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Original Article

Development and Assessment of a Novel Absorption Base and Permeability-Enhanced Diclofenac Diethylamine Transdermal Cream

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ABSTRACT

Background: Background of the present research study was to investigate shea butter as absorption base and nerolidol as permeability enhancer for transdermal delivery of diclofenac diethylamine. **Hypothesis:** In present study, the leading objective is to enhance diffusion and permeability of diclofenac diethylamine by using shea butter as absorption base along with nerolidol as permeability enhancer. **Materials and Methods:** Total six batches were prepared (F0-F5) and estimated for physical evaluation, Viscosity, pH, Spreadability, drug content, *In vitro* drug release and histopathological studies in association with marketed formulation. **Results:** Study showed that prepared transdermal creams were white in color and drug content was around 100% F5 batch was found to be optimized batch among prepared formulation (F0-F5) formulation. *In vitro* release analysis reveals that the F5 batch had higher drug release than the marketed formulation. The histopathological examination on rat skin permeability sample showed that the F5 formulation demonstrated greater permeation compared to the marketed formulation and the F0 batch. **Conclusion:** F5 batch was found to be optimized batch. The release kinetic data shows that an exponent value of F5 batch was found to be 0.6803, which reveals that release kinetic of F5 batch follows non-fickain drug release mechanism. The histopathological examination of *ex vivo* permeability rat skin sample confirmed that F5 formulation has greater permeability as compared to F0 and marketed formulation.

Keywords: Diclofenac diethylamine, Diffusion, Nerolidol and Shea butter.

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INTRODUCTION

A key strategy used to increase the bioavailability of Active Pharmaceutical Ingredients (APIs) is innovation in drug delivery methods. To date, oral delivery systems remain the most preferable method for administrating API because of its many advantages, including a range of dosage forms, painlessness, ease of administration, self-administration, convenience, patient compliance, and high safety. Oral delivery systems continue to be the most popular way to administer API. Oral delivery systems have certain drawbacks despite these benefits, including low drug stability in the gastrointestinal tract and first-pass metabolism. For example, exposure to the stomach's acidic environment or an enzymatic interaction may result in drug breakdown. The skin is the site of drug administration for transdermal drug delivery systems. Through the skin's blood arteries, the delivered medication enters the systemic circulation and travels throughout the body. Transdermal drug delivery systems have several benefits for patients, including the ability to decrease the frequency of administration, bypass first-pass metabolism, be less invasive (some techniques are completely noninvasive), be simple to apply and administer, and not require specialized staff.[1] Many drugs are absorbed primarily through the skin, both locally and systemically, because of the large number of blood capillaries in the dermis.[2] There are two distinct mechanisms for drug absorption from the skin through the SC: trans epidermal and trans appendageal.[3]

It has been discovered that using naturally occurring excipients in pharmaceutical formulations is a lucrative endeavor. This is due to the potential for chemical changes, availability, lack of toxicity, and economic benefits. Shea butter is a natural fat that is made by crushing, roasting, and grinding the nuts (seeds) of the shea tree (*Butyrospermum parkii Kotschy*), which belongs to the Sapotaceae family. Fatty acids include oleic acid (40-60%), stearic acid (20-50%), linoleic acid (3-11%), palmitic acid (2-9%), linoleic acid (<1%), and arachidic acid (<1%). It also contains several non-saponifiable components. In addition to leaving the

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hands feeling smooth and soft without any greasy residue, the off-white, slightly yellowish, or ivory-colored fat doesn't irritate them even after extended usage.[4] Medical ointments are made with shea butter as the base ingredient. According to reports, several of the chemical compounds that were extracted contain humectant, emollient, and anti-inflammatory qualities. It is applied to wounds to promote healing and to treat dislocation, swelling, and bruises. It is also used as a rub to reduce rheumatic and joint problems. It is frequently used to treat skin conditions such dermatitis, burns, ulcers, dryness, and sunburn.[5]

