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Design and optimization of ibuprofen microemulgel using phase titration for effective and enhanced dermal drug delivery

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Abstract: **Background**: The oral administration of ibuprofen is limited due to gastrointestinal adverse effects and inadequate solubility, necessitating the development of enhanced cutaneous delivery systems. **Objectives**: The objective of this study was to create and optimize a microemulgel for ibuprofen to improve solubility, permeability and prolonged release. **Methods**: Microemulsions were prepared using phase titration utilizing Tween 80, butanol and vegetable oil, thereafter incorporating carbopol gel. Preformulation studies encompassed solubility and partition coefficient. Post-formulation characterization involved globule size, zeta potential, pH, drug content and *in-vitro/ex-vivo* release analyses. Compatibility was evaluated by utilizing FTIR and DSC techniques. **Results**: The improved formulation (F3) exhibited a droplet size of 117.5 nm, a zeta potential of -6.47 mV and a drug content of 82.94%. FTIR and DSC analyses validated compatibility. *Ex-vivo* investigations revealed improved skin permeability and drug release conformed to the Korsmeyer–Pappas model (n = 0.626), signifying non-Fickian diffusion. **Conclusion**: The formulated ibuprofen microemulgel demonstrated stability, compatibility with skin and prolonged drug release, indicating its potential as an effective option for topical NSAID administration.

Keywords: Controlled release: Ibuprofen; Microemulgel; Pseudo ternary phase diagram; Skin permeation; Topical drug delivery system

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INTRODUCTION

Chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis and muscular injuries are rather common and add to a major worldwide health burden. Persistent discomfort, oedema, joint rigidity and limited mobility define these diseases and greatly damage the quality of life of people afflicted (Theochari *et al.*, 2021). Older people are especially prone to these diseases as arthritis burden is significantly growing in Pakistan. A cross-sectional study conducted in Nawab Shah demonstrates overall 18.13% prevalence of osteoarthritis out of which 70.1% in rural areas indicating higher rates. Most affected demographic groups include the women and elderly people that impact the economic productivity and quality of life. Regardless of high prevalence, access to affordable and advanced topical therapies is limited in rural areas (Meraj *et al.*, 2025). Ibuprofen and other nonsteroidal anti-inflammatory medications (NSAIDs) are commonly used to reduce fever, discomfort and inflammation. These medications lack selectivity and thereby target cyclooxygenase enzymes (COX-1 and COX-2) (Agboola *et al.*, 2023). Particularly in long-term users, oral ibuprofen is usually linked with gastrointestinal problems including dyspepsia, stomach ulcers and bleeding even if it is rather effective (Hamed *et al.*, 2019). Furthermore, especially in individuals with long-term treatment and comorbidities, systemic dose may cause cardiovascular, nephrotoxic and hepatotoxic side effects. Conventional topical formulations are less effective due to limited drug solubility, thermodynamic instability and scalability challenges (Rathore *et al.*, 2023).

One viable approach to oral NSAIDs is topical medication delivery methods. These techniques bypass the gastrointestinal tract, apply medication at the site of inflammation and lower the incidence of general systemic adverse effects. Still, the largest and unavoidable barrier of the stratum corneum usually results in insufficient skin penetration (Theochari *et al.*, 2021), thereby rendering common topical formulations such as ointments, lotions, creams and basic gels ineffective. Ibuprofen efficiently transit both hydrophilic and lipophilistic pathways in the epidermis due to its intermediate lipophilicity and weak water solubility (~0.076 g/L) (Alkrad *et al.*, 2024). Active research is directed on designing novel transdermal drug delivery systems that overcome the challenges by stability features of microemulsion achieved by the phase titration method and its high drug-loading capacity (Zalavadia B, 2025).

