RESEARCH PAPER

Development and Evaluation of Diclofenac Microemulsion Formulation using Piperine as a Bioenhancer

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ABSTRACT

Background: Diclofenac, generally used as a non-steroidal anti-inflammatory drug (NSAID), is effective in treating pain and inflammatory conditions but causes gastrointestinal and renal side effects upon oral administration. This study aims to develop and evaluate a transdermal microemulsion formulation of diclofenac using piperine as a bio-enhancer, leading to enhanced drug permeability and therapeutic efficacy.

Methods: Pseudo-ternary phase diagrams were formed by using oleic acid (oil phase), Cremophor RH40 (surfactant), and Transcutol (co-surfactant). Optimized microemulsions were assessed for particle size, zeta potential, in vitro release studies of drug, ex vivo permeation and in vivo studies, including drug pharmacokinetics. Scanning electron microscopy (SEM) studies were carried out to assess skin permeability.

Results: Optimized microemulsions exhibited high clarity (transmittance >90%) and nano-sized droplets (A4: 11.41 nm, B1: 12.16 nm). In vitro studies showed A4 released 60% of the drug in 4 hours, while B1 took 6 hours, indicating both immediate and sustained release potential. Ex vivo studies confirmed enhanced drug permeation, with 80% release from A4-based gel and 76% from B1-based gel in 24 hours. SEM studies revealed an increase in skin porosity in the microemulsion, which may be due to the inclusion of piperine. In vivo studies confirmed sustained plasma drug levels with the piperine-enhanced formulation.

Conclusion: The diclofenac-piperine microemulsion gel demonstrated enhanced transdermal absorption, sustained drug release, and reduced systemic toxicity. It offers a promising alternative to oral diclofenac for safer and more effective pain management.

Keywords: Bioenhancers, NSAIDS, Piperine, Transdermal drug delivery, Microemulsion, Pain management

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Introduction

Diclofenac (2-(2,6-dichloranilino) phenylacetic acid) has strong antipyretic and analgesic properties. Diclofenac belongs to BCS class II drug, having short half-life of 1-2 h which results in undesirable side effects such as peptic ulceration, gastritis and renal function impairment when given orally [1]. Topical formulations have grown popularity for dealing pain due to their localized action and reduced systemic side effects. Typically, diclofenac is applied topically to alleviate inflammation [2]. The growing number of topical diclofenac products available in the market, such as Voltaren®, Olfen® and Flector® highlights the increasing interest in transdermal delivery of diclofenac [3]. The therapeutic potential of diclofenac in transdermal applications is often limited by its poor skin permeability, primarily due to its molecular size and physicochemical properties. To address this limitation, incorporating bioenhancers has been explored as an effective strategy to improve its transdermal delivery [4]. Bioenhancers, both natural and synthetic, enhance drug absorption by disrupting the lipid bilayer of the stratum corneum (SC), leading to an increase in skin