One of the most frequently used medications to lessen pain and inflammation is non-steroidal anti-inflammatory medicines, or NSAIDs. By blocking the Cyclooxygenase (COX)-2 enzyme, topical NSAIDs reduce peripheral pain by lowering prostaglandin synthesis, which would otherwise heighten pain sensitivity by making peripheral nociceptors more sensitive to painful stimuli. Diclofenac Diethylamine (DDEA) was our choice since, according to analysis; it is the most effective COX-2 inhibitor when compared to other widely used NSAIDs. DDEA's physicochemical characteristics revealed that it has a log D of 0.85 (pH 7.4), a molecular weight of 369 Da, and a melting point of 157°C. DDEA has a short biological half-life of 2-3 hr, a minimal dose requirement of 25 to 50 mg, and a bioavailability of 40 to 60%. When combined, these traits imply that DDEA ought to be a viable option for the creation of transdermal dosage forms. Because DDEA has a pKa of 4.0, it can effectively traverse membrane barriers, remain unionized at acidic pH levels around inflammatory tissues, and accumulate in the neutral intracellular region where COX-2 enzymes are found.[6] DDEA is regarded as a good option for topical administration in pain management.

Natural terpenes with a high enhancing impact and minimal skin irritation are increasingly being used as permeation enhancers in pharmaceutical and cosmetic formulations. Nerolidol showed the highest enhancing activity for hydrocortisone penetration among the terpene series. Several additional publications agree with this view. Among the series of terpene enhancers that were studied, Cornwell and Barry found that nerolidol was the most effective in facilitating the penetration of 5-fluorouracil via the skin.[7] This was ascribed to nerolidol's amphiphile-like structure, which was suitable for upsetting the SC's lipid packing.[8]

The aim of the present study was to formulate transdermal cream formulation of DDEA using shea butter as absorption base with nerolidol as permeation enhancer to enhance diffusion and permeability of DDEA for better therapeutic effect as compared to marketed formulation.

MATERIALS AND METHODS

Diclofenac Diethylamine was supplied with gift sample by Magnus Biotech Pvt. Ltd., Karnal. TBHQ was supplied as a gift sample by Aarnee International Pvt. Ltd., Ahmedabad. Span 80 (MONEMUL-80Hi) was supplied as gift sample by Mohini Organic Pvt. Ltd., Mumbai. Shea butter purchased from Mangalam Agro CitSpray Aroma Sciences, Nagpur and Dialysis membrane-70 (LA 393) purchased from Dolphin Pharmacy Instruments Pvt. Ltd., Mumbai. Butyl Paraben, Propyl Paraben, Butylated Hydroxy Toluene (BHT), Methanol-AR Grade were procured from Modern Science, Nashik. Nerolidol was supplied by Ambrosial, New Delhi.

Pre-formulation Study

Drug Characterization

Organoleptic Properties of Diclofenac Diethylamine

Color: A tiny amount of Diclofenac Diethylamine was placed in butter paper and examined in a bright area.

Odor: Very less quantity of APIs smelled to get odor.

Appearance: Appearance was detected by visual inspection.

Melting Point

The melting point is the first sign that the sample is pure. Open capillary method was used to find the melting point of diclofenac diethylamine. A glass capillary with one end previously sealed with a flame was filled with diclofenac diethylamine. After that, the capillary was dipped into the liquid paraffin that was inside the melting point device. The liquid paraffin of melting point apparatus was heated, and melting point range was recorded.

Determination of λ_{max} by UV Spectrophotometer

UV-vis Spectra of Diclofenac Diethylamine drug was observed at 200-400 nm on UV Spectrophotometer (Lab India, UV-3200). The λ_{max} of solution of Diclofenac Diethylamine drug was determined in Phosphate buffer (pH 7.4).

Calibration Curve of Diclofenac Diethylamine in Phosphate buffer (pH 7.4)

Standard Stock Solution

Weigh 11.6 mg of diclofenac diethylamine (equivalent to 10 mg of diclofenac sodium) and transfer it into a 100 mL volumetric flask. Make up the volume to 100 mL with phosphate buffer (pH 7.4) and mix thoroughly.

Working Stock Solution

From the above stock solution test solutions ranging from 5, 10, 15, 20, 25 and 30 μg mL^{-1} were prepared in phosphate buffer (pH 7.4) by serial dilution.

Absorbance of ready solution was measured at 276 nm. Calibration curve was created through plotting graphs among concentrations versus absorbance.

Fourier Transform Infrared Spectroscopy (FT-IR)

A Shimadzu 8400 FT-IR analyzer was used to record infrared spectrum of pure diclofenac diethylamine. For the sample, the

KBr disc method was used (2.0 mg sample in 100 mg KBr). It was then tested in transmission mode. The spectrum was measured using a range of frequencies from 4000 to 400 cm^{-1}. After that, the peaks found in the spectrum were compared to diclofenac diethylamine structures that correspond to relevant functional groups of diclofenac diethylamine.

