Borneo Journal of Pharmacy
Vol 9 Issue 1 March 2026
Pages 35 – 47

https://journal.umpr.ac.id/index.php/bjop/article/view/10417
DOI: https://doi.org/10.33084/bjop.v9i1.10417
e-ISSN: 2621-4814

Research Article

Optimization of Gel Cream Containing HAMIN™ and HPMC K100M as Bases for Topical Delivery of Diclofenac Sodium

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Keywords:
Gel cream
HAMIN™
HPMC K100M
Optimization
Simplex lattice design

Abstract

Diclofenac sodium, a widely used NSAID, has limited skin permeability, which reduces its topical efficacy; therefore, a gel-cream formulation combining the rapid absorption of gels with the emollient properties of creams is proposed to enhance drug penetration and patient comfort. To further improve delivery, HAMIN™, a novel natural palm oil–based base with excellent biocompatibility and lipid-enhancing properties, will be combined with HPMC K100M. This thickener stabilises viscosity and prolongs skin contact time, supporting better absorption. This study aimed to develop and optimise a topical gel cream for diclofenac sodium using HAMIN™ and HPMC K100M to achieve ideal physical properties and improved skin penetration. The formulation was statistically optimised using a Simplex Lattice Design (SLD), with HAMIN™ (X_1) and HPMC K100M (X_2) as independent variables, and pH (Y_1), spreadability (Y_2), viscosity (Y_3), extrudability (Y_4), release flux (Y_5), and permeation flux (Y_6) as dependent responses. Optimisation with Design Expert version 13 yielded the ideal composition of 16.84% HAMIN™ and 1.16% HPMC K100M, resulting in predicted values of pH 5.07, spreadability 7 cm, viscosity 4502.25 mPas, extrudability 78.98 N/s, release flux 70.61 µg/cm²/minute, and permeation flux 0.4868 µg/cm²/minute, with a desirability score of 0.829. Despite a slightly lower release flux, the optimised HAMIN™ and HPMC K100M-based gel cream demonstrated superior skin permeation compared to a commercial emulgel for up to 300 minutes. The incorporation of HAMIN™, a natural palm oil base, offers a novel and effective strategy to enhance the topical delivery of diclofenac sodium via a statistically optimised gel cream formulation.

Received: July 30th, 2025
1st Revised: November 13th, 2025
Accepted: December 11th, 2025
Published: March 30th, 2026

How to cite: Winarti L, Gazzali AM, Mufidah FM, Faramayuda F, Ulfa EU, Nurahmanto D, et al. Optimization of Gel Cream Containing HAMIN™ and HPMC K100M as Bases for Topical Delivery of Diclofenac Sodium. Borneo J Pharm. 2026;9(1):35-47. doi:10.33084/bjop.v9i1.10417

INTRODUCTION

HAMIN™ is widely recognized as a sustainable alternative to synthetic base materials in pharmaceutical and cosmetic semi-solid dosage forms[1]. Derived from palm kernel oil, HAMIN™ comprises hydrogenated palm kernel stearin, hydrogenated palm oil stearic acid, and glyceryl monostearate[2]. Its key structural advantages include high physical and chemical stability, non-irritating properties, and a demonstrated capacity to enhance skin hydration by up to 40.7%. This material is also straightforward to process and produces topical preparations with favorable aesthetic and user-friendly characteristics. In addition to its established cosmetic applications, HAMIN™ has gained attention as a natural lipid base that enhances dermal drug absorption, indicating potential value for transdermal and topical therapeutic systems. Palm oil, the source of HAMIN™, has recently been investigated in the pharmaceutical field for its favorable intrinsic properties, such as a rich content of long-chain triglycerides, non-toxicity, cost-effectiveness, and high thermal, oxidative, and production stability[3]. Palm oil serves as a natural emulsifier[4] that can facilitate the diffusion of therapeutics through the skin. Similarly, HAMIN™ acts as a self-emulsifying base containing natural stearate emulsifiers that actively promote skin permeation. This property provides a distinct advantage, as conventional synthetic surfactant-type emulsifiers often disrupt the highly ordered lipid bilayer structure of the stratum corneum, reducing its barrier function and causing irritation[5].

Gel cream dosage forms are increasingly utilized for diclofenac sodium delivery to capitalize on the combined benefits of gels and creams. This dual-phase structure enables efficient drug diffusion from the continuous aqueous phase and improved skin occlusion from the dispersed lipid phase, thereby promoting enhanced drug penetration through the stratum corneum and improving patient compliance due to a non-greasy texture. Gel cream formulations represent a contemporary approach to topical drug delivery, offering favorable sensory attributes, high physical stability, sustained moisturizing effects, and reduced transepidermal water loss[6,7]. Hydroxypropyl methylcellulose (HPMC) K100M, a hydrophilic polymer, is a key excipient for stabilizing these systems, as it forms stable gels without causing mucosal or dermal irritation. Its pH-independent viscosity and long-term stability make it particularly suitable for dermatological applications[8]. Furthermore, HPMC modulates drug release kinetics by forming a dense, diffusion-controlled matrix[9], which sustains diclofenac sodium release and prolongs its localized anti-inflammatory effect.

