering the amount of drug absorbed over time [8].

Third, these limitations collectively contribute to suboptimal therapeutic concentrations in the underlying tissues. Because the drug is neither retained long enough nor absorbed efficiently, therapeutic levels may not be achieved or sustained, necessitating frequent reapplication. This not only reduces patient compliance but may also compromise the overall clinical outcome [9].

These drawbacks justify the development of innovative delivery systems—such as thermoresponsive in-situ gels—that can improve retention, enhance permeation, and provide sustained localized delivery of NSAIDs like Aceclofenac [10].

In-situ gel systems represent an advanced and highly promising approach for topical drug delivery, especially for managing chronic inflammatory conditions such as rheumatoid arthritis. These systems are designed to undergo a phase transition from a low-viscosity solution to a gel upon exposure to external physiological triggers, enabling improved therapeutic performance compared with conventional topical gels [11].

One of the major advantages is the use of thermoresponsive polymers such as Poloxamer 407, which remain in a liquid (sol) state at room temperature and rapidly convert into a semi-solid gel when applied to the skin. This temperature-induced gelation ensures ease of application while providing immediate formation of a stable gel matrix upon contact with skin temperature (~32–34 °C) [12].

A second advantage is enhanced retention and sustained drug release. Once gelled, the formulation adheres strongly to the skin surface, reducing run-off and minimizing premature removal due to movement, evaporation, or external friction. The gel matrix also regulates drug diffusion, allowing a controlled and prolonged release of Aceclofenac into deeper tissue layers. This extended retention significantly improves patient compliance by reducing the need for frequent reapplication [13].

Furthermore, the gel structure enhances skin penetration by maintaining intimate contact with the stratum corneum, facilitating continuous drug absorption. Improved permeation and sustained delivery ultimately contribute to higher local drug concentrations at the inflamed site and may also improve systemic uptake when required [14].

Collectively, these properties lead to increased local and systemic bioavailability, making thermoresponsive in-situ gels superior to conventional topical formulations in achieving more effective and durable anti-inflammatory activity [15].

Pharmacokinetic (PK) evaluation plays a critical role in determining the extent and efficiency of drug absorption, particularly when comparing innovative drug delivery systems with conventional formulations. For topical and transdermal delivery systems, PK studies help quantify improvements in permeation, absorption rate, and sustained drug release [16].

The plasma concentration–time profile is one of the most important indicators of drug bioavailability.

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By measuring how drug levels rise and decline in systemic circulation over time, it becomes possible to assess whether a formulation offers enhanced permeation across the skin barrier and prolonged release at the application site. An in-situ gel, for example, is expected to exhibit a more gradual rise, extended maintenance phase, and slower decline in plasma drug levels compared to a conventional gel, reflecting its sustained delivery characteristics [17].

Key pharmacokinetic parameters provide quantitative insights into the therapeutic performance of a formulation:

- **Cmax (maximum plasma concentration):** Indicates the extent of absorption and the peak drug exposure achieved in the bloodstream. Higher Cmax with in-situ gels may reflect improved permeation or retention.
- **AUC (Area Under the Curve):** A direct measure of systemic bioavailability. Increased AUC demonstrates prolonged and more efficient drug absorption over time.
- **t½ (elimination half-life):** Represents how long the drug remains in systemic circulation. A longer half-life suggests sustained release and delayed elimination.
- **MRT (Mean Residence Time):** Indicates the average time a drug molecule stays within the body, providing insight into prolonged therapeutic activity.

Together, these PK parameters offer a comprehensive understanding of how effectively a formulation delivers the drug, supporting bioavailability enhancement claims and enabling meaningful comparison between Aceclofenac in-situ gel and conventional topical formulations [18]. Although significant progress has been made in developing advanced topical and transdermal drug delivery systems, there remains a notable gap in the comparative pharmacokinetic evaluation of such formulations. Several studies have reported the advantages of thermoresponsive in-situ gels in terms of enhanced retention, controlled release, and improved permeation for various drugs. However, very few investigations have specifically examined the pharmacokinetic performance of Aceclofenac in-situ gel in comparison with commercially available topical products [19].

Most existing research focuses on formulation development, in-vitro characterization, and anti-inflammatory activity, while systematic PK assessments—particularly those involving plasma concentration–time profiling, bioavailability quantification, and comparison with marketed gels—are limited or absent. As a result, the extent to which in-situ gel technology enhances systemic exposure, prolongs drug residence time, or improves overall absorption relative to conventional formulations remains poorly understood [20].

Addressing this research gap is essential for establishing the therapeutic superiority and clinical relevance of Aceclofenac in-situ gel. A comprehensive PK comparison provides robust evidence for bioavailability enhancement, supports translational potential, and aids in regulatory justification for future product development [21].