permeability. This approach results in achieving the therapeutic concentrations at lower doses and also simultaneously minimizes systemic side effects due to high dose [5]. Piperine, an alkaloid component of black pepper (*Piper nigrum*), is one such bioenhancer recognized for its ability to improve drug permeability and absorption. Piperine, with the molecular formula $C_{17}H_{19}NO_3$, has a melting point of 128°C and is optically inactive. It is sparingly soluble in water, exhibits cis-trans isomerism, and demonstrates high lipophilicity. When incorporated into diclofenac-based microemulsions, piperine can enhance transdermal delivery by modulating the skin barrier and promoting deeper penetration of the drug into the skin layers. This synergistic combination shows promise in enhanced therapeutic outcomes while minimizing systemic and gastrointestinal side effects [6,7]. Among various unconventional transdermal drug delivery approaches, microemulsions stand out due to their unique properties. These include thermodynamic stability, ease of preparation, and enhanced drug solubility and permeability [8]. Microemulsions, being thermodynamically stable isotropic mixtures of oil, water, surfactant, and cosurfactant, offer a versatile and efficient platform for transdermal drug delivery. Their ability to enhance drug penetration and stability makes them a valuable system for improving the therapeutic efficacy of diclofenac in transdermal applications [9]. In one of the study, researchers successfully developed and optimized a piperine-loaded binary ethosomal gel (PEES-gel) to enhance transdermal delivery. The optimized gel demonstrated excellent physicochemical properties, biocompatibility, sustained release, and superior skin permeation compared to conventional formulations. Additionally, PEES-gel exhibited significantly improved antimicrobial and antioxidant actions, proving its potential as an effective and natural alternative to synthetic drugs for topical applications. These findings pave the way for further exploration of PEES-gel in therapeutic transdermal delivery systems [10]. In another study, the researchers developed Dissolving Microneedle Piperine (DMNs PIP) formulation demonstrated excellent mechanical strength, high penetration efficiency, and stability without polymer-drug interactions, as confirmed by X-Ray diffraction studies (XRD) and Fourier Transform Infrared analysis (FTIR). *Ex vivo* hemolysis testing further established the safety and non-toxic nature of DMNs PIP, with a hemolysis index below the acceptable threshold. These results highlight the potential of DMNs PIP as a safe and effective alternative in piperine delivery *via* transdermal route in the treatment of inflammation [11]. In another study, investigators successfully developed a transdermal patch using natural rubber latex infused with *Piper nigrum* extract, optimized with the addition of plasticizers. The formulation containing dibutyl phthalate and glycerin demonstrated favorable piperine release profiles, along with exceptional mechanical properties and physical stability. These findings highlight the potential of *Piper nigrum*-based transdermal patches as an effective and innovative approach for managing muscle pain [12].

Material and Methods

Materials

Oleic acid, Cremophore RH40 and Transcutol were procured from Loba Chemie Pvt. Ltd, Mumbai, India; Piperine and Diclofenac sodium is procured from Yarrow Chem Products, Mumbai.

Methods

Selection of components of formulation

Microemulsions were prepared using different components [oil phase, Smix (surfactant and co-surfactant)], which were screened for the construction of pseudo-ternary phase diagrams. These diagrams were constructed to find out the microemulsion region and to get the best composition pertaining to microemulsion. Oleic acid was used as the oil phase, and cremophore RH 40 as surfactant, and Transcutol as co-surfactant. Oil phase was chosen on the basis of extreme drug solubility. Surfactant was selected on the basis of their highest emulsifying ability for the designated oil phase. Co-surfactant was nominated on the basis of the highest nanoemulsifying region area obtained in the developed phase diagram using other designated oil and surfactant [13,14].

Construction of a pseudo-ternary phase diagram

The phase diagrams were formed by the aqueous phase titration method using selected oil phase, S_{mix} phase, and aqueous phase. Surfactant/ co-surfactant (S_{mix}) was mixed properly in ratio of 1:1, 2;1, 1:2 and 1:3 (A-D series), as mentioned in Table 1. S_{mix} was first dissolved in the oil phase in ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 in 10mL volumetric flask. Each mixture of S_{mix} containing oil phase was titrated continuously using drop-by-drop distilled water, followed by vortex mixing till it changed to a turbid appearance. The phase behavior

of each of above formulated ternary systems was observed minutely during the titration process [15].

Table 1: Formulation composition of microemulsions

Formulation code	S_{mix} (Cremophor RH40+ Transcutol)	Oil + S_{mix}
A-series, A1-A9	1:1	1:9-9:1
B-series, B1-B9	2:1	1:9-9:1
C-series, C1-C9	1:2	1:9-9:1
D-series, D1-D9	1:3	1:9-9:1

Preparation of microemulsion: An accurately weighed amount of diclofenac and piperine was taken in a volumetric flask containing S_{mix} (cremophor RH40 and transcutol). The shaking of the mixture was done using a magnetic stirrer until the drug was properly mixed. Oil (oleic acid) was then added to the S_{mix} and again stirred for about 10 min. The mixture was further diluted using distilled water (adding dropwise) under continuous stirring till a transparent microemulsion was achieved [16]. The composition of drug-loaded microemulsion batches is mentioned in Table 2.