Drug-Excipient Compatibility Study

Diclofenac diethylamine drug and other excipients were weighed accurately. The drug excipient compatibility study was conducted by taking Drug-Excipient in 1:1% w/w ratio for test and control samples. The mixtures were then transferred to previously clean and dried vials. Vials were sealed using rubber closure and aluminum crimp. The control samples were kept at room temperature outside the humidity cum photo stability chamber, while test samples were kept within humidity cum photo stability chamber maintained at 40±2°C temperatures and 75±5% RH for a period of 14 days. The samples were then observed visually for a change in color, odor and appearance.

Drug-Excipient Compatibility Assay

In a 10 mL volumetric flask, 2.32 mg of the drug excipient mixture (which is equivalent to 1.16 mg of diclofenac diethylamine, which is equivalent to 1 mg of Diclofenac Sodium) was taken from the test and control samples. Phosphate buffer (pH 7.4) was used to dissolve the material, and 10 mL of the solution were created. 1 mL of the sample was taken out using a pipette from the prepared solution and placed in a 10 mL volumetric flask. The phosphate buffer (pH 7.4) was used to dilute the sample up to 10 mL. A calibration graph was used to determine the concentration after the sample was examined at 276 nm.

Formula Design

Creams were prepared by using trituration method. Drug, excipient, and cream base were taken in different amount as per the formula. The formula with ingredients is shown in Tables 1 and 2.

Formulation of Diclofenac Diethylamine Anti-Inflammatory Cream

The amounts of drug and other materials were measured out according to Table 2, and the formulation was made in the way shown below.

1. All glassware washed and dried in hot air oven.
2. Given quantities of all ingredients and diclofenac diethylamine drug were weighed.
3. Formulation of transdermal cream of diclofenac diethylamine was prepared using previously cleaned and dried mortar and pestle.
4. **Beaker A:** Accurate quantity of shea butter was weighed and allowed to melt by using water bath. To it BHT and TBHQ were added and were mixed well. Diclofenac Diethylamine drug was added in the melt and was mixed well.
5. **Beaker B:** Accurate quantity of glycerol, butyl paraben, propyl paraben and water were taken in a beaker. Add one measured drop (0.1 g) of Span 80 in the mixture. The nerolidol was measured accurately and added into it according to the given batch mixture.
6. **Beaker C:** Shea butter mixture containing drug was mixed in the aqueous mixture by dropwise addition with continuous stirring on ice bath.
7. The cream prepared was stored in a light resistance container.

Evaluation of Transdermal Cream of Diclofenac Diethylamine

The prepared cream was assessed for physical evaluation, viscosity, pH, Spreadability, drug content, *in vitro* drug release and histopathological studies investigations.

Physical Evaluation

Following the cream's setting in the container, each formulation was visually inspected.

Physical Appearance

Prepared creams were evaluated for color, odor and texture.

Viscosity

The viscosity of the prepared formulations (F0 to F5) was determined using a Brookfield DV-II+ Pro Viscometer with Spindle S-61. A sufficient amount of the sample was taken in a beaker. Spindle S-61 was then attached to the viscometer, and the viscosity of the prepared cream was measured at 100 rpm. The measurement was taken for duration of 1 min. at room temperature.

pH

The pH of prepared cream was measured by dipping pH meter in cream formulation. pH of topical cream formulation found to be in between 6.9-7.16.

Determination of Spreadability

The Spreadability apparatus was cleaned and dried. 1 g of the preparation was weighed and placed on the fixed slide. The upper slide, which was connected to a pan through a pulley and thread, was positioned over the fixed slide. A 30 g weight was placed on the upper slide to ensure uniform Spreadability and to remove any air bubbles from the cream for 2 min. After this, additional

weight was gradually added to the pan, and the time taken for the upper slide to move half the distance (20 cm) from the fixed slide was recorded. The spreadability was then calculated using the formula below.

Spreadability=Weight put to upper slide×L/ T

Determination of Drug Content

Diclofenac Diethylamine content in cream was measured by taking 1 g of cream in 100 mL volumetric flask and dissolved by using methanol and making up its volume up to 100 mL after that, 0.1 mL was pipetted out and diluted up to 10 mL in a volumetric flask. A UV Visible Spectrophotometer was used to measure absorbance at 276 nm. The above same procedure was carried out for determination of drug content of marketed formulation i.e., Omnigel.