The combination of HAMIN™ with HPMC K100M is anticipated to produce a synergistic base system, with HAMIN™ enhancing lipid-phase permeability and HPMC providing essential rheological control and sustained drug release. This interaction has the potential to address diclofenac sodium's inherent limitation of poor skin permeability, which often restricts its topical bioavailability. While HAMIN™ has been evaluated in various dosage forms, including creams[10] and suppositories[1], most studies have focused on its function as a general base rather than as a component of a rationally optimized therapeutic system developed through experimental design. For example, a testosterone cream formulated with HAMIN™ demonstrated improved permeability, achieving 40–1400 ng/cm² over five hours, and superior pharmacokinetic parameters compared to conventional formulations[11]. Additionally, an insulin suppository containing HAMIN™ produced a systemic hypoglycemic effect comparable to that of a subcutaneous injection[1]. However, only a limited number of studies have explored palm oil as an alternative base in cream formulations for drug delivery, and no research has specifically investigated the synergistic effects or optimization of HAMIN™ combined with HPMC K100M for the topical delivery of diclofenac sodium.

The clinical need for an improved delivery system is highlighted by the pharmacological profile of diclofenac sodium, a widely used nonsteroidal anti-inflammatory drug (NSAID) prescribed for rheumatoid arthritis and acute pain management[12,13]. The conventional oral administration of diclofenac sodium is limited by low absolute bioavailability (30–70%), extensive first-pass metabolism (40–50%)[14], and severe gastrointestinal side effects, such as systemic ulceration and bleeding[15]. These limitations underscore the necessity for a topical system that provides localized action at the target site while minimizing systemic exposure. Accordingly, this study aims to develop and optimize a diclofenac sodium gel cream utilizing HAMIN™ and HPMC K100M as principal excipients to systematically enhance drug penetration and release characteristics. The formulation is developed using the Simplex Lattice Design (SLD) method to statistically evaluate the interactive effects of these excipients on critical quality attributes, including pH, spreadability, viscosity, extrudability, drug release, and skin permeability, and to benchmark the optimized formulation against leading commercial products for comparative performance[16].

The novelty of this research is the investigation of the previously unreported combination of HAMIN™ and HPMC K100M for optimizing the topical delivery of diclofenac sodium. In contrast to earlier studies that employed HAMIN™ in testosterone or insulin formulations[1], this work directly addresses the therapeutic challenges associated with diclofenac sodium, specifically poor skin permeation and potential irritation, by employing a sustainable palm oil-based material integrated with a biocompatible polymer. Additionally, while previous research by Thakur and Praween[17] demonstrated that diclofenac sodium formulations using Carbopol 934 and HPMC as gelling agents required external glycerin as a permeation enhancer, the gel cream formulation in this study leverages HAMIN™ to serve both as the structural lipid base and as the permeation enhancer. The results of this investigation are expected to advance the development of innovative, stable, and high-performance topical drug delivery systems derived from renewable natural materials.

MATERIALS AND METHODS

Materials

The development of the diclofenac sodium gel-cream formulations, outlined in **Table I**, was adapted from established betamethasone and neomycin protocols documented in the Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products[18]. This investigation optimized the composite gel-cream foundation, specifically examining the interactive effects of HAMIN™ and HPMC K100M. The concentration boundaries for both HAMIN™ and HPMC K100M were delineated from preliminary screening trials that confirmed structural integrity without evidence of phase separation. The specific blending ratios were subsequently generated using Design-Expert software version 13.0 with SLD framework.

Table I. Composition of diclofenac sodium gel-cream formulas based on the SLD method.

Materials	Function	Run 1	Run 2	Run 3
Diclofenac sodium (g)	Active ingredient	1	1	1
HAMIN™ (g)	Lipid base	17	16	15
HPMC K100M (g)	Gelling agent	1	2	3
Methylparaben (g)	Preservative	0.18	0.18	0.18
Propylparaben (g)	Preservative	0.02	0.02	0.02
BHT (g)	Antioxidant	0.1	0.1	0.1
Lactic acid (g)	Acidifying agent	0.8	0.8	0.8
Propylene glycol (g)	Co-solvent	10	10	10
Distilled water (mL)	Vehicle	69.9	69.9	69.9

To prepare the formulations, HPMC K100M was dispersed independently in heated distilled water maintained at 80°C to 90°C to ensure complete polymer hydration. The primary emulsion base was synthesized by separately heating the lipophilic and hydrophilic phases to 80°C. The oil phase comprised HAMIN™, propylparaben, and BHT, whereas the aqueous phase consisted of methylparaben, lactic acid, and distilled water. Emulsification was achieved by combining these two phases under continuous agitation. Concurrently, diclofenac sodium was completely dissolved in the propylene glycol co-solvent prior to its incorporation into the freshly prepared cream base. Finally, the pre-hydrated hydrogel matrix was uniformly blended into the medicated cream component to produce the final, homogenous gel-cream system.