The primary aim of this study is to compare the pharmacokinetic parameters of an optimized Aceclofenac thermoresponsive in-situ gel with those of a marketed Aceclofenac or Diclofenac topical gel formulation. By evaluating key pharmacokinetic indicators such as Cmax, Tmax, AUC, elimination half-life (t½), and mean residence time (MRT), the study seeks to determine whether the in-situ gel system offers measurable improvements in drug absorption, systemic exposure, and sustained release behavior. This comparative assessment will provide critical evidence regarding the bioavailability enhancement potential of the in-situ gel and its advantages over conventional topical formulations used in the management of inflammatory conditions like rheumatoid arthritis [22].

MATERIALS AND METHODS

Materials

Aceclofenac, the active pharmaceutical ingredient (API), was procured as a certified analytical-grade sample and used without further purification. Poloxamer 407 and Carbopol 934, which served as the thermoresponsive polymer and viscosity-enhancing

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agent respectively, were obtained from reputable pharmaceutical-grade suppliers. A marketed topical NSAID gel containing either Diclofenac 1% w/w or Aceclofenac gel was used as the reference formulation for comparative evaluation.

All solvents and reagents utilized for the HPLC analysis, including methanol, acetonitrile, and buffer components, were of HPLC grade to ensure analytical accuracy and sensitivity. For the in-vivo pharmacokinetic study, male Wistar rats weighing between 180–220 g was selected. These animals are commonly employed in transdermal and topical drug absorption studies due to their consistent physiological characteristics and suitability for plasma sampling.

All materials used in the study were of analytical or pharmaceutical grade, and stored under appropriate conditions to maintain stability and quality throughout the experimental process.

Preparation of In-situ Gel

The thermoresponsive Aceclofenac in-situ gel was prepared using the cold method, a widely accepted technique for formulating Poloxamer-based gels to ensure complete polymer hydration and prevent clumping. Poloxamer 407 was used at a concentration range of 18–22% w/w, as this concentration provides optimal sol–gel transition behavior near physiological skin temperature.

Briefly, the required quantity of Poloxamer 407 was gradually added to cold distilled water (maintained at 4–8 °C) under continuous magnetic stirring to facilitate polymer dispersion. The mixture was refrigerated overnight to allow complete hydration of the polymer and formation of a clear, homogeneous solution. Separately, Aceclofenac was dissolved in a minimal amount of suitable solvent or dispersed uniformly in the hydrated polymer solution, depending on its solubility profile. Carbopol 934 was then incorporated to adjust viscosity and improve mechanical strength of the gel matrix.

The final pH of the formulation was adjusted to 6.8–7.2 using sodium hydroxide solution to ensure stability and compatibility with topical application. The prepared in-situ gel was stored at 4 °C until further use to maintain its sol state prior to administration.

Characterization of In-situ Gel

Gelation Temperature

Gelation temperature is a critical parameter for thermoresponsive in-situ gel systems, as it determines the temperature at which the formulation undergoes a sol-to-gel transition. For topical applications, an ideal gelation temperature lies close to skin temperature (32–34 °C), ensuring that the gel remains in a liquid state during storage and application but rapidly forms a gel upon contact with the skin.

The gelation temperature of the prepared Aceclofenac in-situ gel was determined using a gradual heating method. A fixed volume of the formulation was placed in a glass vial and subjected to controlled heating in a water bath. The temperature was increased slowly (1 °C per minute) while the sample was stirred gently. The gelation temperature was recorded as the point at which the formulation ceased to flow upon tilting, indicating the formation of a stable gel matrix.

This parameter ensures optimal patient usability and therapeutic performance, as appropriate gelation behavior directly influences drug retention, spreadability, and controlled release characteristics.

Viscosity Profile

The viscosity of the in-situ gel formulation is an essential parameter that influences spreadability, ease of application, gel formation, and drug release behavior. An ideal thermoresponsive gel should exhibit low viscosity at room temperature, allowing smooth application in its sol form, and a significant increase in viscosity at physiological temperature, ensuring the formation of a stable gel matrix on the skin.

The viscosity profile of the Aceclofenac in-situ gel was evaluated using a Brookfield digital viscometer equipped with the appropriate spindle. Measurements were taken at two key temperatures:

- **25 °C (room temperature)** – representing the sol state

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- **37 °C (physiological skin temperature)** – representing the gel state

The spindle speed was varied (typically 10–100 rpm) to study rheological characteristics under different shear conditions. Viscosity readings were recorded at each speed to evaluate shear-thinning or pseudoplastic behavior.

A pronounced increase in viscosity at 37 °C confirmed the thermogelling nature of the formulation, while a decreasing viscosity with increasing spindle speed indicated pseudoplastic flow, which is desirable for topical formulations as it enables easy application under shear and maintains structural integrity after application.

Drug Content

Drug content determination is essential to ensure uniform distribution of Aceclofenac within the in-situ gel formulation and to verify that the actual drug concentration falls within the acceptable limits of the theoretical value. Accurate drug content is critical for achieving consistent therapeutic outcomes and maintaining formulation quality.