In vitro Drug Release and Comparative Evaluation with Commercial Formulation

A dialysis membrane -70 (LA 393) positioned between the donor and receptor compartments of the Franz diffusion cell apparatus (Dolphin, Mumbai) was used to conduct an *in vitro* drug release study. This cream contained 1.16% diclofenac diethylamine, which is equivalent to 1% diclofenac sodium. On the donor side, 1 g of cream was applied. The water jacket kept circulating to maintain the temperature of Franz diffusion cell at 37±2°C. Entire assembly was maintained on magnetic stirrer, and magnetic beads were used to continually stir diffusion fluid (pH 7.4 solution of phosphate buffer) at a speed of 200 rpm. After 15, 30, 60, 120, 180, 240, and 360 min, 2 mL of sample were removed, and the same volume was replenished with new diffusion fluid to maintained sink condition. Samples were analyzed by spectrophotometer at 276 nm and %CDR was calculated.

Histopathological Studies

Histopathological studies were carried out for elucidation of mechanism of penetration enhancement of the investigated enhancer. In this study, the post-permeation skin were immerse in 10% neutral buffered formalin for at least 24-48 hr to preserve tissue integrity. Each section was dehydrated using ethanol, embedded in paraffin for fixing, and stained with haematoxylin and eosin. These samples were then observed under light microscope and compared with control sample. In each skin sample, two different sites were scanned and evaluated for elucidation of mechanism of penetration enhancement.

RESULTS AND DISCUSSION

Drug Characterization

Organoleptic Properties

The drug samples were observed to be white to light beige in color, odorless, and crystalline in appearance, indicating good purity in alignment with standard pharmacopeial descriptions.

Melting Point of Diclofenac Diethylamine

The melting point determined by capillary tube method Diclofenac Diethylamine was observed to have a melting point between 135 and 141°C, which is extremely close to the published standard. Thus, we deduce that diclofenac diethylamine was pure.

UV-visible Spectrophotometric Analysis of Diclofenac Diethylamine

Absorption Maxima Wavelength (λ_{max}) of Diclofenac Diethylamine in Phosphate Buffer (pH 7.4)

Diclofenac diethylamine showed the maximum absorbance at 276 nm in pH 7.4 phosphate buffer.

Construction of Beer's Lamberts Plot of Diclofenac Diethylamine in Phosphate Buffer (pH 7.4)

The Beer's lamberts plot for Diclofenac Diethylamine in phosphate buffer (pH 7.4) was constructed. The regression coefficient of the lines obtained in phosphate buffer (pH 7.4) was found to be 0.999 which is shown in Figure 1. The linearity in phosphate buffer (pH 7.4) was found in concentration range of 5-30 µg/mL.

Fourier Transforms Infrared Spectroscopic Study

The FTIR spectra of Diclofenac Diethylamine showed that it is pure in nature. Outcomes are shown in Figure 2.

The FTIR spectrum of diclofenac diethylamine showed characteristic peaks near 1570 cm^{-1} corresponding to aromatic C=C stretching, and a peak at 1550 cm^{-1} indicating N-H bending of a secondary amine. Peaks around 1300-1350 cm^{-1} were attributed to C-N stretching, and a broad absorption near 3300 cm^{-1} confirmed the presence of N-H or O-H groups. The peak around 2950-3000 cm^{-1} was due to C-H stretching of aliphatic chains.

Drug-Excipients Compatibility Study

Physical appearance

In the physical compatibility evaluation conducted over 14 days, no significant changes in color or odor were observed in both control or test samples of Diclofenac Diethylamine and its combinations with various excipients. The drug alone and in combination with BHT, TBHQ, butyl paraben, propyl paraben, and shea butter remained white with a characteristic odor. Only the combination with nerolidol showed a stable pale yellow color with no change in odor. These results confirm the physical compatibility of Diclofenac Diethylamine with the tested excipients.

Drug-Excipients Compatibility Assay

Control and test samples were evaluated by UV-visible spectrophotometer to determine % drug content respectively after 14 days.