Table 2: Composition of the drug-loaded microemulsion batches

Formulation code	Smix	Smix / Oleic acid	Diclofenac	Piperine
ME A (ME A1-ME A9)	1:1	1:9-9:1	200mg	10mg
ME B (ME B1-ME B9)	2:1	1:9-9:1	200mg	10mg
ME C (ME C1-ME C9)	1:2	1:9-9:1	200mg	10mg
ME D (ME D1-ME D9)	1:3	1:9-9:1	200mg	10mg

Determination of percent transmittance: Percent transmittance was determined for prepared formulations in order to approve the clarity and for the determination of particle size.

Particle size determination:

The optimized drug-loaded microemulsions were assessed for particle size *via* Malvern zeta sizer and using dynamic light scattering (DLS) technique.

***In vitro* release of drug:** Dialysis bag technique was used to carry out a 24-hour drug release of optimized diclofenac microemulsions. 5 mL of microemulsion were added to a pre-soaked dialysis membrane (12–14 kDa), which was then tightly sealed. The bag was kept at 37 ± 0.5°C with constant stirring at 50–100 rpm while submerged in 100 mL phosphate buffer of pH 6.8. To maintain sink conditions, 2 mL of the dissolution media was pipetted out, filtered, and replaced with new buffer at predetermined intervals (0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h). UV-Vis spectrophotometry was utilized to estimate the concentration of pure drug (diclofenac) [17].

Formulation of topical gel incorporating microemulsions

2% of carbopol 934 was allowed to swell overnight in 100 mL of distilled water. The optimized microemulsions were added to formed carbopol gel and mixed properly. The formed hydrogel was allowed to stand for 15 minutes without stirring to expel the trapped air and was then stored in tightly closed screw-capped glass bottles at room temperature for further studies [18].

pH determination

The pH values of microemulsion loaded topical gel were measured by a pH meter at ambient temperature with a glass electrode.

Viscosity measurement

The viscosity estimation of the formulated gel was done by Brookfield viscometer.

***In vitro* drug release studies:**

In vivo performance of a drug formulation is related to its release in *In vitro.* Microemulsions having a drug equivalent to 100 mg were kept into dialysis membrane and positioned in a flask containing phosphate buffer 6.8 pH at 37±0.5°C. Samples were withdrawn at specified periodic intervals (15 min, 30 min, 45 min, 60min, 90 min, 120 min, 180min, 240min, 300 min, 360 min). Every sample removal was followed by replacing the same volume of fresh dissolution medium. Aliquots were suitably diluted for further measuring the absorbance using a UV-spectrophotometer at a particular wavelength. Percent release of the drug from various formulations at different time intervals was then calculated.

***Ex vivo* release studies**

The *ex vivo* drug release from Microemulsions and microemulsion gels of selected formulations was carried out using Franz diffusion cell apparatus. The selected formulations were applied to skin. The skin was placed

in a container containing phosphate buffer 6.8 pH at 37±0.5°C. Samples were withdrawn at specific intervals (0.5, 1h, 2h, 3h, 4h, 6h, 8h, 12h, and 24 h). Each withdrawal of sample was followed by replacement of fresh dissolution media of same volume. The absorbance of samples was taken using a UV-vis spectrophotometer at a wavelength (276 nm) after appropriate dilution [19].

Scanning electron microscopy (SEM) studies

Surface morphological study of skin was assessed using SEM (Leo, VP-435, UK). Skin samples were prepared in 5 steps. First, the skin sample was collected and kept in a fixative (glutaraldehyde, formaldehyde, *etc.*) for 2-3 days. The samples were then dehydrated using ethanol 30-100%, respectively. Afterwards, small-sized samples were dried overnight at 50°C on a double-sided adhesive tape separately. The dried samples were sputter-coated with gold particles under reduced pressure conditions and evaluated under SEM at a constant 15 kV accelerating voltage.

5 *In vivo* studies

Extraction Procedure

Diclofenac was extracted from the blood samples as reported by Yilmaz *et al.,* 2011 [20]. Blood samples were collected and placed in tubes containing disodium EDTA, and then centrifuged at 4500 × *g* for 10 min. 1.0 mL of the obtained plasma sample was spiked with 1.0 mL of diclofenac (1 µg/ml), 0.1 mL of the internal standard (Ibuprofen) (1 µg/ml), and 0.5 mL of H_3PO_4 solutions were then added. Vortex mixing was done for 5s, and then 3 mL of ethyl acetate was added. The mixture was again vortexed for 2 min and further centrifuged at 3000 × *g* for 3 min. The organic layer was then transferred into another 5 mL tube and evaporated to dryness under a stream of nitrogen gas at 40° C. The residue was reconstituted in 1.0 mL methanol, and a 20 µL aliquot was injected into the HPLC system.