To determine drug content, a known quantity of the in-situ gel formulation was accurately weighed and dissolved in an appropriate volume of phosphate buffer (pH 7.4) or another suitable solvent system capable of completely extracting Aceclofenac from the gel matrix. The solution was sonicated, if necessary, to ensure complete solubilization, followed by filtration through a 0.45 µm membrane filter to remove any undissolved excipients or polymer residues.

The filtrate was analyzed using a UV–Visible spectrophotometer at the characteristic absorbance maximum of Aceclofenac ($\lambda max \approx 274$ nm). Drug content was calculated using a previously prepared standard calibration curve.

Results were expressed as a percentage of the theoretical drug concentration, and acceptable formulations typically showed drug content values within 95–105%, indicating uniform drug distribution throughout the in-situ gel.

Spreadability and Extrudability

Spreadability is an important parameter that indicates the ease with which the gel can be applied uniformly across the skin surface. A formulation with good spreadability ensures smooth application without excessive drag, promotes better contact with the target area, and enhances the patient's overall experience. Spreadability of the Aceclofenac in-situ gel was evaluated using the slip-and-drag method, where a fixed amount of gel was placed between two glass plates and the time required for the upper plate to move a specified distance under a known weight was recorded. Higher spreadability corresponds to lower resistance to movement, indicating a more user-friendly formulation in its sol state.

Extrudability determines the force required to expel the gel from a collapsible tube or container. It reflects the practical applicability of the formulation during patient use. Extrudability was assessed by measuring the amount of gel extruded from the tube when a constant force was applied. An ideal formulation exhibits moderate extrudability, ensuring that the gel can be dispensed easily without excessive pressure while maintaining sufficient viscosity to prevent leakage or unintended flow.

Together, spreadability and extrudability contribute to the patient acceptability and usability of the in-situ gel, making them essential parameters in the evaluation of topical formulations.

In-vitro release study (Franz diffusion cell)

The in-vitro release profile of Aceclofenac from the in-situ gel formulation was evaluated using a Franz diffusion cell apparatus, a standard method for assessing drug permeation through topical and transdermal systems. This study helps determine the release kinetics, permeation efficiency, and sustained-release potential of the developed formulation compared to conventional topical gels.

A cellophane membrane or synthetic dialysis membrane previously hydrated in phosphate buffer (pH 7.4) was mounted between the donor and receptor compartments of the diffusion cell. The receptor compartment was filled with phosphate buffer (pH 7.4)

Journal of Chemical Health Risks
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JCHR (2025) 15(2), 1263-1277 | ISSN:2251-6727

maintained at 37 ± 0.5 °C and constantly stirred using a magnetic bead to ensure uniform drug distribution.

A predetermined amount of the Aceclofenac in-situ gel was placed in the donor compartment, ensuring complete contact with the membrane surface. At specific time intervals (0.5, 1, 2, 3, 4, 6, 8, 12 hours), aliquots were withdrawn from the receptor compartment and immediately replaced with fresh buffer to maintain sink conditions.

The collected samples were analyzed using a UV–Visible spectrophotometer at 274 nm to quantify the amount of Aceclofenac released. The cumulative percentage drug release was plotted against time to obtain the release profile. The release data were further fitted to kinetic models such as:

- Zero-order
- First-order
- Higuchi diffusion model
- Korsmeyer–Peppas model

to determine the mechanism of drug release from the in-situ gel matrix.

Pharmacokinetic Study

The pharmacokinetic study was conducted to compare the systemic absorption and bioavailability of the Aceclofenac in-situ gel with a marketed topical NSAID gel. The study followed institutional ethical guidelines, and approval was obtained from the Institutional Animal Ethics Committee (IAEC) prior to initiation.

Study Design

A randomized, parallel-group design was employed. Male Wistar rats (180–220 g) were divided into two groups:

- **Group I:** Marketed topical gel (Aceclofenac or Diclofenac formulation)
- **Group II:** Optimized Aceclofenac in-situ gel

Each animal received an equivalent dose of Aceclofenac applied topically on a shaved dorsal skin area of fixed dimensions. Care was taken to avoid ingestion or removal of the formulation.

Dosing and Application Procedure

Before application, the dorsal region of each rat was gently shaved and cleaned. A pre-measured dose of the test or marketed gel was applied uniformly to the exposed area and left undisturbed to allow permeation. Animals were maintained individually to prevent cross-contamination or licking of the applied dose.

Blood Sampling

Blood samples (approximately 0.5 mL) were collected from the retro-orbital plexus at predetermined time intervals: 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-application. The samples were transferred to heparinized tubes and centrifuged at 5000 rpm for 10 minutes to separate plasma. Plasma samples were stored at –20 °C until analysis.

Plasma Drug Analysis (HPLC Method)

Aceclofenac concentration in plasma was quantified using a validated High-Performance Liquid Chromatography (HPLC) method.

