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Original Article

A Central Composite Design Optimized Diclofenac Potassium Loaded Niosomal Gel: Fabrication and Evaluation

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ABSTRACT

Aim: The goal of this study was to create niosomal carriers for delivering diclofenac potassium through the skin, aiming to understand how these niosomal vesicles can improve skin penetration and absorption. **Materials and Methods:** Niosomes containing diclofenac potassium were prepared using a thin film hydration method. This involved varying the ratios of non-ionic surfactants (span-60 and span-80) with Cholesterol (CHO). We optimized the niosomes using a central composite design, treating the concentrations of span-60, span-80 and cholesterol as independent variables and measuring vesicle size and entrapment efficiency as dependent variables. The optimized niosome batch was then mixed into a 1% carbopol gel and assessed for various properties, including pH, viscosity, extrudability and *in vitro* release. **Results:** The vesicle sizes of the formulations ranged from 0.35±0.01 µm to 2.04±0.04 µm. Entrapment Efficiency (% EE) varied from 65.00±0.91% to 86.29±0.12%. Polydispersity Index (PDI) values ranged from 0.352±0.01 to 0.652±0.02. Zeta potential ranged from -47.13±0.71 to -37.09±0.51 mV. The optimized batch showed a particle size of 0.39±0.01 µm and an entrapment efficiency of 86.29±0.12%. The diclofenac potassium niosomes formulated with 40% span 60, 20% span 80 and 20% Cholesterol (CHO) showed promising results and were mixed into a 1% Carbopol gel. The resulting niosomal gel was tested for several physicochemical properties, including pH, viscosity and extrudability. An *in vitro* drug release study conducted using phosphate-buffered saline at pH 6.8 revealed that 72.01%±1.23 of the drug was released over 10 hr. **Conclusion:** The study concludes that the gel formulations containing niosomes loaded with Diclofenac Potassium showed prolonged action than formulations containing Diclofenac potassium in non-niosomal form.

Keywords: Central Composite Design, Diclofenac potassium, Entrapment Efficiency, Gel, *In vitro* Drug Release Studies, Niosomes.

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INTRODUCTION

Diclofenac possesses anti-inflammatory, analgesic and antipyretic properties. Diclofenac potassium's exact mode of action is uncertain, just like that of other NSAIDs, however, it is known to block the cyclooxygenase enzymes (COX-1 and COX-2).[1] Diclofenac is a potent inhibitor of prostaglandin synthesis *in vitro* and at therapeutic doses, effects have been seen *in vivo*. As mediators of inflammation, prostaglandins work by increasing bradykinin's ability to elicit pain and sensitize afferent neurons. Diclofenac's effectiveness may stem from its ability to reduce prostaglandin levels in peripheral tissues.[2]

Topical gels are semi-solid, homogeneous compositions used to treat various skin conditions. Gels' hydrophilic nature allows for a faster release of the drug or active ingredient. A gel typically consists of two components: a substantial amount of liquid media and a material that has been cross-linked in three dimensions. This structure forms a rigid, stable network that immobilizes the liquid continuous phase. The gel's structural network may consist of inorganic particles or organic macromolecules.[3] Weaker, reversible secondary intermolecular forces such hydrogen bonding, electrostatic interactions, hydrophobic contacts and Van der Waals forces are what form physical topical gels. Particles in gels with a chemical basis are bonded together by strong covalent bonds.[4]

A gel is a two-component, three-dimensional network consisting of structural elements combined with a sizable amount of liquid

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to create a hard structure that keeps the liquid phase inside stationary. A gel's structural network can consist of both inorganic particles and organic macromolecules, mainly polymers. Gels can be classified into two types-chemical and physical based on how the cross-links in this network are formed through chemical or physical interactions.[5] Chemical gels are formed through strong, permanent covalent bonds, while physical gels are created through weaker, reversible interactions such as hydrogen bonding, electrostatic forces, dipole-dipole interactions, Van der Waals forces and hydrophobic interactions. According to the U.S.P., gels are semisolid systems made up of dispersions of large organic molecules or small inorganic molecules.[6]

Gels can be either one-phase systems, where big organic molecules dissolve in the continuous phase to disperse rather than dissolve, or two-phase systems, where large organic molecules dissolve in the continuous phase to create randomly coiled flexible chains. For usage in pharmaceutical or cosmetic applications, a gelling agent should be inert, safe and non-reactive with other compounds in the formulation. It should produce a gel that rapidly breaks down but maintains a solid-like consistency during storage when subjected to shear forces, like shaking a bottle, compressing a tube, or applying it.[7] The gelling agent should not create a sticky texture and possess the necessary antibacterial properties to prevent microbiological contamination.[8]

Niosomes, which are highly effective drug carriers, were first discovered by researchers in the cosmetics industry during the 1970s when they observed that non-ionic surfactants could self-assemble into vesicles.[9] When non-ionic surfactants from the alkyl or dialkyl polyglycerol ether class are mixed with water and cholesterol, they create tiny lamellar structures called niosomes.[10] Because of their amphiphilic properties, these surfactants can form closed bilayer vesicles in water; however, to keep this structure stable, they often need to be heated or agitated.[11]

These bilayers have hydrophobic tails that are oriented away from the aqueous environment, while their hydrophilic heads remain in contact with it. Niosome characteristics such as vesicle size, lamellarity, surface charge and encapsulation capacity can be adjusted by varying the composition and concentration of the surfactants.[12] Van der Waals interactions, electrostatic repulsion between charged surfactant groups and entropic forces from the surfactant head groups all affect the stability of the vesicular structure. However, a variety of factors could influence how stable niosomes are, such as the type of surfactant used, the medication encapsulated, storage conditions, the presence of detergents and the addition of charged molecules.[13]

Niosomes can encapsulate a variety of therapeutic compounds because of their hydrophilic, amphiphilic and lipophilic properties. These niosomes then function as a depot to release the medication in a regulated manner.[14] Because it targets particular cells, shields the medication from the biological environment and decreases its clearance from circulation, controlled release can improve the therapeutic efficacy of the medication.[15] The surfactants employed in niosome formulation must be non-immunogenic, biodegradable and biocompatible. Niosome dispersions can be made by hydrating proniosomes, a dry version of niosomes, right before usage. Proniosomes have benefits such as less aggregation, fusion and leakage problems as well as more ease of dosage, storage and transportation. Similar to liposomes, niosomes function *in vivo* by prolonging the drug's circulation duration and changing its distribution and metabolic stability. The bilayer's composition and the process of formation both affect the characteristics of niosomes. It has been noted that adding cholesterol to the bilayers lowers the volume of entrapment during formulation, which lowers the efficacy of entrapment.[16] The objective of this research is to create a niosomal drug delivery system that, in comparison to free drug components, minimizes toxicity while preserving or improving efficacy. Using a central composite design as a guide, the work focuses on creating and assessing a niosomal gel using the polymers Span-60, Span-80 and cholesterol. Central Composite Design (CCD) holds significant importance in the optimization of niosomal gel preparation, offering advantages that distinguish it from other experimental designs.