HPLC Conditions:

The analysis of diclofenac was performed on Shimadzu HPLC LC 2010 CHT series combined system furnished with a quaternary constant flow pump, auto injector, UV detector, and all the data was processed on LC Solution Version 1.22 SP1 software. A reverse phase C18 column (250 mm × 4.6 mm i.d., 5µm) (XTerra®, Waters, Miliford, USA) was used for the chromatographic separations. The chromatographic separation of diclofenac and piperine was achieved on XTerra® RP18 column (250 mm × 4.6 mm i.d., 5µm) using a mobile phase composed of acetonitrile and phosphate buffer (20 mM, pH 4.5 with orthophosphoric acid) (65:35, *v/v*) at a flow rate of 1.0 mL/min. Eluent was detected at 300 nm and the injection volume was fixed at 20 µL.

Results

Pseudoternary phase diagram: A microemulsion zone or area was observed in the obtained ternary phase diagrams of various mixtures of S_{mix} with the oil phase. The ternary diagrams for various batches are shown in Figure 1. The shaded area in each ternary diagram represents the microemulsion region, where stable microemulsions are formed. Batch A shows a relatively wide microemulsion region, indicating that the combination of oil, water, and S_{mix} has good capacity for forming stable microemulsions over a broader composition range. Batch B region is slightly bigger in comparison to batch A, indicating that the component proportions are less versatile batch C shows the smallest microemulsion region among other batches, which suggests limited stability for microemulsion formation. Batch D is discreetly large but lesser than batch C, indicating intermediate stability for microemulsion formation [21].

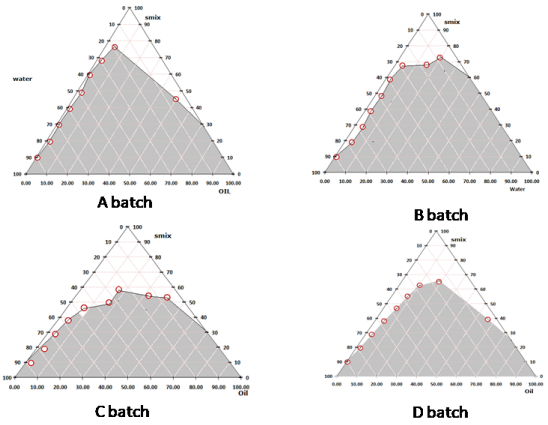


Figure 1: Pseudoternary phase diagrams of various batches (A-1:1; B-2:1; C-1:2; D-1:3)

Preparation of microemulsions: The drug incorporated microemulsions were formulated successfully using the titration method.

Determination of percent transmittance: Percent transmittance was determined to confirm the clarity, with the higher the transmittance value, the smaller the particle size due to better light transmission. The percentage transmittance of various compositions is shown in the

Table 3. Using percent transmittance as a basis, A4 and B1 were further opted for the further analysis [22].

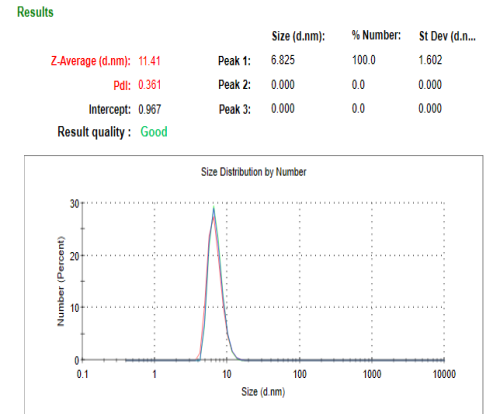
Table 3: Percent transmittance studies of the various compositions (n=3, mean±S.D)