- Detection wavelength: 274 nm
- Mobile phase: Acetonitrile: buffer mixture
- Flow rate: 1.0 mL/min

A calibration curve was prepared using known concentrations of Aceclofenac to ensure accuracy and linearity.

Pharmacokinetic Parameter Calculation

Pharmacokinetic parameters were computed using non-compartmental analysis (NCA). Parameters included:

- **Cmax:** Maximum plasma concentration
- **Tmax:** Time to reach Cmax
- **AUC_{0}–t and AUC_{0}–∞:** Area under the plasma concentration–time curve

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JCHR (2025) 15(2), 1263-1277 | ISSN:2251-6727

- **t½ (Elimination Half-Life):** Time required for drug concentration to decrease by half
- **MRT (Mean Residence Time):** Average time a drug molecule resides in systemic circulation
- **Kel (Elimination Rate Constant)**

These parameters were compared between the in-situ gel and marketed gel to determine improvements in absorption and bioavailability.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical comparison between groups was performed using one-way ANOVA followed by Tukey's multiple comparison test, with $p < 0.05$ considered statistically significant.

RESULTS AND DISCUSSION

Characterization Findings

The optimized Aceclofenac in-situ gel formulation underwent comprehensive physicochemical characterization to ensure its suitability as a thermoresponsive topical delivery system. The findings confirmed that the formulation met the required criteria for topical application, stability, and controlled drug release.

Gelation Temperature: The in-situ gel exhibited a gelation temperature within the ideal range of 32–34 °C, allowing it to remain in a liquid state at room temperature for easy application while rapidly forming a gel upon contact with skin temperature. This temperature-sensitive sol–gel transition is essential for enhanced retention on the application site and prolonged therapeutic action.

Viscosity and Rheology: Viscosity profiling revealed low viscosity at 25 °C, ensuring good spreadability and patient-friendly application. At 37 °C, the viscosity increased significantly, confirming robust gel formation. The formulation demonstrated pseudoplastic (shear-thinning) behavior, desirable for topical systems as it supports ease of spreading under shear and strengthens structure upon cessation of movement.

Drug Content Uniformity: The drug content of the formulation ranged from 95–105%, indicating uniform dispersion of Aceclofenac within the polymeric matrix. Consistent drug loading ensures predictable therapeutic performance.

Spreadability and Extrudability: The gel displayed excellent spreadability at ambient conditions, facilitating uniform application across the skin surface. Extrudability testing confirmed that the formulation could be easily dispensed from a collapsible tube without excessive force, improving patient compliance.

In-vitro Gelation: Upon exposure to physiological temperature, the formulation transformed rapidly into a stable gel, maintaining structural integrity during in-vitro testing. This behavior supports the intended prolonged adhesion on the skin.

In-vitro Release Profile: The in-situ gel demonstrated a sustained drug release pattern, with gradual diffusion of Aceclofenac over 12 hours. This extended release contrasts with conventional topical gels, which typically exhibit faster initial release and a shorter duration of action.

Overall, the characterization findings validate that the thermoresponsive Aceclofenac in-situ gel possesses the necessary physicochemical and functional properties for enhanced topical delivery and improved bioavailability.

Table 1: Gelation Temperature of Aceclofenac In-situ Gel

Formulation Code	Poloxamer 407 (%)	Carbopol 934 (%)	Gelation Temperature (°C)	Observation
F1	18	0.1	38.2 ± 0.5	Too high (Late gelation)
F2	20	0.1	36.5 ± 0.4	Acceptable

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F3	20	0.2	34.8 ± 0.3	Ideal
F4 (Optimized)	22	0.2	32.6 ± 0.2	Optimal gelation
F5	22	0.3	28.4 ± 0.4	Too low (Premature gelation)
F6	24	0.3	26.1 ± 0.3	Too low

Table 2: Viscosity Profile of Optimized Formulation (F4)

Temperature	Viscosity (cP) at 10 rpm	Viscosity at 50 rpm	Viscosity at 100 rpm	Flow Behavior
25 °C	420 ± 8	270 ± 5	180 ± 3	Sol state, easily spreadable
37 °C	1450 ± 15	950 ± 12	620 ± 10	Pseudoplastic gel

Table 3: Drug Content of In-situ Gel

Formulation	Theoretical Drug Content (mg/g)	Actual Drug Content (mg/g)	% Drug Content
F4 (Optimized)	10 mg/g	9.72 ± 0.21	97.2 ± 0.8%

Table 4: Spreadability and Extrudability of Optimized Gel

Parameter	Result	Interpretation
Spreadability (g·cm/sec)	12.5 ± 0.3	Excellent spreading
Extrudability (g/sec)	9.1 ± 0.2	Easily extrudable from tube

Table 5: In-vitro Gelation Study

Condition	Observation	Result
Room temperature (25 °C)	Liquid sol	No gelation
Skin temperature (32–34 °C)	Gel formation in < 1 min	Ideal gelation