Key Advantages of CCD in Niosomal Gel Optimization are

Efficiency in Exploring Variable Interactions

CCD is particularly effective in mapping the response surface, allowing researchers to understand how different formulation variables interact with each other. This is crucial in niosomal gel preparation, where factors like surfactant concentration, cholesterol ratio and hydration medium can have complex, interconnected effects

It enables the identification of synergistic or antagonistic interactions between these variables, leading to a more refined and optimized formulation.

Quadratic Modeling Capability Unlike simpler designs, CCD can model quadratic relationships between variables and responses.

MATERIALS AND METHODS

Diclofenac was gifted from Walksman Selman Pharmaceutical Ltd. Anantapur. Span 60, Span 80, Cholesterol and Propylene Glycol (PG), were procured from Qualigens, India. All reagents and chemicals of AR grade.

Formulation of Niosomes

Making niosomes is a typical process that involves thin-film hydration. This process is also called the "sand shaking method." An organic solvent, a non-ionic surfactant and cholesterol are combined in a flask with a circular bottom to create niosomes. The organic solvent is extracted using a rotating vacuum evaporator.

A thin film forms on the inside of a flask with a circular bottom when the liquid evaporates from it. At a temperature higher than the transition temperature of the surfactant, the thin layer becomes hydrated. Phosphate buffer or water is employed in the hydration process. Rehydrating causes the layer to enlarge and the development of drug-containing multilamellar vesicles. After that, these multilamellar vesicles can be sonicated to create unilamellar vesicles or to help niosomes with a consistent size distribution form.[17,18]

Preparation of niosomal gel

A stock result of the Carbopol 934P was prepared in distilled water and propylene glycol to create Carbopol 934P gels. Propylene glycol was dissolved in pre-weighted amounts of Diclofenac niosomal formulation separately. The solvent mixture was moved to a Carbopol934P jar and stirred for an additional 20 min. Additionally, the dissipation was given 60 min to hydrate and swell before the triethanolamine result and stir were used to condition the pH to be neutral. Before completing rheological measurements, let the sample equalize for at least 24 hr at room temperature (Tables 1 and 2).[19,20]

The selection of independent variables and dependent variables for niosomal formulation involves a systematic approach. Conducted a thorough literature review to identify the critical factors that affect niosomal formulation. Conducted preliminary experiments to identify the most critical variables that impact niosomal formulation. Selected independent variables based on criteria such as:

- Relevance to niosomal formulation.

- Potential impact on niosome properties (e.g., particle size, entrapment efficiency).

- Ease of manipulation and control.

- Cost and feasibility considerations.

Evaluation of niosomes

The niosomal formulations were analyzed to determine the impact of varying cholesterol (CHL), Span 60 (S-60) and Span 80 (S-80) concentrations on Vesicle Size (VS), Entrapment Efficiency (EE%), Polydispersity Index (PDI) and zeta potential. The results are as follows.[21]

Vesicle size and PDI

Transfer an aliquot of the niosome dispersion into a clean sample cuvette, insert it into the DLS instrument and set the measurement angle to 90 degrees with a temperature of 25°C. Run the DLS measurement to obtain data on vesicle size and PDI, then record these values from the instrument's software. The PDI indicates the width of the vesicle size distribution.[22,23]

Entrapment efficiency

To evaluate the trapping of DS, the niosomal formulations were ultracentrifuged for 30 min at 4°C at 18,000 rpm. The loaded dispersion and DS were separated using an ultracentrifuge (Sigma, Germany). Next, using Ultraviolet-visible (UV-vis) spectroscopy (UV-vis Jasco V-630, UK) at the DS wavelength of 276 nm, the drug concentration in the supernatant was determined.[24] The Entrapment Efficiency percentage (EE %) was calculated using the following formula. eq.1.

$$EE\ \% = \frac{W\ (initial) - W(free)}{W\ (initial)} \times 100 \text{--- (1)}$$

Zeta potential

To measure the zeta potential, use a zeta potential analyzer such as the Zetasizer Nano ZS. Prepare the niosome dispersion in a clean, disposable cuvette, then insert it into the zeta potential analyzer. Ensure the dispersion is at the correct concentration of measurement and run the zeta potential test. Record the zeta potential values from the analyzer's software, which reflects the surface charge of the niosomes. Finally, analyze the collected data for VS, EE, PDI and zeta potential to evaluate the quality and performance of the niosomal formulations.[25]

Optimization of niosomes

The study employed a CCD to optimize the composition of excipients used in niosomal formulation, focusing on the concentrations of span-60, span-80 and cholesterol. This design method, involving three distinct levels-1 (low), 0 (medium) and +(High) allowed for a comprehensive evaluation of their effects on the vesicle size and entrapment efficiency. A total of 15 experimental runs were generated, providing a robust dataset to analyze the interactions between the independent variable and their impact on the dependent variable. The results guided the optimization of the formulation.[26]

Statistical analysis

Very researches were formulated in a tricycle to ensure the reproducibility and reliability of the data. The modeling of the D-optimal design was conducted using a quadratic equation to capture the relationship between the variables. For model validation and accuracy assessment, key statistical parameters were utilized, including the Probability (p) value, the regression coefficient (R') and the F-statistic. These parameters were critical in evaluating the model's fit and significance. The experimental outcomes are stated as the mean Standard Deviation (SD) to reflect variability and consistency regarding results.

Evaluation of niosomal gel

FTIR compatibility studies

To assess the compatibility of diclofenac with excipients using FTIR spectroscopy, first, prepare samples by grinding diclofenac

and each excipient into fine powders. Mix diclofenac with each excipient in a specified ratio (e.g., 1:1) and then combine with KBr in a 1:100 ratio to form a homogeneous mixture. Press this mixture into thin, transparent pellets using a hydraulic press. Calibrate the FTIR instrument according to the manufacturer's instructions and then place the KBr pellet containing the drug-excipient mixture into the sample holder. Record the FTIR spectrum over a range of 4000 cm^{-1} to 400 cm^{-1}, ensuring baseline correction for background noise. Analyze the spectra to compare with those of pure diclofenac and excipients, noting any significant changes in peak positions or intensities that may indicate interactions. Document and report the findings, summarizing any potential interactions or effects on the formulation's stability and efficacy.[27]

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was used to analyze the thermal behavior of cholesterol, DS and freeze-dried niosome powder with a Pyris 6 instrument from PerkinElmer (US). Approximately 5 mg of each sample was placed in a sealed aluminum pan. To ensure equilibrium, the sealed pans were maintained at 20°C for 30 min. The DSC pans were then heated from 20°C to 250°C at a rate of 20°C per minute. Indium was used for calibration before conducting experiments on the samples.[28]