Methods

Physicochemical evaluation and characterization

Organoleptic characteristics of the finalized diclofenac sodium gel-cream preparations, including color, odor, and surface texture, were documented through standardized visual and sensory inspections. Structural adhesiveness was quantified by placing a 0.5 g sample of the gel-cream onto a localized glass plate, which was then occluded by a secondary glass plate. A 1 kg weight was uniformly applied to the assembly for 5 minutes to standardize the film thickness. The configuration was subsequently transferred to a mechanical adhesion tester, where an 80 g pulling load was applied, and the precise duration required for total plate separation was recorded[19]. Emulsion type was verified by incorporating a water-soluble methylene blue dye into the matrices, followed by light microscopy to distinguish the continuous phase[20]. Systemic homogeneity was evaluated qualitatively by spreading a 0.5 g sample across a transparent glass plate and checking under intense cross-illumination for particle clustering or structural irregularities[21].

Accelerated physical stability was evaluated by subjecting a 5 g sample to centrifugation at 5000 rpm for 30 minutes; a lack of phase separation indicated a stable system[22]. Thermal robustness was assessed through a six-cycle testing regime, with each cycle comprising 24 hours of storage at 4°C followed immediately by a 24-hour transfer to 40°C, and organoleptic and physical properties monitored at the boundaries of each cycle[23]. The critical quality attributes under the SLD matrix were rigorously quantified. The formulation pH was measured using a calibrated digital pH meter after diluting a 1 g sample in 10 mL of neutral distilled water, benchmarked against the ideal topical range of 4.5 to 6.5[24]. Dynamic viscosity was determined at room temperature utilizing a RION VT-04F viscometer equipped with spindle No. 2, referencing the target semisolid threshold of 4000 to 40,000 cPs[25]. Matrix spreadability was evaluated by placing 1 g of the preparation between two parallel glass plates, overlaying a standardized weight, and measuring the resulting horizontal expansion diameter after 1 minute, targeting an acceptable topical spreadability window of 5 to 7 cm[26]. Extrudability performance was evaluated via a Texture Analyzer configured with a specialized Tube Extrusion Rig; the system operated at a test speed of 20 mm/s, a post-test speed of 100 mm/s, and a linear travel distance of 78 mm. A 10 g sample was loaded into the standard tube, unsealed, and the work required for expulsion was derived by plotting the continuous force-versus-time profile[27].

Biopharmaceutical and in vivo safety studies

In vitro drug release was evaluated using the paddle-over-disk method at 37 ± 0.5°C inside a dissolution apparatus operating at 100 rpm in a pH 7.4 ± 0.05 phosphate buffer medium[28]. Aliquots of 5 mL were sampled at predetermined time intervals, and the overall kinetic release rate was computed by plotting the cumulative mass of drug released against the square root of time. Dermal permeation was conducted following formal ethical clearance from the Faculty of Dentistry, Universitas Jember (No. 2551/UN25.8/KEPK/DL/2024). The *ex vivo* permeation assays utilized full-thickness excised mouse skin, clamped securely within horizontal static Franz diffusion cells, with the stratum corneum oriented toward the donor chamber and the dermal surface contacting the receptor phase[29], and computed core permeability metrics according to established transdermal equations[30]. Steady-state flux (J_{ss}) was determined from the linear slope of the cumulative drug mass permeated per unit area plotted against time up to 8 hours using the following **Equation 1**:

$$J_{ss} = \frac{\mathrm{dM}}{\mathrm{S}\,.\mathrm{dt}} \qquad [1]$$

Where dM represents the mass of drug permeated, S denotes the cross-sectional diffusion area (cm^2), and dt is the operational time unit. The corresponding permeability coefficient (K_p) was computed using **Equation 2**:

$$K_p = \frac{\mathrm{J}_{ss}\,.\,H}{\mathrm{C}_0} \qquad [2]$$

Where H signifies the biological membrane thickness, and C_0 represents the initial donor concentration of the active drug. The enhancement ratio (E_r) was calculated to assess relative flux improvements using the following **Equation 3**:

$$E_r = \frac{\mathrm{J}_{ss}\,formulation}{\mathrm{J}_{ss}\,reference} \qquad [3]$$

In vivo skin irritation studies were conducted on six healthy Wistar rats, with institutional ethical approval (No. 1904/UN25.8/KEPK/DL/2023). The animals were distributed into three distinct cohorts: Group I received the optimized gel-cream formulation, Group II served as the untreated negative control, and Group III received a matching commercial reference product. Each respective preparation was applied over a shaved 4 cm^2 dorsal area, and localized erythema and edema responses were visually scored at 24, 48, and 72 hours post-application[31].