Formulation code/ Batches	A (1:1)	B (2:1)	C (1:2)	D (1:3)
1	67.41±7.30	**99.77±4.82**	64.51±13.19	90.48±2.31
2	60.96±9.19	74.35±16.22	88.36±16.51	78.71±8.26
3	62.87±6.13	76.53±9.21	88.61±17.41	**90.93±14.66**
4	**92.59±11.51**	73.18±9.55	**91.63±15.67**	84.3±13.24
5	63.62±12.91	98.4±19.78	87.69±16.25	61.78±15.64
6	68.77±8.36	95.87±3.45	76.81±17.15	86.29±5.88
7	88.22±18.21	91.59±3.40	85.38±15.67	92.99±7.54
8	82.23±6.53	82.11±17.57	92.49±12.32	87.21±4.52
9	86.58±7.48	63.23±15.11	91.75±14.33	60.42±5.34

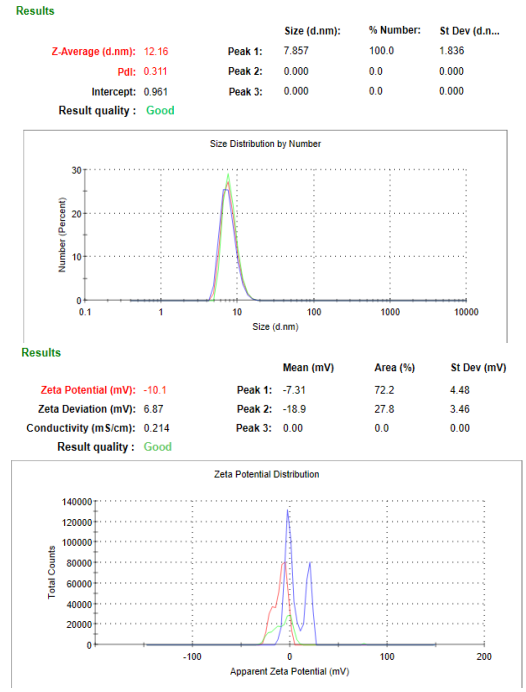
Particle size determination: The drug incorporated microemulsions (A4 and B1) were assessed for particle size *via* Malvern zeta sizer using the techniques of dynamic light scattering (DLS). The results of particle size, polydispersity index (PDI) values, and Zeta potential values of selected formulations are summarized in Table 4 and shown in Figure 2. A4 formulation indicates that the formulation falls within the nanoemulsion size range. Smaller particle sizes improve drug solubility, stability and bioavailability. B1 is slightly larger than A4, but still in the nanoemulsion range. Based on the zeta potential, A4 is more stable than B1, indicating moderate stability [23].

Table 4: Particle size, PDI values, Zeta Potential of optimized batches (mean±S.D; n=3)

Formulation code	Particle size	PDI	Zeta Potential
A4	11.41±2.51	0.361±0.14	-14.1±2.5
B1	12.16±4.14	0.311±0.11	-10.1±1.8



Particle size-A4 **Zeta Potential - A4**



Particle size- B1 **Zeta Potential-B1**

Figure 2: Particle size analysis and Zeta Potential values of A4 and B1 formulations

***In vitro* drug release studies:** The release profiles of optimized formulations are revealed in Figure 3. Batch

A4 showed 60% release of drug in 4 hrs and batch B1 showed 60% in 6 hrs. Batch A4 is better suitable for systems requiring rapid and 100% equivalent release of drug as it contains higher S_{mix} content, creating a less viscous emulsion, facilitating faster drug release whereas, Batch B1 creates a barrier to drug diffusion, slowing the release [24].

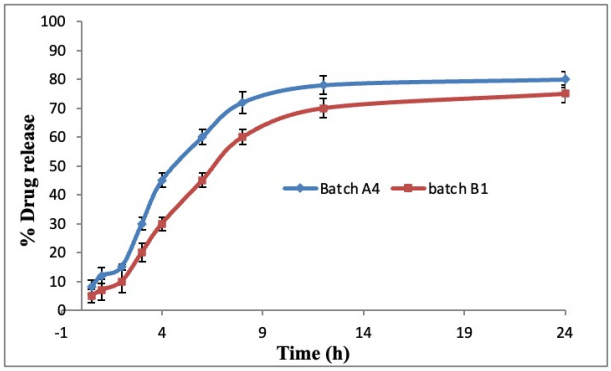


Figure 3*: In-vitro* drug release of Batch A4 and Batch B1 microemulsions (mean±S.D; n=3)