Homogeneity

The diclofenac niosome gel formulations were visually examined for various attributes including color, consistency and texture. After application on the skin, the gels were assessed for their sensory feel. Additional evaluations included checking the colour intensity, measuring pH and determining the consistency and extrudability of the gels. Homogeneity was verified through visual inspection before transferring the gels into containers. The gels were also inspected for appearance and the presence of any aggregates.[29]

Spreadability

In this test, a normal process was used to extrude the gel sample from the tube. The gel-filled, closed collapsible tube was tightly squeezed at the crimped end. The gel was extruded until the pressure was released after the cap was removed. The weight, expressed in grams, needed to extrude a gel ribbon measuring 0.5 cm in 10 sec was noted. The extrusion pressure in grams was recorded for each formulation.[30]

Extrudability

By measuring the amount of gel that extruded from the tube when pressure was applied, the extrudability of the niosomal gels was evaluated. A 5 g capacity, 5 mm aperture, clean lacquered collapsible aluminum tube was used for each recipe. The crimped end of the tube was tightly squeezed and a clamp was used to stop any rollback. The amount of gel that was extruded was weighed and collected with care. The percentage of gel that extruded through the opening under pressure was used to determine extrudability. To guarantee the precision and dependability of the findings, the experiment was carried out three times.[31]

pH determination

After precisely weighing 1.0 g of gel, it was mixed with 100 mL of distilled water. A digital pH meter was used to measure the pH of the resultant dispersion. The meter was calibrated using standard buffer solutions at pH 4.0, 7.0 and 9.0 before use. To ensure accuracy and consistency, the pH measurements were done three times and the average value was determined. The gel compositions' pH was measured using a digital pH meter (Systronics India, 361). Before taking any measurements, the pH meter was calibrated. The glass rod was dipped into the gel compositions to obtain readings. A digital pH meter was employed to ascertain the gel compositions' pH. Prior to taking any measurements, the pH meter was calibrated. The glass rod was dipped into the gel compositions to obtain readings. Prior to taking any measurements, the pH meter was calibrated. The glass rod was dipped into the gel compositions to obtain readings.[28]

Viscosity

To determine the viscosity of niosomal gels using a Brookfield viscometer with spindle no. 64, first ensure the gels are well-mixed and at room temperature (25°C). Set up the viscometer with spindle no. 64 and adjust the temperature to 25°C using a temperature control unit if available. Place the niosomal gel into a clean container that fits the viscometer's sample chamber and insert the spindle, making sure it is properly aligned and fully submerged to avoid air bubbles. Set the viscometer to rotate the spindle at 5 rpm and allow it to operate for 5 min to achieve a steady state. Record the viscosity value displayed on the viscometer, along with details such as spindle number, rotational speed and temperature. To ensure accuracy, perform multiple measurements and calculate the average viscosity if needed. Afterward, clean the spindle and container thoroughly according to the manufacturer's instructions. Analyze the viscosity data about the gel's formulation and performance and prepare a report summarizing the viscosity measurements and any relevant observations.[32]

In vitro drug permeation study of niosomal gel

The device is made up of a glass cylinder that is open on both ends and a dialysis membrane that has been adhered to one end of the cylinder using adhesive after being soaked in distilled water for 24 hr before usage. The cell (donor compartment) is filled with gels that contain 10 mg of diclofenac. The receptor compartment, which is 100 mL of PBS at pH 6.8 with 10% v/v methanol to maintain sink conditions, is submerged in the beaker. The assembly is set up so that the gel-containing cell's lower end is situated slightly above the diffusion medium's surface (1-2 mm deep). A magnetic stirrer is used to agitate the medium at

37±0.5°C. 5 mL aliquots are periodically taken out of the receptor compartment and replaced with brand-new buffers. Utilizing a UV-visible spectrophotometer set at 276 nm, the samples are examined. To guarantee accuracy, the tests are run in triplicate.

Statistical and kinetic analysis

Several mathematical models, including zero order, first order, Higuchi and Korsemeyer-Peppas release models, were used to analyze the data from all formulations. When the release process is complicated or unclear, the Korsemeyer-Peppas model is especially useful. It makes a distinction between various release mechanism kinds. When the release mechanism is not entirely diffusion-controlled, it is referred to as a non-Fickian release, with the exponent 'n' usually falling between 0.5 and 1.0. 'n', on the other hand, is equal to or less than 0.5 for Fickian diffusion.

RESULTS

Results of Niosomes

The study revealed that varying cholesterol, Span-60 and Span-80 concentrations significantly impacted Vesicle Size (VS) and Entrapment Efficiency (% EE) of diclofenac-loaded niosomes. Increasing cholesterol led to larger vesicles and altered % EE, with higher levels initially improving and later reducing drug encapsulation. Span-60 optimization enhanced vesicle size and % EE, while Span-80 increased vesicle size, but decreased % EE at higher concentrations. The niosomal dispersions appeared as a pale white, milky solution, uniform in appearance, with no odor or visible impurities, indicating well-prepared and consistent formulations.

Physicochemical assets of the Niosomes

The vesicle sizes of the formulations ranged from 0.35±0.01 µm to 2.04±0.04 µm, with larger sizes observed in formulations containing higher concentrations of cholesterol and Span-80. For example, formulation N1 (20 mg cholesterol, 40 mg Span-60, 20 mg Span-80) had a vesicle size of 0.39±0.01 µm, while N6 (40 mg cholesterol, 40 mg Span-60, 30 mg Span-80) exhibited a larger vesicle size of 1.59±0.06 µm. Entrapment efficiency (% EE) varied from 65.00±0.91% to 86.29±0.12%, with formulation N1 achieving the highest % EE at 86.29±0.12% and N10 (46.82 mg cholesterol, 50 mg Span-60, 25 mg Span-80) the lowest at 74.45±0.52%. Polydispersity Index (PDI) values ranged from 0.352±0.01 to 0.652±0.02. Formulations with higher PDI, such as N5 (0.652±0.02) and N6 (0.528±0.03), showed broader size distributions, while formulations like N1 (0.358±0.01) indicated a more uniform size distribution. Zeta potential ranged from -47.13±0.71 to -37.09±0.51 mV, with formulation N10 exhibiting the highest negative zeta potential (-47.13±0.71 mV), suggesting good stability, whereas lower values such as -37.09±0.51 mV in N14 indicated reduced stability (Table 3).

Table 1: Experimental plan for niosomal dispersion formulation: coded level translation in actual units.