Data analysis

All experimental measurements were performed in triplicate (n = 3) to guarantee reproducibility and precision, and the resulting values were expressed as the mean ± SD. Statistical evaluation, response surface modeling, and formulation optimization were executed using Design-Expert® software Version 13. The experimental data generated by SLD points

were fitted to a second-order polynomial response surface **Equation 4**, where y represents the predicted response variable, b_0 is the intercept term, b_1 and b_2 represent the linear coefficients for the individual independent components, and b_{12} denotes the interactive coefficient indicating the synergistic or antagonistic effect between the two formulation excipients.

$$y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_{12} \quad [4]$$

The structural and predictive adequacy of the mathematical models was validated statistically using ANOVA. The significance of the complete model and its separate parameters was verified using p-values; $p < 0.05$ indicated statistical significance. A Lack-of-Fit test was simultaneously evaluated to confirm that the mathematical model adequately described the experimental variation without exhibiting significant unexplained error. Furthermore, the coefficient of determination (R^2), adjusted R^2, and predicted R^2 values were evaluated to confirm goodness-of-fit and the robustness of the predictive correlations. Adequate Precision values exceeding 4 were utilized to verify a satisfactory signal-to-noise ratio. Finally, multi-response numerical optimization was performed using a desirability function approach, with the optimization parameters customized to maintain pH and spreadability within acceptable physiological ranges, maintain viscosity within processing thresholds, minimize the mechanical extrusion force, and maximize drug release rates and transdermal permeation flux.

RESULTS AND DISCUSSION

Organoleptic evaluations revealed that the synthesized diclofenac sodium gel-creams exhibited a vivid white color and a smooth, silky texture, with no detectable odor. Variations in the localized structural consistency were directly attributable to the varying ratios of the palm oil lipid base and the HPMC K100M polymer matrix. Elevated concentrations of HPMC K100M significantly heightened internal viscosity, which subsequently restricted the overall spreadability of the gel matrix[32]. The characteristic bright white hue and uniform silky texture were strongly influenced by the stearic acid constituents within the palm oil fraction[27]. In this framework, HPMC K100M functions as a primary gelling agent that systematically increases preparation thickness[33], while the stearic acid present within the palm oil acts as a natural co-emulsifier that stabilizes the reflective white matrix. These baseline physical observations align seamlessly with previous characterizations, demonstrating that palm oil bases yield highly uniform and cosmetically elegant gel textures[27].

Mechanical adhesion profiles showed a linear relationship with polymer density, with the adhesive capacity of the gel-cream increasing significantly at higher HPMC K100 M concentrations. This phenomenon is governed by the hydration kinetics of HPMC K100M, which absorbs water to establish an extensive colloidal framework that improves structural attachment to biological surfaces[33]. The resulting dense colloidal network increases both bulk viscosity and cohesive stickiness[32], a finding that directly supports previous conclusions that elevated HPMC levels optimize topical adhesion by producing a highly compact, interlinked polymer grid[33]. Phase-type determinations classified formulations F1, F2, and F3 as oil-in-water (O/W) systems, with an internal oil phase concentration ranging from 15% to 17%. Utilizing a palm oil-derived base within this 15–17% boundary consistently yielded an O/W gel-cream that was highly spreadable and cosmetically non-greasy. Because O/W systems inherently possess a larger continuous aqueous phase, they facilitate easier application and present a significantly less oily residue upon the skin, corroborating established cosmetic assertions that O/W systems maximize user satisfaction and eliminate topical greasiness[34].

Systemic homogeneity testing verified the absence of phase separation, particulate agglomeration, or entrapped air bubbles across all prepared batches. This high structural consistency is mediated by the self-emulsifying properties of the palm oil base, which actively lowers interfacial tension to preserve emulsion stability and prevent localized coalescence[35]. The intrinsic emulsifying properties of palm oil prevent macroseparation and preserve systemic phase uniformity over time, consistent with the findings of Khodari *et al.*[10], who demonstrated that palm oil's self-emulsifying capacity effectively prevents phase separation in complex topical formulations. Furthermore, accelerated stability testing via centrifugation and thermal cycling revealed that the gel-creams maintained exceptional organoleptic stability and total phase uniformity throughout all stress testing conditions. Formulations built upon this natural lipid base showed robust resistance to severe temperature shifts. The self-emulsifying infrastructure of HAMIN™ imparts notable thermal and mechanical stability to