Formulation of topical gel incorporating microemulsions

2% of carbopol 934 was allowed to swell overnight in 100 mL of distilled water. The prepared microemulsions were added to the formed carbopol gel and mixed properly. The formed hydrogels, named TG1 (incorporating A4 microemulsion) and TG2 (incorporating B1 microemulsion), were allowed to stand for 15 minutes without stirring to expel the trapped air and were then stored in tightly closed screw-capped glass bottles at room temperature for other studies.

pH determination

The pH values of microemulsions were measured by a pH meter at ambient temperature with a glass electrode. The pH of TG1 and TG2 is found to be 6.15±0.05 and 6.42±0.07, respectively.

Viscosity measurement

The viscosity of the gel was measured by a Brookfield viscometer. The viscosity of selected formulations (TG1 and TG2) lies in the range of 28.5± 1.2 and 32.7 ±1.5.

***In- vitro* drug release**: The *in vitro* drug release of topical gels (TG1 and TG2) is shown in Figure 4. The TG1 showed 85% drug release, and TG2 showed 80%. The higher surfactant content in TG2 leads to stronger emulsion stabilization, slowing drug release compared to TG1. Thus, it is concluded that TG1 is more suitable for faster drug delivery, while TG2 provides a more controlled, sustained release, potentially benefiting prolonged therapeutic effects [25].

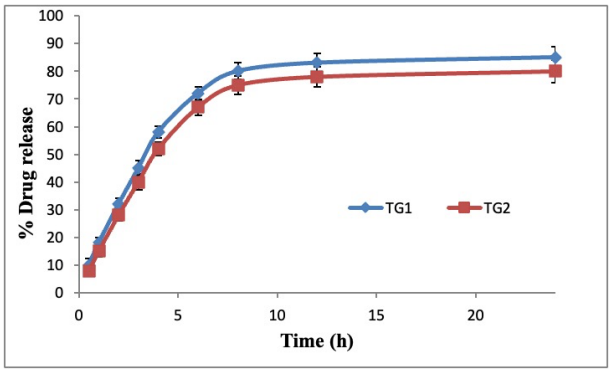


Figure 4: *In-Vitro* drug release of topical gel (TG1 and TG2) (mean±S.D; n=3)

***Ex vivo* release studies:** In accordance with the *in vitro* results, the *ex vivo* drug release investigation verifies that the topical gel formulations of TG1 and TG2 demonstrated improved drug release in comparison to respective microemulsions, as revealed in Figure 5. Both TG1 and TG2 gels outperformed their respective microemulsions, exhibiting 80% and 76% release at 24 hours, respectively. This implies that the gel's hydrating properties promote medication dispersion, enhancing skin penetration and bioavailability. According to the results, the gel formulation is better than microemulsions alone for topical distribution, guaranteeing quicker and more effective drug absorption [26].