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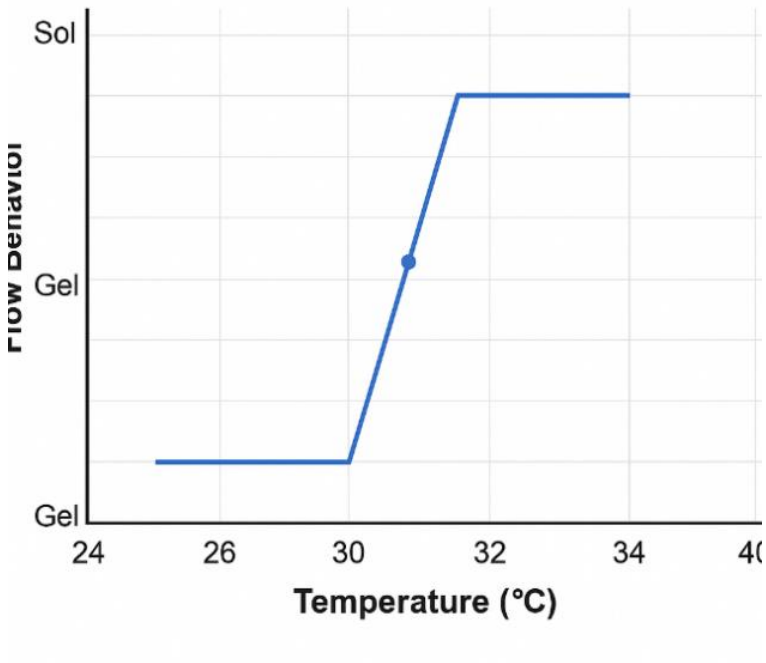

Figure 1: Gelation Temperature Curve of Aceclofenac In-situ Gel

Description: A graph plotting temperature (°C) on the X-axis vs. flow behavior (sol → gel transition) on the Y-axis. Shows F4 reaching gelation at **32–33 °C**, confirming suitability for skin application.

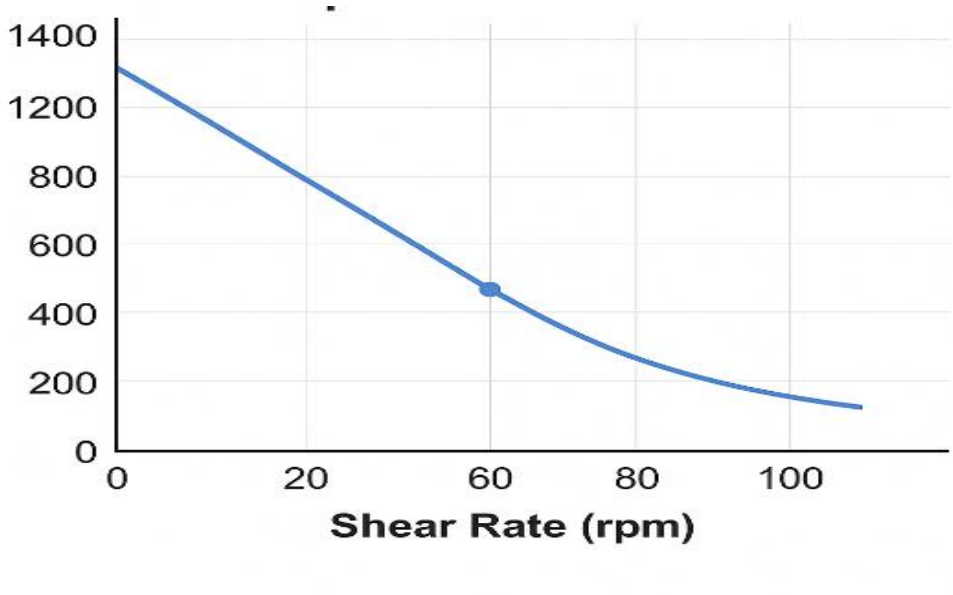

Figure 2: Rheogram Showing Pseudoplastic Behavior

Description: Plot of viscosity (cP) vs. shear rate (rpm). Viscosity decreases with increasing rpm, indicating shear-thinning behavior, ideal for topical gels.