In the drug-excipient compatibility study of Diclofenac Diethylamine, the assay values for all control and test samples were consistently above 90%, indicating good stability across the various combinations. The control and test samples of Diclofenac Diethylamine alone both showed an assay value of 108%. When combined with the excipient nerolidol, the assay values remained consistent at 108% for both samples. In the presence of the antioxidant BHT, the control sample showed an assay of 109%, while the test sample was slightly lower at 107%. With TBHQ, the assay values were 108% and 109% for control and test samples, respectively. The preservative excipients butyl paraben and propyl paraben both showed identical assay values of 109% in both control and test samples. Similarly, the combination with shea butter yielded consistent assay results of 108%. Based on these findings, it was concluded that Diclofenac Diethylamine is compatible with the selected excipients, making them suitable candidates for the formulation of a transdermal cream.

Evaluation Results of Transdermal Cream of Diclofenac Diethylamine

Physical Appearance

Prepared creams were evaluated for color, odor and texture. Result shown in Figure 3. The prepared cream was white in color with a characteristic odor and with smooth texture.

Viscosity

Viscosity was measured using Brookfield DV-II+ Pro Viscometer and the results as follows,

The viscosity of the various formulations was measured and found to be relatively consistent across all batches. Formulation F0 showed a viscosity of 112.3 cP. Formulations F1, F3, and F5 had viscosities of 113.2 cP, while F2 and F4 showed slightly higher values of 113.4 cP.

pH

The pH of the cream formulations was measured using a digital pH meter, and the values ranged from 6.96±0.05 to 7.16±0.15. Specifically, formulation F0 showed a pH of 7.16±0.15, F1 was 6.96±0.05, F2 and F3 recorded 7.16±0.05 and 7.13±0.05, respectively. F4 and F5 showed pH values of 7.00±0.10 and 7.06±0.15, respectively. In comparison, the marketed formulation (Omnigel) exhibited a lower pH of 6.43±0.05. All test formulations were within an acceptable pH range for topical application and were slightly more neutral than the marketed product.

Spreadability

Spreadability of the cream formulations was assessed, where a shorter time to cover a given distance indicates better spreadability. The results showed that formulation F0 exhibited the highest spreadability (19.78±0.37 g·cm/s), followed closely

Table 1: **Ingredients and Category of Cream.**

Sl. No.	Ingredient	Category
1	Diclofenac Diethylamine	Anti-inflammatory Drug
2	Shea Butter	Absorption base and Skin smoothing
3	Span 80	Emulsifier
4	Tert-Butylhydroquinone (TBHQ)	Anti-oxidant
5	Butyl Paraben	Preservative
6	Propyl Paraben	Preservative
7	Butylated Hydroxytoluene (BHT)	Anti-oxidant
8	Nerolidol	Penetration enhancer
9	Glycerol	Humectant
10	Water	Vehicle

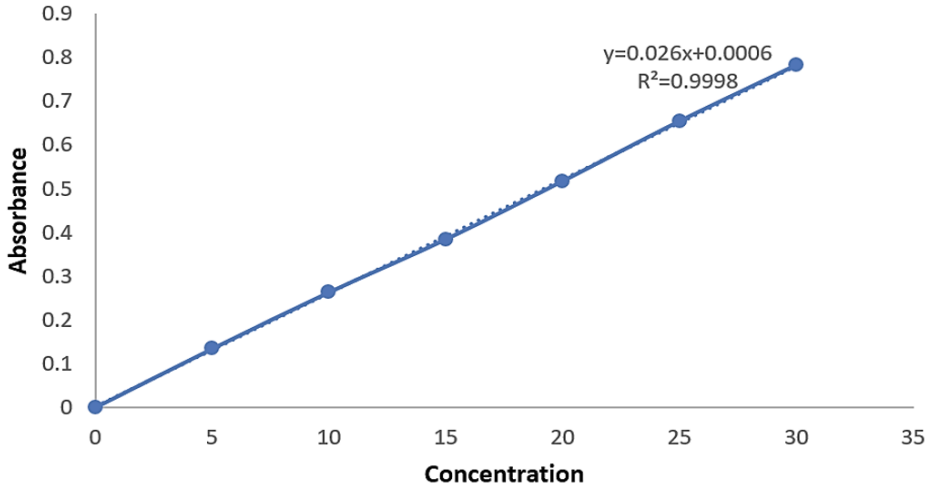

Figure 1: Calibration Curve of Diclofenac Diethylamine in Phosphate buffer (pH 7.4).