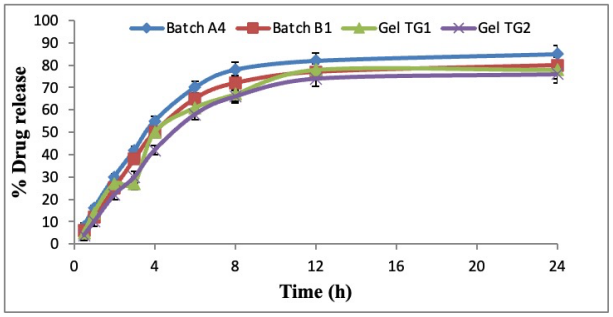
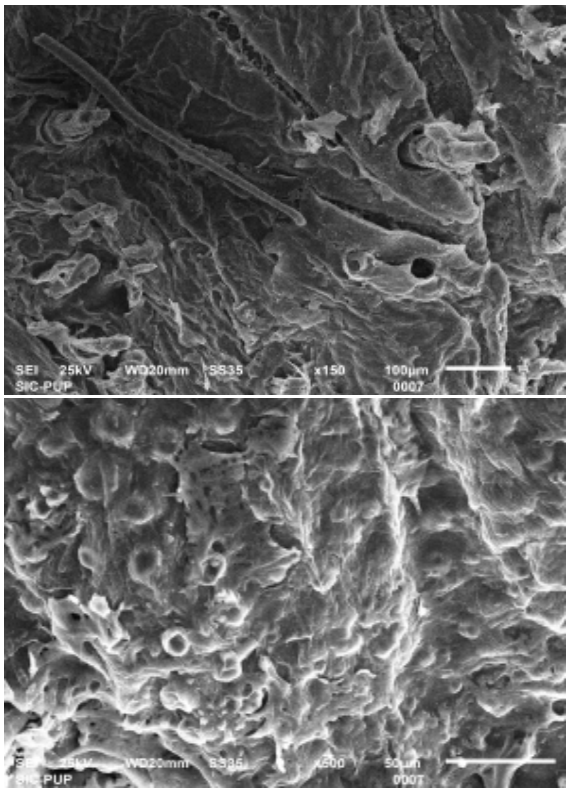


Figure 5: *Ex-vivo* drug release of microemulsions (Batch B4 and Batch A1) and Topical gel (TG1 and TG2) (mean±S.D; n=3)

SEM studies: The SEM analysis of skin treatment with simple diclofenac gel (a) and TG1 formulation (b) shows significant variations in skin shape, demonstrating that piperine acts as a penetration enhancer (Figure 6). An image (a) shows the skin to be reasonably intact, with fewer pores and minor structural disturbance, implying that diclofenac gel absorption is restricted. The fibrous structures and smoother surface show that the formulation did not significantly affect the epidermal

barrier, resulting in less drug penetration. In contrast, image (b) shows a more porous and disordered surface morphology with greater roughness, indicating improved permeability. The existence of open structures and increased porosity indicates that piperine efficiently promoted drug penetration by altering the epidermal barrier.



(a)

(b)

Figure 6: SEM image of application of (a) Diclofenac gel and (b) TG1 at 1000X

***In vivo* studies:** The Pharmacokinetic analysis demonstrates that TG1 formulation showed enhanced absorption and retention with higher Cmax, Tmax, AUC as shown in Table 5. TG1 showed higher mean residence time (MRT) indicating the extended systemic circulation of drug. The graphical representation of various pharmacokinetic parameters is shown in Figure 7.

Table 5: Various Pharmacokinetic parameters comparing diclofenac gel and TG1

PK Parameters	Diclofenac gel	TG1
C_{max} (µg/mL)	2.526 ±0.358	3.248±0.266*
T_{max} (min)	240.0±34.0143	240.0±19.66
AUC total (µg/mL*min)	818.194±115.96	4827.307±393.10***
$T_{1/2}$ (min)	80.739±11.34	1002.919±81.8965***
MRT (min)	307.612±43.51	1574.307±122.85***

All Value are mean±SD (n=5), * indicates p<0.01, ***indicates p<0.0001

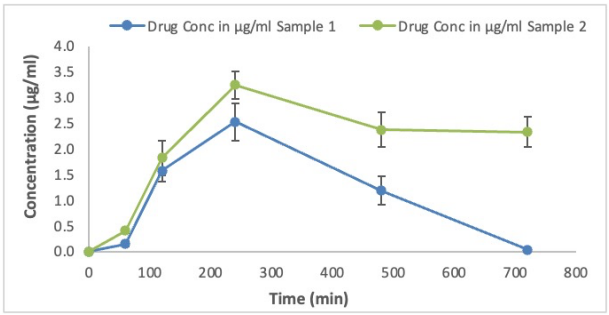


Figure 7: Plasma concentration vs. time graph for pure Diclofenac gel and Diclofenac-piperine gel (TG2) (mean±SD; n=5)