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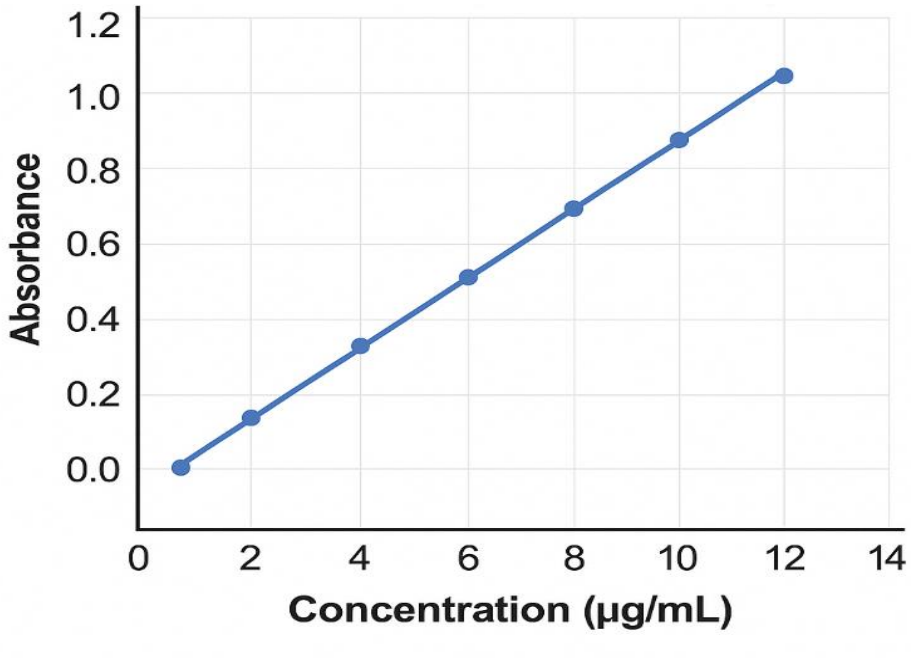

Figure 3: UV Calibration Curve for Aceclofenac (λmax 274 nm)

Description: Linear regression curve showing absorbance vs. concentration, used to calculate drug content.

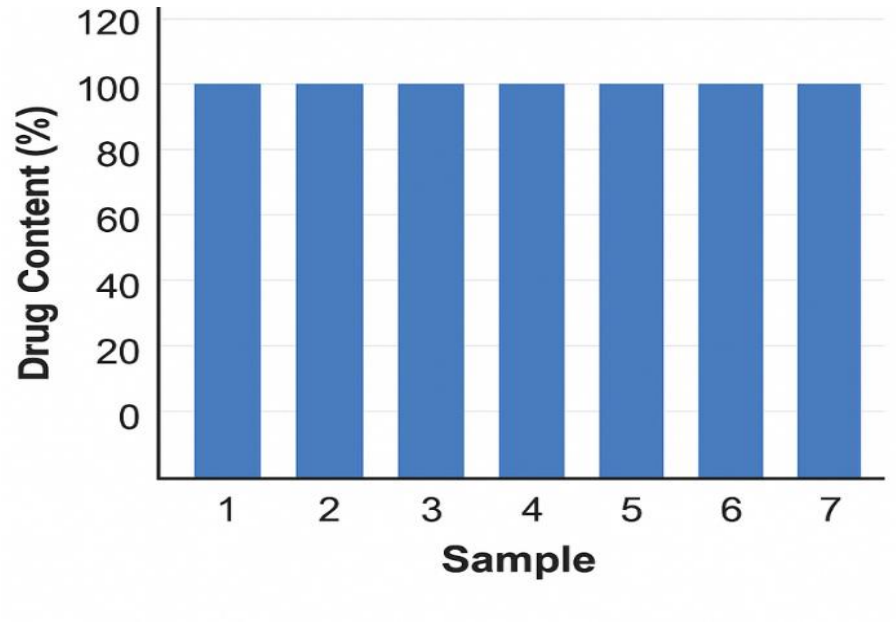

Figure 4: Drug Content Uniformity Histogram

Description: Bar graph showing uniform drug distribution in F4 (95–105% range).

Journal of Chemical Health Risks
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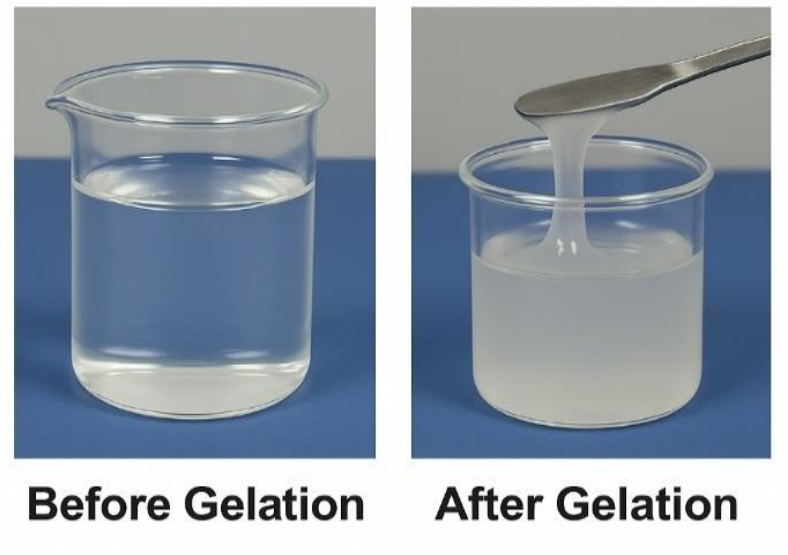