Table 2: **Composition of Diclofenac Diethylamine Transdermal Cream in gram quantities.**

Ingredients	F0 (I, II, III)	F1(0.1)% (I, II, III)	F2 (0.2%) (I, II, III)	F3 (0.3%w/v) (I, II, III)	F4 (0.4%) (I, II, III)	F5 (0.5%) (I, II, III)
Diclofenac Diethylamine	0.116	0.116	0.116	0.116	0.116	0.116
Shea butter (Purified)	7.232	7.222	7.212	7.202	7.192	7.182
Nerolidol (µL)	-	0.011	0.022	0.033	0.044	0.055
Span 80	0.1	0.1	0.1	0.1	0.1	0.1
Glycerol	2	2	2	2	2	2
BHT	0.01	0.01	0.01	0.01	0.01	0.01
TBHQ	0.002	0.002	0.002	0.002	0.002	0.002
Butyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01
Propyl Paraben	0.03	0.3	0.03	0.03	0.03	0.03
Water	0.5	0.5	0.5	0.5	0.5	0.5

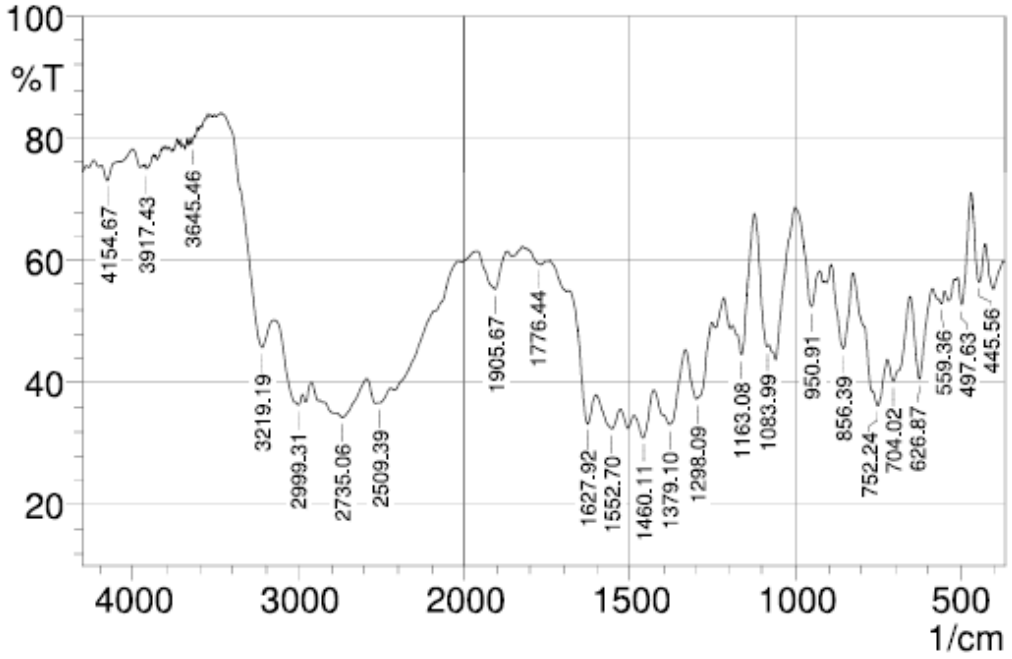

Figure 2: FTIR Spectrum of Diclofenac Diethylamine.

by F5 (19.56±0.37 g·cm/s) and the marketed formulation (19.36±0.62 g·cm/s). Other formulations demonstrated slightly lower spreadability: F1 (18.56±0.88 g·cm/s), F2 (18.37±0.32 g·cm/s), F3 (18.56±0.32 g·cm/s), and F4 (18.76±0.58 g·cm/s). Notably, F5 and the marketed product showed nearly identical spreadability values, suggesting comparable application ease.

Drug Content

The drug content of the prepared cream formulations was found to range from 100% to 105%, indicating that the active pharmaceutical ingredient was present within the acceptable limits and showed no signs of degradation. Specifically, F0 and F1 exhibited slightly higher drug content at 104%±0.4 and 105%±1.6, respectively. Formulations F2, F3, F4, and F5 showed drug content values of 100%±1.6, 101%±1.6, 103%±2.4, and 102%±1.6, respectively. The marketed formulation showed a comparable drug content of 102%±1.2. These results confirm the uniform distribution and stability of diclofenac diethylamine in all formulations.