the entire formulation, mitigating the impact of external temperature fluctuations, as previously observed by Haron *et al.*[11], thereby confirming that palm oil-based semi-solids remain physically stable even under extreme environmental conditions. The pH of the developed gel-creams fell within an optimal dermally compatible range of 5.05 to 5.25, making them highly suitable for topical application (**Table II**). The addition of HPMC K100M resulted in a statistically significant increase in the final formulation pH, due to the polymer's higher baseline alkalinity compared to the raw HAMIN™ base. Maintaining a strict pH range of 4.5-6.5 in gel-cream systems is imperative to protect the skin barrier and prevent chemical irritation. This upward pH drift is mathematically justified by the alkaline nature of HPMC K100M, which aligns with dermatological safety standards validated in historical skincare research[36]. Statistical analysis indicated that the recommended predictive model for the pH response surface was a linear equation with an outstanding p-value of 0.0183 ($p < 0.05$). Equation 5 (**Table III**) demonstrates that both HAMIN™ and HPMC K100M exert positive linear effects on the pH of the diclofenac sodium gel-creams. HPMC K100M (+5.26) displayed a higher mathematical coefficient than HAMIN™ (+5.06), verifying that HPMC K100M exerts a more dominant influence on this parameter due to its higher native pH value of approximately 8.0 in a 2% w/w aqueous solution, compared to the near-neutral pH of 7.0 exhibited by HAMIN™[36]. The contour plot in **Figure 1A** reveals an uninflected linear trend, indicating a direct relationship between the excipient factors and the pH response, with no observable interaction.

Table II. Evaluation results of the gel cream formulations and the commercial product.

Parameter	1	2	3	Commercial
pH	5.05 ± 0.05	5.17 ± 0.10	5.25 ± 0.10	7.42 ± 0.02
Viscosity (mPa.s)	3333.33 ± 577.35	15333.33 ± 1154.70	38666.67 ± 577.35	27333.33 ± 107.56
Spreadability (cm)	7.17 ± 0.25	6.13 ± 0.12	5.10 ± 0.22	6.70 ± 0.15
Extrudability (N/s)	75.34 ± 5.23	93.91 ± 11.20	104.96 ± 14.60	103.81 ± 9.46
Release flux (µg/cm^2·minute$^{0.5}$)	74.59 ± 3.45	54.38 ± 2.23	44.41 ± 1.36	163.99 ± 6.00
Permeation flux (µg/cm^2·minute)	0.52 ± 0.21	0.34 ± 0.03	0.19 ± 0.01	0.72 ± 0.02
Permeability coefficient (mm/cm^2)	5.17 ± 0.21	3.44 ± 0.03	1.98 ± 0.01	7.20 ± 0.02
Improvement Ratio	0.72	0.48	0.28	1.00

Table III. Effect of the independent variables in the equation.

Parameter	Response surface polynomial equation	Equation number
pH	$y_1 = 5.06A + 5.26B$	5
Viscosity (mPa·s)	$y_2 = 3333.33A + 38666.67B - 22666.67AB$	6
Spreadability (cm)	$y_3 = 7.17A + 5.10B$	7
Extrudability (N/s)	$y_4 = 76.59A + 106.21B$	8
Release flux (µg/cm^2·minute$^{0.5}$)	$y_5 = 74.57A + 44.41B - 20.52AB$	9
Permeation flux (µg/cm^2·minute)	$y_6 = 0.5125A + 0.1933B$	10

Note: A = concentration proportion of HAMIN™ base; B = concentration proportion of HPMC K100M polymer.

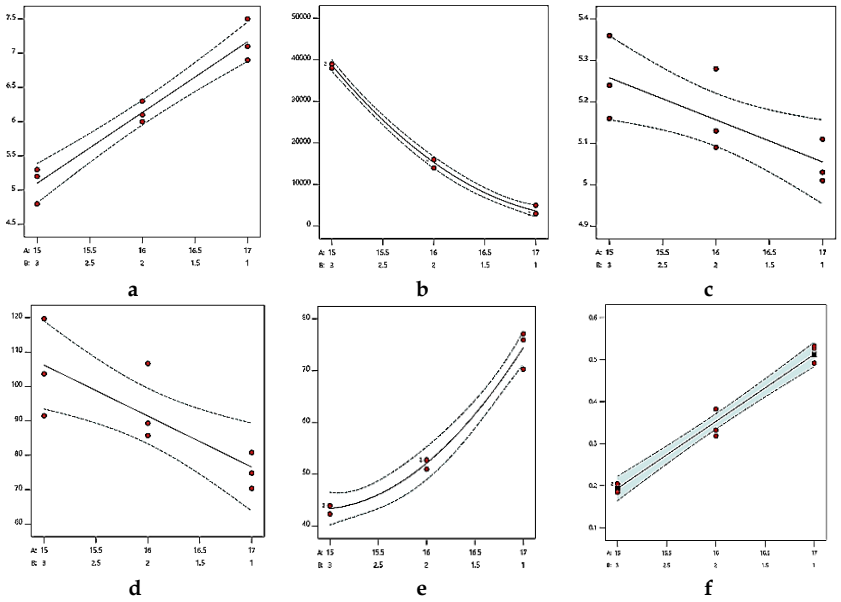


Figure 1. Contour plots of experimental responses generated by the SLD: (**a**) pH; (**b**) Viscosity; (**c**) Spreadability; (**d**) Extrudability; (**e**) Release flux; and (**f**) Permeation flux.