Discussions

The study successfully demonstrated the development of a piperine-enhanced microemulsion gel for the transdermal delivery of diclofenac, with clear improvements in drug release, permeability and pharmacokinetics. Formulations A4 and B1, selected based on their high percent transmittance and favorable droplet size (11.41 nm and 12.16 nm, respectively) confirmed the formation of stable nanoemulsions. These small droplets contribute to increased surface area and better drug dispersion, essential for efficient transdermal delivery. The in vitro release profiles highlighted that A4 achieved 60% drug release within 4 hours, while B1 reached similar levels by 6 hours. These differences were probably the result from the higher S_{mix} content in A4, reducing viscosity and allowing faster drug diffusion. When incorporated into carbopol-based gels, both formulations demonstrated improved released profiles, with Tg1 (based on A4) releasing 85% of diclofenac, compared to 80% for Tg2 (based on B1). This enhancement in gel formulations supports the role of hydrated gel matrices in facilitating drug migration across the skin. *Ex vivo* permeation studies further confirmed these observations with TG1 achieving 80% drug release and TG2 76% after 24 hr both outperforming their microemulsion counterparts. These findings

underscore the synergistic role of piperine and the gel matrix in disrupting the stratum corneum and enhancing transdermal drug transport. The morphological deviations seen in SEM imaging provide direct evidence of piperine's penetration-enhancing effect. Skin treated with TG1 displayed increased porosity and disrupted surface architecture compared to the relatively intact morphology seen with plain diclofenac gel, suggesting deeper drug permeation.

Pharmacokinetic evaluation offered strong in vivo confirmation of these enhancements. TG1 showed significantly higher Cmax (3.248 µg/mL) and AUC (4827.31 µg/mL*min) compared to the standard diclofenac gel. Moreover, the increased half-life (1002.92 min) and mean residence time (1574.31 min) suggest prolonged systemic availability, which may reduce dosing frequency and improve patient compliance. Overall, these findings demonstrate the effectiveness of piperine as a natural permeation enhancer in transdermal systems. The optimized microemulsion gel formulation not only improves drug release kinetics but also ensures deeper skin penetration and sustained systemic levels of diclofenac, potentially minimizing the gastrointestinal side effects related to oral administration.

Conclusion

The study successfully created and improved a diclofenac transdermal microemulsion formulation that included piperine as a bioenhancer. The improved formulation exhibited superior physicochemical stability, increased drug permeability, and sustained release qualities. *Ex vivo* and *in vivo* studies validated the formulation's better transdermal absorption, emphasizing its potential to improve therapeutic outcomes while limiting systemic side effects. These findings pave the way for additional clinical research and commercialization of this innovative transdermal delivery technology, which represents a promising alternative to oral diclofenac administration for pain management and inflammatory diseases.

Abbreviations

Abbreviated form	Full form
NSAID	Non-Steroidal Anti-Inflammatory Drug
TDDS	Transdermal Drug Delivery System
XRD	X-Ray Diffraction
FTIR	Fourier Transform Infrared
DLS	Dynamic light scattering
SEM	Scanning Electron Microscopy
TG	Topical Gel
AUC	Area Under Curve

Consent for publication

I, the undersigned, give my consent for the publication of identifiable details, which include Figures and Tables within the manuscript to be published in the International Journal of Drug Delivery Technology.

Availability of data and material

All data generated or analyzed during this study are included in this manuscript.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding statement

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Authors Contribution

Manju Nagpal and Geeta Aggarwal designed the study; Malkiet kaur performed experimental work and manuscript writing; Balraj Singh contributed in analytical method. Thakur Gurjeet Singh designed *In Vivo* studies. Manjinder Singh and Gitika Arora Dhingra helped in manuscript draft and result interpretation.

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Figures Legend

Figure 1: Pseudoternary phase diagrams of various batches (A-1:1; B-2:1; C-1:2; D-1:3)

Figure 2: Particle size and zeta potential of A4 and B1 formulations

Figure 3*: In-vitro* drug release of Batch A4 and Batch B1 microemulsions

Figure 4: *In-Vitro* drug release of topical gel (TG1 and TG2)

Figure 5: *Ex-vivo* drug release of microemulsions (Batch B4 and Batch A1) and Topical gel (TG1 and TG2)

Figure 6: SEM image of application of (a) Diclofenac gel and (b) TG1 at 1000X

Figure 7: Plasma concentration vs. time graph for pure Diclofenac geland Diclofenac-piperine gel (TG2)