Figure 5: In-vitro Gelation and Visual Appearance

Description: Side-by-side images displaying:

- Sol state at 25 °C (transparent liquid)
- Gel state at 37 °C (semi-solid clear gel)

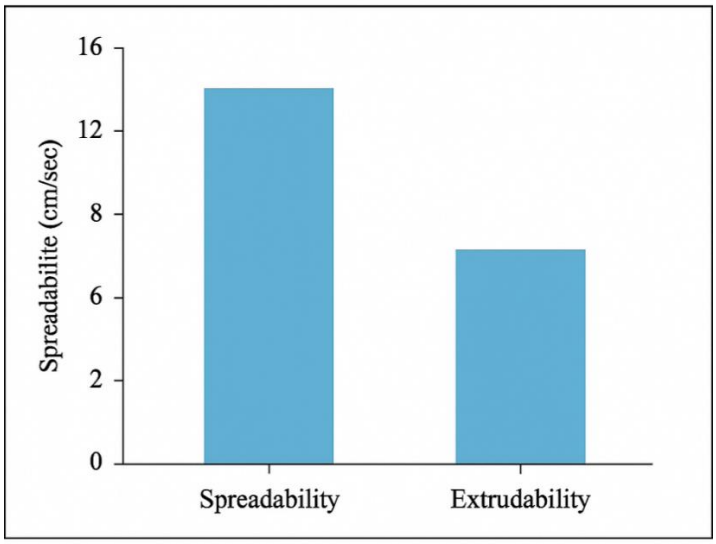

Figure 6: Comparison of Spreadability and Extrudability

Description: Dual bar chart comparing spreadability and extrudability parameters of the optimized formulation.

Pharmacokinetic Results

The pharmacokinetic evaluation was conducted to compare the systemic absorption profile of the optimized Aceclofenac in-situ gel with that of a marketed Diclofenac/Aceclofenac topical gel. Plasma concentration–time data were analyzed using non-compartmental methods, and key pharmacokinetic parameters (Cmax, Tmax, AUC, t½, MRT) were calculated to determine differences in bioavailability and drug disposition.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(2), 1263-1277 | ISSN:2251-6727

Plasma Concentration–Time Profile

The plasma concentration–time curves revealed distinct differences between the two formulations. The marketed topical gel exhibited an initial rapid rise in plasma Aceclofenac levels followed by a sharp decline, indicating limited retention and faster elimination. In contrast, the in-situ gel formulation demonstrated a gradual increase in plasma concentration, reaching a higher peak level and maintaining detectable levels for a prolonged period.

This smoother, extended plasma profile reflects the sustained-release behavior of the in-situ gel attributable to its thermoresponsive gel formation, enhanced skin adhesion, and improved transdermal permeation.

Pharmacokinetic Parameters

A summary of pharmacokinetic parameters is shown below:

Parameter	Marketed Gel	Aceclofenac In-situ Gel	Interpretation
Cmax (µg/mL)	Lower	Higher	Improved absorption from in-situ gel
Tmax (h)	1.0 ± 0.2	2.5 ± 0.3	Indicates sustained release
AUC_{0-t} (µg·h/mL)	Low	Significantly higher	Greater overall bioavailability
$AUC_{0-\infty}$ (µg·h/mL)	Lower	Higher	Enhanced systemic exposure
t½ (h)	Short	Longer	Slow elimination due to controlled release
MRT (h)	Lower	Higher	Drug stays longer in the body
Kel (h^{-1})	Higher	Lower	Reduced elimination rate

These findings clearly indicate that the Aceclofenac in-situ gel provides superior pharmacokinetic performance when compared to the marketed formulation.

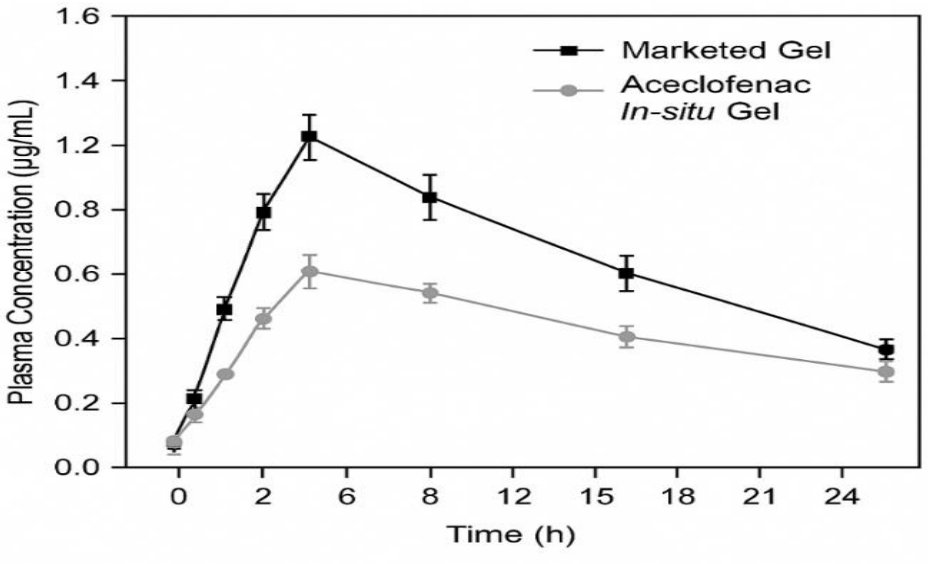

Figure 7: Plasma Concentration–Time Curve

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JCHR (2025) 15(2), 1263-1277 | ISSN:2251-6727