Niosome	Coded factors			Composition of factors		
	A (-1)	B (0)	C (+1)	A (cholesterol)	B (Span-60)	C (Span-80)
N1	-	-	-	20	40	20
N2	+	-	-	40	40	20
N3	-	+	-	20	60	20
N4	+	+	-	40	60	20
N5	-	-	+	20	40	30
N6	+	-	+	40	40	30
N7	-	+	+	20	60	30
N8	+	+	+	40	60	30
N9		0	0	13.18	50	25
N10		0	0	46.82	50	25
N11	0		0	30	33.18	25
N12	0		0	30	66.82	25
N13	0	0		30	50	16.59
N14	0	0		30	50	33.41
N15	0	0	0	30	50	25
A(Cholesterol)	20	30	40			
B(Span-60)	40	50	60			
C(Span-80)	20	25	30			

FTIR analysis

The FTIR spectra of the niosomal gel containing Diclofenac and its primary components, including cholesterol, span-60, span-80 and carbopol 934P, revealed the characteristic functional groups present in each component. Diclofenac exhibited distinctive peaks associated with the C-H group and phenyl group related to maleate salts. Cholesterol displayed broad peaks indicative of aromatic stretching, acetyl groups, hydroxyl groups and symmetric -CH3 and vinyl groups. The spectra of span-60 showed prominent peaks related to the aromatic-CH3 group, C=O ester bonds and hydroxyl (OH) groups, along with smaller peaks reflective of its aliphatic structure. Span-80's spectrum featured key peaks for the -OH group, a five-membered ring and -CH_3, while carbopol 934P showed broad peaks linked to the amine group. In the niosomal gel spectrum, sharp peaks were observed at wavenumbers corresponding to the phenyl group, which were more pronounced than in the spectra of carbopol 934P alone. Broad peaks related to the -OH group also appeared sharper in the niosomal gel spectrum. Additionally, slight peak shifts and smoothening of peaks were noted, suggesting a strong physical interaction between Diclofenac and its components in the gel formulation. Importantly, no new peaks were detected, indicating no chemical interactions between Diclofenac and the other components (Figure 1A).

DSC Studies

The DSC spectra of Diclofenac and its excipients, as depicted in Figure 1B, provide critical insight into the thermal behavior of the drug. Pure Diclofenac exhibited a sharp, distinct endothermic peak at approximately 288.66°C, which corresponds to its melting point, indicating its crystalline nature. The absence of new peaks or significant alterations in the Diclofenac-related peaks when combined with the excipients suggests that there is no chemical interaction between the drug and the excipients. This implies that the thermal properties of Diclofenac remain unchanged in the presence of these excipients, confirming their compatibility. Such findings are essential in drug formulation, as they ensure that the excipients do not interfere with the stability or efficacy of the Diclofenac, thus supporting the integrity of the formulation.

Optimization of niosome

The analysis results show the following significance levels and model fits for different regression models. The linear model has a sequential *p*-value of 0.0002, indicating statistical significance, with an adjusted R^2 of 0.7697 and a predicted R^2 of 0.6573. The 2-factor interaction (2F1) model has a higher *p*-value of 0.5319, suggesting weaker significance, along with adjusted and predicted R^2 values of 0.7558 and 0.6471, respectively. The quadratic model is suggested, with a sequential *p*-value of 0.0389 and notably better adjusted and predicted R^2 values of 0.9171 and 0.7194, respectively. The cubic model, although having high adjusted and predicted R^2 values of 0.9911 and 0.8049, is aliased with a *p*-value of 0.2176, indicating that it is less suitable.[33]

ANOVA for Quadratic model

The Analysis of Variance (ANOVA) results for the model indicate that the model is significant, with an F-value of 18.20 and a *p*-value of 0.0026, suggesting a strong statistical significance. Among the factors studied, the variable A (CHL) demonstrated a highly significant effect on the response, with a sum of squares of 2.84, an F-value of 128.53 and a *p*-value of less than 0.0001. Factor C (S-80) also showed a significant impact, with a sum of squares of 0.2062, an F-value of 9.32 and a *p*-value of 0.0283. The interaction between A and C (AC) was found to be significant, with a *p*-value of 0.0461 and an F-value of 6.96. Other factors, such as B (S-60), AB, BC, B^2 and C^2, did not exhibit significant effects, as indicated by their high *p*-values (all above 0.05), suggesting that these variables have a minimal or no impact on the response. The residual sum of squares was 0.1106, with a mean square value

Table 2: Formula of niosomal Gel.

Ingredients	Quantity
Diclofenac niosomal gel equivalent to	1%
Carbopol 934P (g)	1
Propylene Glycol (mL)	15
Methyl Paraben (g)	0.1
Triethanolamine (mL)	0.30
Water	Q.S

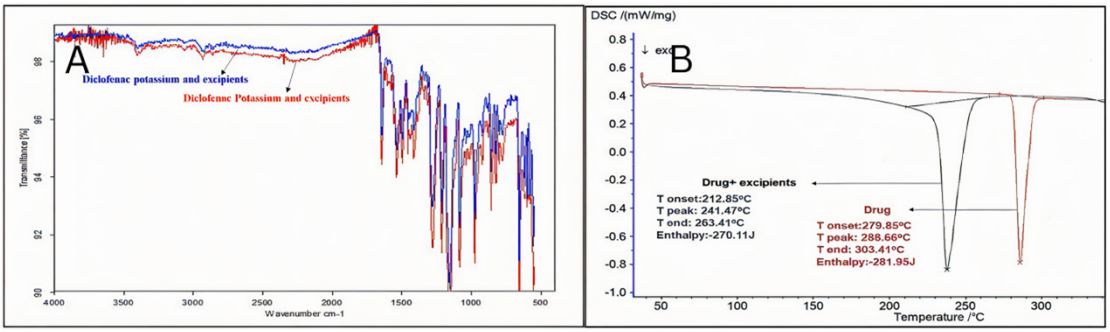

Figure 1: A) FTIR Spectroscopy; B) DSC thermograms of Diclofenac alone and along with excipients.

Table 3: Physical characterization of niosome formulations.

Niosomes	Parameters assessed			
	VS (µm)	EE (%)	PDI	Zeta potential (mV)
N1	0.39±0.01	86.29±0.12	0.358±0.02	-45.21±0.25
N2	0.93±0.02	83.36±0.02	0.369±0.03	-43.74±0.31
N3	0.42±0.02	84.51±0.14	0.352±0.01	-39.19±0.05
N4	1.02±0.01	82.96±0.36	0.452±0.02	-38.11±0.60
N5	0.45±0.01	73.26±0.65	0.652±0.02	-44.31±0.81
N6	1.59±0.06	71.05±0.84	0.528±0.03	-38.27±0.71
N7	0.56±0.02	72.28±0.72	0.457±0.01	-42.81±0.61
N8	1.67±0.03	70.39±0.64	0.478±0.01	-40.96±0.94
N9	0.35±0.01	80.28±0.49	0.528±0.03	-46.07±0.61
N10	2.04±0.04	74.45±0.52	0.519±0.01	-47.13±0.71
N11	0.59±0.02	78.59±0.81	0.481±0.01	-44.25±0.51
N12	0.62±0.05	76.26±0.37	0.532±0.01	-42.25±0.33
N13	0.68±0.06	83.69±0.49	0.571±0.02	-40.85±0.11
N14	0.78±0.01	69.39±0.71	0.601±0.03	-37.09±0.51
N15	0.71±0.04	65.00±0.91	0.467±0.02	-41.56±0.69

Values in mean±SD; *n*=3.