In vitro Diffusion Studies

Result of *in vitro* drug release of prepared formulation from F0 to F5 batch, which compared with marketed formulation are shown in Table 3.

In vitro diffusion study shows that highest % drug release was obtained with F5 batch i.e., 49.319%±2.887 % which higher in compared to marketed formulation value of 36.83±2.06 % in 6

hr. Hence, from this study we deduced that F5 batch is optimized batch.

Kinetic assessment of *in vitro* release of drug from prepared cream

Many mathematical models were used to suit the released data that had been studied. These models included the Zero order, First order, Hixon-Crowell, Higuchi, and Korsmeyer-Peppas models. Table 4 displayed the results.

Diclofenac Diethylamine is integrated into semisolid matrices, as demonstrated by the kinetic data used to *in vitro* diffusion tests, which reveal that optimized batch F5 follows zero order kinetics and Higuchi model, indicating that drug release from formulation F5 is by diffusion. F5 batch's n exponent value came out to be 0.6803. F5 batch follows the non-fickain drug release mechanism, since n value was between 0.5 to 0.89.

Histopathology Studies

Result shown in Figure 4 for Control Sample, F0, F5 batch and Marketed Formulation with 10x and 40x magnification.

Control (untreated)

The photomicrographs of untreated rat skin (control) showed normal skin. Epidermal and dermal layers are well defined.

F0 (Not treated with enhancer)

The skin section (not treated with enhancer) showed slight dermal (keratin) Protein and lipid structure breakdown but at moderate level. Although it induced mild impairment of the barrier function of the skin, it did not alter the viability of skin.

F5 (Optimized Formulation)

Skin section (enhancer treated) showed marginal focal disruption of epidermis with thinning, which might be related to the conformational changes of the lipid bilayer. The disruption and extraction of lipid bilayers was clear as distinct voids and empty spaces visible in the epidermal region. This indicates that both nerolidol and oleic acid of shea butter contributes to dissolving lipids of stratum cornea of skin and disruption of protein molecules of skin by synergistic mechanism.

STD Marketed Formulation Omnigel®

Diclofenac diethylamine (Omnigel) contains linseed oil for improving penetration of drug. The linseed oil contains 12-14% oleic acid as percent composition.

The histopathological slide of rat skin treated with omnigel formulation showed that skin integrity was maintained. The image showed that there was slight disruption of lipid layer and keratin layer but at marginal level.

Figure 3: Prepared Transdermal Diclofenac Diethylamine Cream.

Table 3: *In vitro* Drug Diffusion Studies.

Time (min)	% Release						
	F0	F1	F2	F3	F4	F5	Marketed
0	0	0	0	0	0	0	0
15	3.039±0.833	1.441±0.377	1.823±0.390	3.251±0.288	6.591±0.890	5.855±0.197	4.750±0.506
30	4.290±0.492	6.816±1.159	3.375±0.123	5.524±0.428	7.511±1.151	6.072±0.309	5.176±0.506
60	8.050±1.370	13.284±3.810	9.000±0.829	10.187±1.685	21.710±0.350	7.232±0.880	8.872±1.747
120	12.515±1.416	19.389±3.323	19.297±2.527	14.204±0.271	27.259±0.895	18.107±0.777	27.044±1.030
180	17.091±2.652	25.048±1.767	28.121±2.025	22.661±2.855	45.097±0.640	26.131±3.592	33.558±0.829
240	22.749±3.121	28.297±0.844	32.276±2.272	32.144±1.685	46.138±0.335	39.367±3.315	36.410±2.495
360	32.431±4.945	36.167±2.992	42.776±2.990	44.080±3.809	46.637±0.591	49.319±2.887	36.830±2.062

Values represented as mean±SD, n=3, Where n=Number of replicates.

Table 4: Regression Coefficient Value of *in vitro* Diffusion Studies.