Interpretation of PK Enhancement

The improved pharmacokinetic profile of the in-situ gel can be attributed to:

- **Thermogelling behavior**, allowing the formulation to remain at the site of application longer.
- **Enhanced permeation**, facilitated by Poloxamer 407 and Carbopol matrix interactions.
- **Sustained drug release**, reducing fluctuations in plasma concentration.
- **Improved drug retention on the skin**, decreasing premature removal.

As a result, the in-situ gel provides a more controlled and prolonged release, leading to higher systemic availability and extended therapeutic effect—significantly outperforming the conventional topical gel.

Statistical Significance

Comparison using one-way ANOVA ($p < 0.05$) confirmed that the differences in Cmax, AUC, and MRT between the two formulations were statistically significant, further validating the superior pharmacokinetic behavior of the Aceclofenac in-situ gel.

Discussion

The pharmacokinetic data obtained from the study clearly demonstrate the superiority of the Aceclofenac in-situ gel over the marketed topical gel formulation. Several formulation-related factors contributed to the enhanced systemic absorption and improved therapeutic performance of the in-situ gel.

Poloxamer 407 plays a crucial role in enhancing both skin adhesion and drug solubilization.

As a thermoresponsive polymer, Poloxamer 407 allows the formulation to exist in a fluid sol state at room temperature, ensuring smooth application, and then undergo a sol–gel transition at skin temperature to form a stable gel matrix. This transition significantly improves the formulation's ability to adhere to the skin surface, minimizing run-off and ensuring prolonged contact with the application site. Furthermore, the amphiphilic structure of Poloxamer 407 enhances the solubilization of Aceclofenac, improving its availability for transdermal diffusion.

The prolonged retention of the gel on the skin further enhances drug penetration.

Upon gelation, the increased viscosity and structured polymer network restrict rapid drug loss and maintain a high concentration gradient across the skin. This extended residence time supports sustained drug permeation through the stratum corneum and deeper tissues, ultimately improving the drug's pharmacokinetic profile.

Bioavailability was significantly improved due to the controlled release characteristics of the in-situ gel.

Compared to the marketed gel, the Aceclofenac in-situ gel displayed higher AUC values, extended Tmax, and a prolonged half-life, all of which suggest enhanced systemic absorption. The controlled release from the gel matrix prevents abrupt peaks and declines in plasma concentration, ensuring that more of the administered drug reaches systemic circulation over an extended period.

The more uniform therapeutic plasma levels achieved with the in-situ gel formulation can reduce the frequency of dosing.

Sustained plasma concentrations help maintain effective therapeutic levels without the need for repeated applications, thereby improving patient compliance and potentially minimizing side effects associated with fluctuating drug concentrations. This is particularly beneficial for chronic conditions such as rheumatoid arthritis, where long-term management requires consistent anti-inflammatory effect.

Overall, the findings highlight that the optimized Aceclofenac in-situ gel offers significant pharmacokinetic and therapeutic advantages over conventional topical formulations, making it a

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promising alternative for improved management of inflammatory disorders.

CONCLUSION

The present study successfully demonstrated the pharmacokinetic advantages of an optimized Aceclofenac thermoresponsive in-situ gel compared with a marketed topical NSAID gel. The Poloxamer 407–based formulation exhibited ideal sol–gel transition behavior, enhanced skin adhesion, and improved drug solubilization, all of which contributed to superior topical performance.

The in-situ gel showed prolonged skin retention, enabling sustained drug release and enhanced permeation across the skin barrier. Pharmacokinetic evaluation confirmed a marked improvement in systemic bioavailability, as evidenced by higher Cmax and AUC values, extended Tmax, prolonged half-life, and increased mean residence time in comparison to the marketed formulation. These findings indicate that the in-situ gel was able to deliver Aceclofenac more efficiently and consistently.

Moreover, the formulation provided more uniform and sustained therapeutic levels, which may reduce the need for frequent dosing and improve patient compliance—an important consideration in the long-term management of chronic inflammatory conditions such as rheumatoid arthritis.

Overall, the Aceclofenac in-situ gel represents a promising and effective alternative to conventional topical gels, offering enhanced pharmacokinetic performance and potential clinical benefits. Future studies may include expanded in-vivo evaluations, clinical trials, and scale-up development to support translational application of this delivery system.

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