Formulation N1 was selected for the preparation of niosomal loaded gel due to its low vesicle size and effective drug entrapment.

of 0.0221, contributing to the overall error of the model. The total sum of squares for the model was 3.74, highlighting the overall variance explained by the model and the residual error.

The contour and 3D surface plots visually demonstrated the significant impact of cholesterol, Span-60 and Span-80 concentrations on Vesicle Size (VS) and entrapment efficiency in the prepared niosomes. The contour plots for vesicle size revealed that increasing cholesterol and Span-80 concentrations generally led to larger vesicle sizes, with Span-60 playing a critical role in balancing this effect. Formulation regions with low cholesterol and Span-80, but moderate Span-60 levels, exhibited smaller vesicles (Figure 2).

The Model F-value of 18.20 suggests that the model is significant, with only a 0.26% chance that such a large F-value could arise from random noise. *p*-values below 0.05 indicate that the model terms are significant. In this analysis, the terms A, C, AC and A^2 are considered significant. Conversely, terms with *p*-values greater than 0.10 are not significant. If many terms are insignificant (excluding those necessary to maintain hierarchy), reducing the model may enhance its performance. The polynomial equation for the response variable (VS) is as follows:

$$VS=+0.7048+0.4563A+0.0264B+0.1229C+0.0038AB+0.1388AC+0.0088BC+0.1787A^2-0.0299B^2+0.0143\ C^2$$

Fit Summary for the response- particle size

The sequential analysis of the model reveals the significance and predictive capabilities of the different terms. The linear model has a sequential *p*-value of 0.0023, with an adjusted R^2 of 0.6435 and a predicted R^2 of 0.6398, indicating a moderately strong fit and good predictive ability at this stage. However, the two-factor interaction (2F1) model shows a much higher sequential *p*-value of 0.9992, with a lower adjusted R^2 of 0.5110 and a predicted R^2 of 0.4334, suggesting poor contribution to the model. The quadratic model, which is suggested for further consideration, shows substantial improvement with a sequential p-value of 0.0049, an adjusted R^2 of 0.9286 and a predicted R^2 of 0.7925, highlighting its better fit and enhanced predictive power. Finally, the cubic model, while exhibiting a very high adjusted R^2 of 0.9979 and a predicted R^2 of 0.9542, is aliased with a sequential *p*-value of 0.1143, indicating potential overfitting and limited reliability. Therefore, the quadratic model is suggested as the best fit for the data (Figure 3).

ANOVA for Quadratic model

The ANOVA results for the model show that it is statistically significant, with a sum of squares of 585.04, an F-value of 21.25 and a *p*-value of 0.0018. Among the individual factors, factor C (S-80) has the most significant influence on the model, with a sum of squares of 403.03, an F-value of 131.72 and a *p*-value of less than 0.0001. Factor a (CHL) also shows a significant effect, with a sum of squares of 24.75, an F-value of 8.09 and a *p*-value of 0.0361. In contrast, factor B (S-60) has a higher *p*-value of 0.2849, indicating that it is not significant. The interaction terms (AB, AC and BC) all exhibit very high *p*-values (greater than 0.74), suggesting minimal to no interaction effects between these variables. The quadratic

terms A^2, B^2 and C^2 are highly significant, with *p*-values ranging from 0.0015 to 0.0021, indicating their strong contribution to the model. The residual error is relatively low, with a sum of squares of 15.30 and a mean square of 3.06. Overall, the total sum of squares for the model is 600.34, demonstrating that the model explains a substantial portion of the variance in the data. The polynomial equation for the percentage of Entrapment Efficiency (% EE) is as follows (Figure 4):

$$\%EE=+64.97-1.35A-0.56B-5.43C+0.2125AB+0.047AC+0.067BC+4.42A^2+4.44B^2+4.12C^2$$

Results of the niosomal gel

Homogeneity

The Diclofenac niosomal gel exhibited a translucent appearance, with a color range from milky white to off-white, without any noticeable variations in color intensity across the formulation. The gel was clear, free of any visible aggregates and showed no signs of phase separation, indicating good physical stability. It had a consistent opacity, was odorless and demonstrated good consistency. Additionally, the gel was free from grittiness and displayed a homogeneous texture throughout, which is essential for even drug distribution and application.

Spreadability

The study on the spreadability and extrudability of the Diclofenac niosomal gel, as reported by Kamboj, showed positive outcomes due to the optimal concentrations of the formulation components, leading to a lower viscosity compared to earlier formulations. The spreadability of the optimized Diclofenac potassium niosomal gel was measured at 3.91±0.1 g cm/s in triplicate, indicating an inverse relationship with viscosity, similar to the findings reported by Goyal. The improved spreadability with minimal force application was attributed to the well-balanced concentrations of key formulation components, particularly the loose gel matrix created by the niosome vesicles. It was found that factors such as cholesterol, Span-60, PEG-1000 and Span-80 significantly influenced the gel's spreadability, making it easy to apply with little shear force. These results align with previous research by Boushra and Goyal, which noted that the addition of Propylene Glycol (PG) as a permeation enhancer also improved the spreadability and consistency of niosomal gel formulations.

Extrudability

The Diclofenac Potassium niosomal gel demonstrated optimal viscosity, facilitating easy and quick dispensing from plastic collapsible tubes with minimal force. The average extrudability was measured at 0.95±0.03 g/cm, based on three separate measurements (*n*=3), which aligns well with values reported for similar formulations of Diclofenac Potassium niosomal gel. Physical examination tests confirmed that the gel exhibited good homogeneity, optimal viscosity, desirable pH, sufficient spreadability and effective extrudability.[33]

pH determination

The pH of the optimized Diclofenac niosomal gel was measured at 6.06±0.15 (*n*=3). This pH level falls within a suitable range for topical delivery, which helps minimize the risk of skin irritation. The pH readings obtained are consistent with those reported for similar niosomal gels.[34]