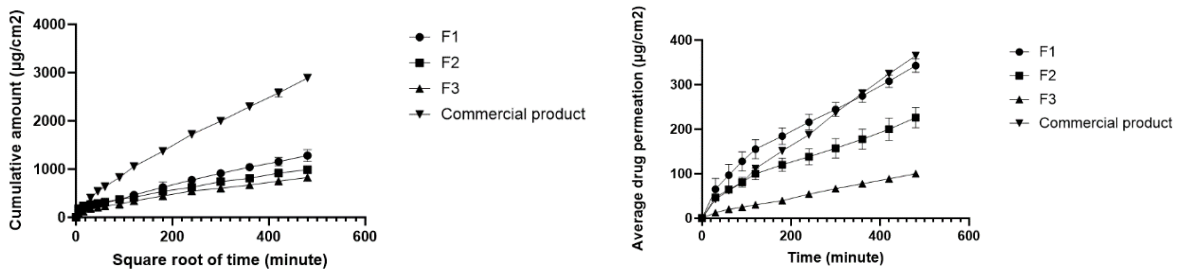
Viscosity testing demonstrated that all experimental runs met the pharmaceutical requirements for semisolid formulations. In topical systems, insufficient viscosity results in poor retention and structural runoff during application, whereas an excessively elevated viscosity restricts the thermodynamic activity and subsequent release rate of the active drug from the vehicle[37]. The SLD recommended a quadratic model for the viscosity response surface, yielding an exceptional p-value of $p < 0.0001$ and an insignificant Lack-of-Fit parameter. As shown by Equation 6, both HAMIN™ and HPMC K100M act as powerful individual thickening agents. However, the negative interactive coefficient assigned to the cross-product term (AB = -22666.67) indicates that their combined blending produces an antagonistic effect that effectively lowers bulk viscosity. HPMC K100M demonstrated a significantly more potent individual thickening capacity than HAMIN™. This behavior is driven by the fact that increasing the hydrophilic polymer content increases the density of polymer strands per unit volume, multiplying chain entanglements and slowing molecular motion, which causes an upward shift in viscosity. Binder *et al*.[38] demonstrated a similar phenomenon regarding viscosity control over skin penetration in cellulose ether hydrogels, noting that denser gel networks limit macro-fluidity. This negative interactive behavior is illustrated visually by the downward-curving profile in the contour plot of **Figure 1B**.

Spreadability testing confirmed that runs F1, F2, and F3 settled comfortably within the acceptable limits defined for topical preparations. According to the polynomial relationship in Equation 7, HAMIN™ exerts a substantially greater positive effect on spreadability than HPMC K100M. The contour plot in **Figure 1C** shows a uniform linear slope to the right, indicating a direct relationship in which increasing the HAMIN™ fraction linearly increases the overall spreading area, with no mutual interaction between the variables. HAMIN™ displays this dominant role in expanding the spreadability because it is derived from hydrogenated palm oil and contains a balanced assembly of long-chain triglycerides that lubricate the matrix and soften the formulation[39]. This internal lubrication minimizes friction between moving polymer chains, making the gel easy to spread under mild shear. When integrated into the hydrophilic polymer grid, the lipid particles of HAMIN™ physically disrupt the rigid hydrogen-bonding network of HPMC K100M, reducing baseline matrix rigidity and yielding a pliable, user-friendly formulation that responds well to digital application.

Extrudability testing was conducted to quantify the mechanical force required for the product to exit its primary packaging, a critical parameter that dictates patient adherence and usability[40]. The mathematical model in Equation 8 shows that HPMC K100M exerts a significantly greater impact on extrudability than HAMIN™. Formulations containing high concentrations of the HPMC K100M hydrogel phase exhibited a notable increase in extrusion resistance due to the formation of dense polymer net configurations[39], which increased the mechanical work required to expel the gel-cream from the tube container. The contour plot in **Figure 1D** shows a leftward-sloping linear profile, indicating that extrudability scales linearly with increasing levels of the independent component, without any cooperative or interactive effects between the excipients.