Batches	Coefficient of regression R^2					
	Zero Order	First Order	Higuchi model	Hixon model	Korsmeyer Peppas	
					R^2	N
F0	0.9945	0.9956	0.9506	0.8199	0.3096	0.4513
F1	0.9353	0.9962	0.9804	0.8609	0.4460	0.5853
F2	0.9736	0.9914	0.9556	0.8434	0.4206	0.5710
F3	0.9932	0.9910	0.9314	0.8105	0.3921	0.5231
F4	0.8345	0.9908	0.9324	0.9048	0.5628	0.8725
F5	0.9812	0.9874	0.9194	0.8713	0.4211	0.6803
Marketed	0.8386	0.9902	0.9159	0.8780	0.4692	0.7141

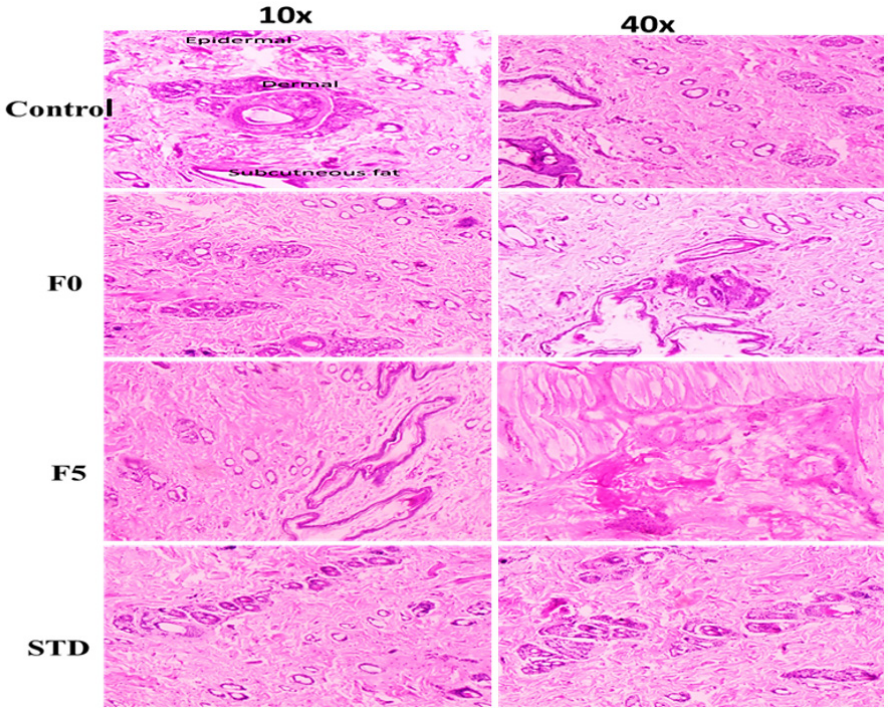

Figure 4: Histological Sections (H&E staining, 10x and 40x magnification) of Rat Skin after Treatment with control, F0, F5 and marketed formulation, Illustrating the Penetration of Diclofenac diethylamine formulation.

CONCLUSION

In conclusion, the study demonstrated that the F5 batch of Diclofenac Diethylamine transdermal cream, prepared with shea butter as an absorption base and nerolidol as a permeability enhancer, showed promising results. The cream exhibited good organoleptic properties, optimal pH, and excellent drug content.

In vitro diffusion studies revealed that F5 batch had higher drug release compared to the marketed formulation, following zero-order kinetics and a non-Fickian release mechanism.

Histopathology studies confirmed the effective permeation of the drug through rat skin. Overall, the F5 formulation demonstrated enhanced drug diffusion and permeability, as compared to the other formulations, supporting its potential for improved therapeutic outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredients; **SC:** Stratum Corneum; **NSAID:** Non-Steroidal Anti-Inflammatory; **COX:** Cyclooxygenase.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is based on *ex vivo* permeability study using rat skin. The rat skin was taken from the rat that was scarified during M. Pharm Pharmacology regular practical and hence it does not require any ethical approval.

SUMMARY

This study investigates the transdermal delivery of diclofenac diethylamine using Shea Butter as absorption base with nerolidol as permeation enhancer. Six batches (F0 to F5) of DDEA transdermal cream were prepared and evaluated for physical properties, Viscosity, pH, Spreadability, drug content; *in vitro* drug release and histopathological permeability studies on rat skin were carried out using F0, F5 and marketed formulation. Among the batches, the F5 formulation was identified as the optimized batch, showing the highest drug release and permeation.

Histopathological analysis confirmed enhanced permeation through rat skin with the F5 formulation. The study concludes that the combination of shea butter and nerolidol effectively enhances the diffusion and permeability of DDEA, making the F5 formulation a promising candidate for improved transdermal therapeutic outcomes compared to the marketed formulation.

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