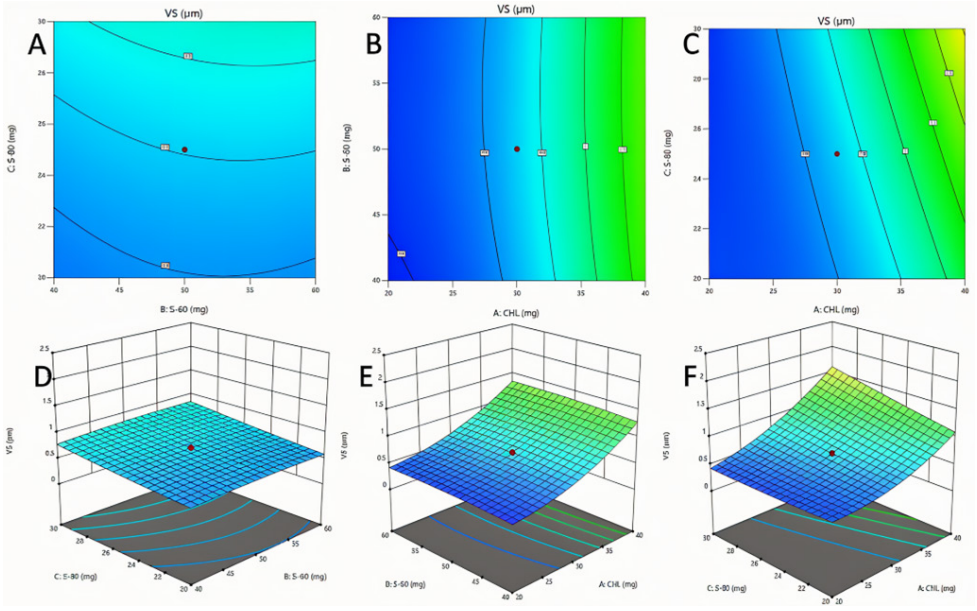

Figure 2: A-C: Contour plots showing the impact of span 60, span 80 and cholesterol on vesicle size; D-F: 3D plots showing the impact of span 60, span 80 and cholesterol on vesicle size.

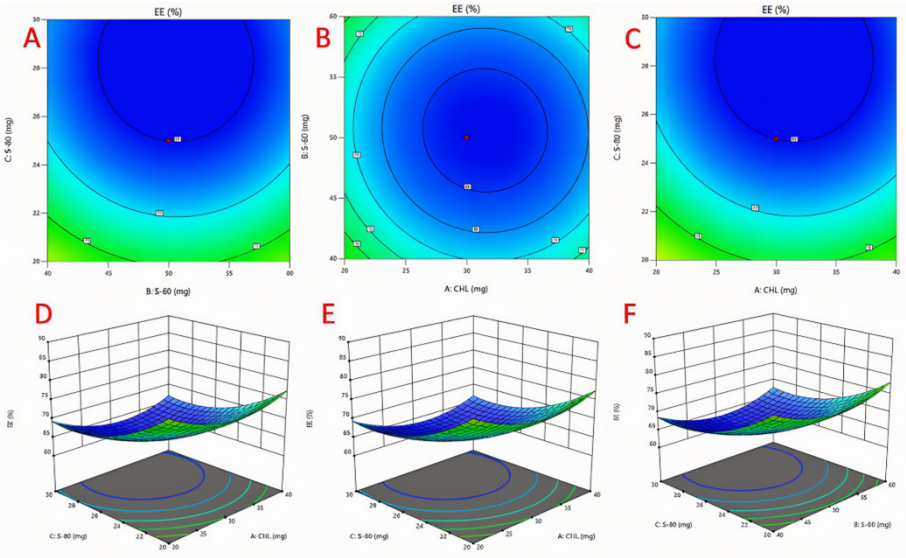

Figure 3: A-C: Contour plots showing the impact of span 60, span 80 and cholesterol on entrapment efficiency; D-F: 3D plots showing the impact of span 60, span 80 and cholesterol on entrapment efficiency.

Viscosity

The viscosity of the optimized Diclofenac niosomal gel was measured using a Brookfield viscometer (GT-21089-1512-T3) with spindle 06 at 2.5 rpm and 25±1°C. The viscosity recorded was 3768±0.57×10² cps (n=3). This viscosity level falls within the desirable range for topical gels, ensuring appropriate consistency, spreadability and extrudability (Table 4).

In vitro permeation results

In vitro, permeation studies demonstrated that Diclofenac permeation was significantly enhanced in the Diclofenac niosomal gel compared to the plain Diclofenac gel. The niosomal gel exhibited a higher rate of drug permeation through the skin, indicating improved delivery of Diclofenac.[34]

Release comparisons among niosomal gel and normal gel

The release of Diclofenac from the niosomal gel formulation is significantly improved compared to the conventional gel, primarily due to the unique characteristics of niosomes. Niosomes are non-ionic surfactant-based vesicles that encapsulate the drug, providing a controlled and sustained release profile. In contrast to conventional gels, where Diclofenac may be released rapidly and unevenly, niosomes offer a more gradual and consistent drug release, enhancing therapeutic efficacy. The niosomal structure enhances the permeability of Diclofenac through the skin by facilitating its transport across biological membranes. This is because niosomes can fuse with skin lipids, creating pathways that allow the drug to penetrate deeper into the skin layers, ensuring a more efficient and prolonged release. As a result, the drug remains in the therapeutic window for longer periods, reducing the frequency of administration and potentially minimizing side effects. Moreover, the encapsulation of Diclofenac in niosomes protects the drug from premature degradation, ensuring that a higher percentage of the drug reaches its target site in its active form. This contrasts with conventional gels, where the drug may be more exposed to environmental factors or undergo faster degradation, leading to a reduced therapeutic effect. Overall, the improved release from the niosomal gel not only enhances the bioavailability of Diclofenac but also provides a more controlled and sustained release, offering potential benefits such as increased patient compliance and better management of pain and inflammation over extended periods.[35]

Release kinetics results

The *in vitro* release kinetics of the normal gel and niosomal gel were evaluated using various kinetic models, including zero order, first order, Higuchi Model and Korsemeyer-Peppas Model. The release characteristics of the niosomal gel and normal gel were evaluated using various models. The zero-order model showed a higher R^2 value for the niosomal gel (0.9829), indicating that it follows a zero-order release pattern, where drug release is independent of concentration. In comparison, the normal gel had a lesser fit with an R^2 value of 0.9729. For first-order release, the niosomal gel exhibited an R^2 value of 0.9648, suggesting a poorer fit, while the normal gel demonstrated a better fit with an R^2 value of 0.987, indicating that its drug release is concentration-dependent. The Higuchi Model revealed R^2 values of 0.9628 for the niosomal gel and 0.9706 for the normal gel, indicating that drug release is influenced by diffusion through the polymer matrix. The Korsemeyer-Peppas Model showed R^2 values of 0.9284 for the niosomal gel and 0.9687 for the normal gel, suggesting moderate applicability of this model in describing the drug release mechanism.