The *in vitro* dissolution data summarized in **Table II** indicate that Run 1 achieved the highest release flux among the tested configurations. The time required to attain a steady-state release profile (**Figure 2**) is closely related to the bulk viscosity of the vehicle, as well as the drug's relative partition coefficient and baseline solubility within the base components. Highly viscous formulations restrict the diffusion of dissolved drug molecules, blocking release pathways and lowering the external flux[41]. The release flux of the commercial reference product was 163.99 ± 6.00 $\mu g/cm^2 \cdot minute^{0.5}$, outperforming those of formulations F1, F2, and F3. Several parameters govern active ingredient release from semi-solid bases, including vehicle composition, rheological viscosity, dispersed-phase droplet size, interfacial boundaries, and the active ingredient's chemical affinity for the carrier matrix. Visually, the commercial reference product displayed a lower viscosity than the test formulations, which were thickened by the HPMC K100M hydrogel network. This lower viscosity profile is a key contributor to its superior release rate. HPMC, as a dense hydrophilic matrix, can slow down drug release from a gel-cream vehicle[42].

Equation 9 shows that both HAMIN™ and HPMC K100M contribute positively to the release model. The mathematical coefficients confirm that higher individual fractions of HAMIN™ improve drug release flux by maximizing molecular mobility within the vehicle[42]. Conversely, high concentrations of HPMC K100M increase bulk viscosity, thereby restricting molecular diffusion[8]. Consequently, the localized diffusion coefficient of the drug within the base decreases, slowing down release at the site of application[43]. For this reason, Run 1 (which possessed the lowest viscosity) released the greatest mass of diclofenac sodium, whereas the highly viscous Run 3 released the lowest amount. The negative coefficient assigned to the AB interaction term confirms that combining HAMIN™ with HPMC K100M acts as a negative modifier that slows the release flux, an effect captured by the downward-curving contour lines in **Figure 1E**.



a **b**

Figure 2. Study profiles of (a) release and (b) permeation.

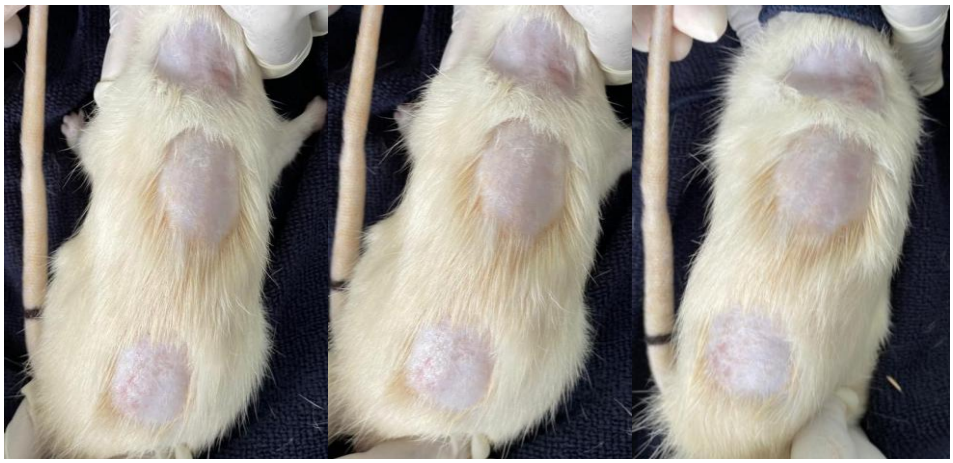
Ex vivo skin permeation studies in rats showed that formulations with a higher proportion of HAMIN™ achieved superior transdermal permeation. Palm oil-based materials improve skin permeability by increasing stratum corneum hydration and altering lipid organization, thereby increasing the permeability of the barrier layer to foreign molecules[44]. As a natural emulsifying agent, palm oil enhances drug diffusion into the skin[4]. HAMIN™ contains natural stearate emulsifiers that promote skin permeation, providing a distinct safety advantage over synthetic surfactant-type emulsifiers, which often disrupt the lipid bilayers of the stratum corneum and compromise its barrier function[45]. The transdermal transport of diclofenac sodium varied across runs 1, 2, and 3, tracking with these structural differences. This pattern matches the findings of Keng *et al.*[44], who reported that palm oil improves transdermal absorption due to its high content of natural fatty acids, such as lauric, palmitic, and linoleic acids, and beneficial phytonutrients, such as tocotrienols and carotenes.

The high concentration of HAMIN™ in Run 1 yielded the highest permeability coefficient, which correlates with its superior performance in the release tests, driven by its low viscosity and high natural emulsifier content. Drug release from the carrier vehicle is a key driver of the total mass of drug that shows up in the skin. Because runs 1, 2, and 3 exhibited enhancement up to below 1, their total drug transport was lower than that of the commercial reference formulation. HAMIN™ had a greater impact on transdermal permeation flux than HPMC K100M, and **Figure 1F** shows a linear response surface that slopes directly to the right, with no variable interactions.

The optimal formulation was identified by calculating the multi-response desirability intersection point, which determined an ideal configuration of 16.84% HAMIN™ and 1.161% HPMC K100M. This optimized configuration produced a pH of 5.07, a spreadability of 7.0 cm, a viscosity of 4,502.25 mPa·s, an extrudability of 78.980 N/s, and a release flux of 70.0614 µg/cm^2·minute$^{0.5}$. The overall desirability score was 0.805, confirming that the formulation closely approached the targeted product profile. This performance highlights the potential of HAMIN™ as a natural gel-cream base for topical delivery systems, providing excellent physical behavior and skin permeation. In this study, the commercial reference product was Emulgel, as natural gel-creams that match it are not yet commercially available. Khodari *et al.*[10] previously demonstrated that HAMIN™ can deliver slightly higher permeation and cumulative drug amounts for certain actives than commercial products such as EMLA cream. Clinical studies have also confirmed that palm oil-based lidocaine creams produce a comparable localized numbing effect during venipuncture to that of EMLA cream[46].

The dissolution data indicated that the developed gel-cream released less total drug than the commercial Emulgel reference. This is likely due to the HPMC hydrophilic matrix, which can slow down drug release from a gel-cream vehicle[38]. However, the transdermal permeation profiles showed that the HAMIN™-rich formulation (Run 1) exhibited faster diffusion up to 300 minutes. After this point, the commercial product showed slightly higher diffusion rates than the F1 formulation. The accelerated initial permeation of the HAMIN™ formulation is due to its built-in permeation-enhancing characteristics, which support topical drug delivery.

Preclinical skin irritation assays showed no signs of localized irritation on rat skin after applying the gel-cream (**Figure 3**). The components of the matrix, including the HAMIN™ lipid base, did not cause any irritation. HAMIN™ is a stable, non-irritating substance that is highly compatible with various active pharmaceutical ingredients. It remains stable during long-term storage, without exhibiting unintended pharmacological activity or interfering with drug release. Aside from the palm oil base, the other excipients in the gel-cream are non-irritating, ensuring the final product is safe for dermal use.



a **b** **c**

Figure 3. Skin irritation test for the optimized formulation of diclofenac sodium gel-cream on the dorsal region of Wistar rats over a 4 cm^2 application area, with localized skin reactions observed at (**a**) 24 hours, (**b**) 48 hours, and (**c**) 72 hours post-application.

The optimized diclofenac sodium gel-cream formulation, combining HAMIN™ and HPMC K100M, shows promising potential for both industrial and clinical applications. From a pharmaceutical manufacturing perspective, the formulation's favorable viscosity, spreadability, and stability profiles support its scalability and suitability for large-scale production using standard semi-solid processing equipment. Clinically, its enhanced release and permeation characteristics suggest the potential for improved local drug delivery and better patient adherence due to its non-greasy, easily spreadable texture. These attributes make the formulation a viable candidate for further development into a commercial topical product aimed at the management of inflammatory and musculoskeletal conditions.

From a clinical perspective, these optimized properties indicate that this gel-cream formulation can enhance patient adherence and localized therapeutic efficacy by supporting rapid initial transdermal absorption and preserving sustained local anti-inflammatory effects. Such performance traits are highly advantageous for the localized management of acute musculoskeletal pain, arthritis, and deep-tissue inflammation, where targeted topical delivery avoids the gastrointestinal and systemic side effects associated with standard oral delivery routes[47]. While this study successfully completed rigorous *in vitro* physicochemical indexing and *ex vivo* transdermal skin permeation profiles, it remains limited by a lack of long-term *in vivo* human pharmacokinetic data or comparative clinical efficacy profiling. Consequently, future clinical investigations are required to track in-human pharmacokinetics, validate therapeutic bioequivalence, and confirm long-term skin safety profiles in human subjects before commercial scale-up.

CONCLUSION

The optimization of a topical diclofenac sodium gel-cream formulation was successfully achieved using a multi-response surface methodology, establishing an optimal excipient composition of 16.84% HAMIN™ and 1.161% HPMC K100M. This specific combination yielded excellent physicochemical and mechanical attributes, characterized by a physiological pH of 5.07, an ideal structural spreadability of 7.0 cm, a dynamic viscosity of 4,502.25 mPa·s, a balanced mechanical extrudability work profile of 78.980 N/s, and a Higuchi drug release flux of 70.0614 $\mu g/cm^2 \cdot minute^{0.5}$. The resulting overall desirability value of 0.805 confirms that this engineered matrix aligns closely with predefined target criteria. These experimental findings reveal that the natural lipid properties of HAMIN™ work effectively alongside the hydrophilic polymer network of HPMC K100M, providing stable structural consistency, robust accelerated thermal stability, and enhanced transdermal delivery of the active drug.

ACKNOWLEDGMENT

None.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to this research.

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