DISCUSSION

The results emphasize the critical role of cholesterol, Span-60 and Span-80 concentrations in determining vesicle size and drug entrapment efficiency in diclofenac-loaded niosomes. Cholesterol stabilized the bilayer, increasing vesicle size, but reducing % EE at higher levels. Span-60 improved both vesicle stability and drug retention, while Span-80 increased vesicle size but compromised drug encapsulation. The uniform, stable appearance of the dispersions suggests successful formulation, highlighting the importance of optimizing surfactant and cholesterol levels for effective niosomal drug delivery systems.

The results indicate a clear relationship between the concentrations of cholesterol and Span-80 and vesicle size, with higher concentrations leading to larger vesicles. This trend suggests that cholesterol and Span-80 contribute to the rigidity and fluidity of the vesicle membrane, respectively, impacting vesicle size. Formulation N1, with lower cholesterol and Span-80 concentrations, exhibited the smallest vesicle size, while N6, with higher levels, showed a significant increase in size. Entrapment efficiency followed a similar pattern, with higher cholesterol and Span-60 levels in formulation N1 leading to the highest % EE. In contrast, N10, despite having the highest cholesterol concentration, showed the lowest % EE, potentially due to the presence of excess cholesterol, which may have disrupted optimal drug encapsulation. PDI values highlighted differences in size distribution, with higher PDI values, as seen in N5 and N6, indicating a broader distribution, suggesting less uniform vesicle sizes. Lower PDI values, as seen in N1, reflected a more homogeneous formulation, likely contributing to improved drug encapsulation. The zeta potential results suggest that most formulations exhibited good stability, with highly negative zeta potentials such as that of N10 (-47.13±0.71 mV) indicating the strong repulsion between vesicles, reducing aggregation and enhancing stability. Formulations with lower zeta potential, such as N14 (-37.09±0.51 mV), indicated a decrease in stability, potentially leading to vesicle aggregation over time. Overall, the study underscores the importance of optimizing cholesterol, span-60 and span-80 concentrations to achieve desirable vesicle sizes, efficient drug encapsulation and stable formulations.

The results from the contour and 3D surface plots highlight the interactive effects of cholesterol, span-60 and span-80 concentrations on both vesicle size and entrapment efficiency. Cholesterol, known for its membrane-stabilizing properties, contributed to an increase in vesicle size, especially when used in conjunction with Span-80, a surfactant that promotes bilayer fluidity. Larger vesicles were observed at higher cholesterol and Span-80 levels, as these ingredients lead to a more fluid and flexible membrane, allowing vesicles to expand. Span-60, on the other hand, acted as a stabilizing surfactant, controlling the vesicle size and preventing excessive enlargement, particularly at lower cholesterol concentrations. In terms of entrapment efficiency, plots suggested that moderate concentrations of span-60 and span-80 were optimal for drug encapsulation, achieving the highest % EE. Cholesterol also played a key role in enhancing vesicle stability, which initially improved entrapment efficiency. However, excessive cholesterol led to overly rigid membranes, limiting the space for drug loading and causing a decline in encapsulation. These findings underscore the importance of balancing surfactant and cholesterol concentrations to achieve both optimal vesicle size and efficient drug encapsulation.

The FTIR analysis provided valuable insights into the compatibility and interactions of Diclofenac with the excipients in the niosomal gel formulation. The characteristic peaks of Diclofenac, cholesterol, span-60, span-80 and carbopol 934 were well-preserved in the niosomal gel spectrum, with no new peaks indicating that there were no chemical interactions between the drug and its components. This finding is crucial, as it confirms that the incorporation of Diclofenac into the gel did not alter its chemical structure, ensuring its stability and efficacy in the final formulation. The sharper peaks observed in the niosomal gel spectrum, particularly those corresponding to the phenyl and -OH groups, suggest that there were strong physical interactions between Diclofenac and the other ingredients, likely contributing to the formation of a stable niosomal structure within the gel. These interactions are essential for enhancing the drug's encapsulation and release properties. The absence of significant peak shifts or the appearance of new peaks further confirms the chemical compatibility of Diclofenac with cholesterol, span-60, span-80 and carbopol 934. This lack of chemical interaction ensures that the excipients used in the formulation do not interfere with the drug's activity, allowing for optimal drug delivery. The FTIR results strongly support the conclusion that Diclofenac can be successfully incorporated into a niosomal gel formulation with cholesterol, span-60, span-80 and carbopol 934, maintaining the integrity of the drug and excipients without any unwanted chemical reactions.

Table 4: Evaluation of the prepared Niosomal Gel.

Formulation	pH	Extrudability (g/cm)	Viscosity (cps) 2.5 rpm and 25±1°C	Spreadability (g/cm/sec)
Diclofenac loaded Niosomal Gel	6.06±0.15	0.95±0.03	3768±0.57×10²	3.91±0.10

Values in Mean±SD; *n*=3.

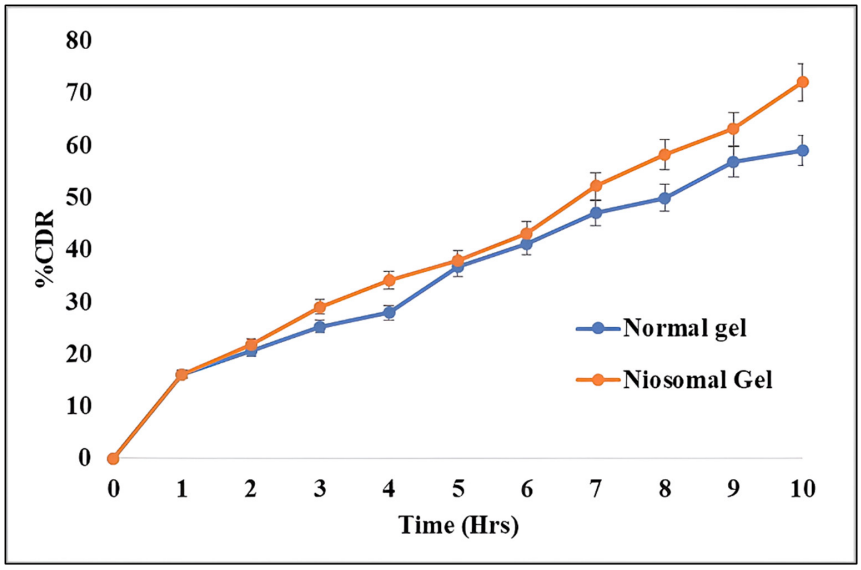

Figure 4: *In vitro* release comparison of both the niosomal gel and the normal gel of Diclofenac potassium.

The physical examination of the Diclofenac niosomal gel revealed several key attributes necessary for a stable and effective topical formulation. The translucent, consistent appearance without any color variations or phase separation is a positive indicator of the formulation's stability, suggesting that the components were well incorporated without the risk of phase instability over time. The absence of aggregates and the homogeneous nature of the gel ensure even distribution of the active drug within the formulation, which is critical for consistent therapeutic effects. The gel's smooth texture, free from grittiness, enhances its user-friendliness, ensuring patient compliance, especially in topical applications where comfort and spreadability are important factors. Furthermore, the odorless characteristic of the gel contributes to its appeal, making it suitable for a wide range of users. Overall, these physical attributes confirm that the Diclofenac niosomal gel is well-formulated, stable and suitable for topical drug delivery.

The findings from this study confirm that the Diclofenac niosomal gel exhibits optimal spreadability and extrudability due to the carefully selected formulation components. The lower viscosity observed in the formulation, compared to that reported by Kamboj and enhances its ease of application, allowing the gel to spread smoothly with minimal force. This is consistent with the inverse relationship between spreadability and viscosity, where lower viscosity results in higher spreadability. The presence of niosome vesicles in the gel matrix contributes to its loose structure, which facilitates better spreadability. The optimal concentrations of cholesterol, Span-60, PEG-1000 and Span-80 play a crucial role in achieving this property. The findings are consistent with those of Boushra and Goyal, who reported similar improvements in spreadability with the inclusion of these components. Furthermore, the enhancement of spreadability and consistency through the use of PEG-1000 and PG, as noted by Garg, underscores the importance of permeation enhancers in formulating effective niosomal gels.

The optimal viscosity of the Diclofenac Potassium niosomal gel ensures that it can be dispensed smoothly and efficiently from plastic collapsible tubes with minimal force, which is advantageous for user convenience and practical application. The measured extrudability of 0.95±0.03 g/cm further supports the ease of application and consistency of the formulation, consistent with previously reported values for similar gels. The comprehensive physical examination indicates that the optimized gel formulation possesses excellent homogeneity, a desirable viscosity range and appropriate pH, all of which are crucial for effective topical delivery. The gel's sufficient spreadability and effective extrudability contribute to its overall performance, making it a suitable and user-friendly option for the topical administration of Diclofenac Potassium. These attributes collectively ensure that the gel is both safe and effective for its intended therapeutic use.

The pH of 6.06±0.15 for the Diclofenac niosomal gel is ideal for topical applications, aligning well with the pH ranges found in similar formulations. Maintaining a pH within this range is crucial as it helps in preventing skin irritation and ensures compatibility with the skin's natural pH. The consistency of these pH values with those reported for other niosomal gels (such as Benzoyl peroxide, Meloxicam and Mefenamic acid) underscores the formulation's suitability for safe and effective topical use. This pH stability confirms that the optimized Diclofenac niosomal gel is both effective and gentle on the skin, making it a reliable choice for topical delivery. Such gels were prepared using benzoyl peroxide by Goyal (2015)[36] with a pH of 6.2±0.162, Meloxicam by Usama (2016)[37] with a pH of 6.2±0.4 and Mefenamic acid by Kamboj (2013)[38] with a pH range of 6.4-6.±0.12.

The measured viscosity of $3768\pm0.57\times10^2$ cP indicates that the Diclofenac niosomal gel has optimal characteristics for effective topical application. This viscosity ensures that the gel maintains adequate consistency and spreadability, allowing it to be applied easily in a thin, even film. The non-Newtonian flow behavior of the gel under minimal stress contributes to its low resistance to flow, making it easier to dispense and apply. These properties not only enhance user comfort and sensory experience but also support effective skin permeability. The viscosity measurement confirms that the gel is well-formulated to meet the practical needs of topical delivery, providing a balance between ease of application and effective therapeutic performance. Extrudability and spreadability are crucial properties of a gel formulation that impact patient compliance and application ease. These properties are closely related to the gel's viscosity and pH. A gel's viscosity affects its extrudability and spreadability. A lower viscosity gel is more easily extruded from a tube and spreads more readily on the skin. Conversely, a higher viscosity gel may be more difficult to extrude and spread. The pH of a gel can influence its viscosity and stability. A gel with a pH close to the skin's natural pH (around 5.5) is more likely to be comfortable and non-irritating. However, significant deviations from this pH range can affect the gel's viscosity and stability.

A gel that is easy to extrude from a tube is more likely to be used correctly by patients. If a gel is too difficult to extrude, patients may struggle to dispense the correct amount, leading to reduced.

A gel that spreads easily and evenly on the skin is more likely to be applied correctly by patients. If a gel is too thick or difficult to spread, patients may experience difficulty applying it, leading to reduced compliance. By carefully balancing these factors, a gel formulation can be developed that is easy to extrude, spreads evenly and has a comfortable pH, ultimately enhancing patient compliance and application ease.

The improved permeation of Diclofenac in the niosomal gel formulation can be attributed to the unique properties of niosomes. Niosomes, being vesicular structures, facilitate better drug encapsulation and enhance the penetration of the active ingredient through the skin barrier. The niosomal gel's superior permeation compared to the plain gel suggests that the niosomal delivery system effectively improves the drug's bioavailability and therapeutic efficacy. This finding underscores the advantage of using niosomes for topical drug delivery, as they offer enhanced permeation and potentially better clinical outcomes for treatments requiring deep skin penetration.

CONCLUSION

The findings from this study indicate that the developed Diclofenac Potassium-loaded niosomal gel demonstrates significant potential for enhancing the topical delivery of Diclofenac Potassium. This innovative formulation addresses the common challenges associated with conventional topical drug administration, primarily the issues of low skin penetration and the resultant limited therapeutic efficacy. By utilizing niosomal carriers, the gel facilitates better drug absorption through the skin, thereby increasing the bioavailability of Diclofenac Potassium at the targeted site of action. Furthermore, the use of niosomes can minimize systemic absorption, which is crucial in reducing the side effects commonly associated with conventional formulations of Diclofenac, such as gastrointestinal complications and other adverse reactions. This targeted delivery not only enhances the drug's therapeutic effects but also contributes to a safer treatment profile for patients. Additionally, the improved formulation may lead to increased patient compliance, as it offers a more effective and potentially less painful alternative to traditional dosage forms. Patients may find the niosomal gel easier to apply and more effective, which could encourage consistent use and adherence to treatment regimens. Overall, this study underscores the promise of niosomal technology in improving topical drug delivery systems, ultimately enhancing patient outcomes in managing conditions requiring Diclofenac Potassium therapy.

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ABBREVIATIONS

NSAIDs: Non-steroidal anti-inflammatory Drugs; **COX-1:** Cyclooxygenase-1; **COX-2:** Cyclooxygenase-2; **USP:** United States Pharmacopeia; **PG:** Propylene Glycol; **DLS:** Dynamic Light Scattering; **EE:** Entrapment Efficiency; **PDI:** Polydispersity Index; **UV-vis:** Ultraviolet-Visible Spectroscopy; **CHL:** Cholesterol; **S-60:** Span-60; **S-80:** Span-80; **VS:** Vesicle Size; **DS:** Diclofenac Sodium; **DSC:** Differential Scanning Calorimetry; **PBS:** Phosphate Buffer Solution.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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