The novel strategy is to combine the benefits of both gels and microemulsions to create the microemulsion-based gel (MEG). Microemulsions are isotropic, thermodynamically stable mixtures of oil, water, surfactants and cosurfactants often formed spontaneously with particles less than 100 nm in diameter (Mancini *et al.*, 2021). Through disruption of stratum corneum lipids, these techniques improve the solubility of drugs that are

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insufficiently water-soluble, so improving drug partitioning and skin penetration. Using Tween 80 (nonionic surfactant), butanol (cosurfactant), distilled water (aquatic phase), vegetable oil (oil phase) and ibuprofen as the active pharmaceutical component, a microemulsion gel formulation of ibuprofen was created in this study. Butanol was employed to increase interfacial film flexibility and lower surfactant requirement, whereas tween 80 was selected for its capacity to stabilize oil-in-water emulsions and lower interfacial tension (Anuar *et al.*, 2020). Vegetable oil also increases skin hydration; a solubilizing agent for lipophilic drugs. Carbopol was used as the gelling agent since it offers best viscosity, spreadability and longer skin residence duration. Incorporation of the Carbopol gel into a microemulsion produces a formulation that is easy to use and preserves the efficacy of drug distribution. Still, by adjusting surfactant and cosurfactant concentrations, the formulation guarantees long-term physical stability as well as avoidance of any skin irritation (Zhang *et al.*, 2020).

Ibuprofen non-selectively inhibit the cyclooxygenase enzymes (COX-1 and COX-2) reduces the synthesis of prostaglandins controlling pain, fever and inflammation when acting therapeutically. BCS Class II classification of ibuprofen indicates that it has a high permeability but poor solubility, therefore complicating its oral and transdermal distribution. Thermodynamically stable oil in water microemulsion was formulated. Skin penetration and anti-inflammatory effect were greatly increased when oleic acid and Labrasol mixed with ethanol, were added to microemulsion-based gels (MEBG) containing ibuprofen as compared to traditional gels (Naeem *et al.*, 2020). Apart from improved drug penetration and continuous skin retention, these systems show favourable physicochemical qualities like ideal pH, small droplets (~60 nm) and non-irritating nature. These characteristics highlight the microemulsion formulations as a safe and efficient transdermal delivery strategy for ibuprofen (Anuar *et al.*, 2020).

A systematic strategy was followed to develop a stable and efficacious formulation. Initially, pseudo-ternary phase diagrams were constructed to find the ideal ratios of surfactant, cosurfactant, water and oil to develop a stable microemulsion. Later on solubility studies were carried out to find the necessary excipient quantities in order to maximize the packing of ibuprofen. Droplets size, polydispersity index and zeta potential measurement ensured colloidal stability. Lastly, microemulsion was mixed with a gel matrix made from carbopol to improve topical dispersion, spreadability and user compliance. Final characterization involved pH, refractive index and uniformity of drug content (Dhepe *et al.*, 2022). In vitro drug release and skin permeation studies employing Franz diffusion cells showed that the microemulsion gel acquired better ibuprofen penetration and retention compared to normal gels (Wen *et al.*, 2021). Additionally, ex vivo permeation study in Wistar rat skin confirmed enhanced permeability. Thus microemulsion-based gels are efficient drug delivery system to enhance the therapeutic performance while reducing the risks associated with the systemic NSAIDs exposure.

MATERIALS AND METHODS

Materials

Ibuprofen was gifted by Getz Pharma Pvt. Ltd., Pakistan. Carbopol 940, Tween 80, Butanol and Ethanol were all purchased from Merck, Pakistan. In addition, distilled water was freshly prepared in the laboratory. All the solvents used in the research were of analytical grade.

Method

The oil phase was mixed with the Smix to develop ibuprofen loaded microemulgel. The oil phase consisted of 9.16% w/w vegetable oil. The Smix comprised of 72.34% w/w Tween 80 (surfactant) and 18.49% w/w butanol (co-surfactant), with a surfactant-to-co-surfactant ratio of 3:1 in all cases to keep a clear and stable microemulsion. The mixture was stirred on magnetic stirrer for about 10 minutes until a clear solution was obtained. After proper mixing of oil and Smix, 9.16% w/w purified water was added drop wise with continuous stirring to help spontaneous emulsification. It produced a thermodynamically stable, translucent microemulsion.

For the preparation of the gel base, carbopol 940 was added drop wise with stirring to the aqueous phase in a 1:1 proportion. Triethanolamine was deliberately omitted as a neutralizing agent to avoid skin irritation and since the pH of the preparation was in a desired skin-compatible pH range without it. 5% w/w of ibuprofen was added slowly to the emulgel vehicle and mixed well until uniform dispersion of drug was achieved within the microemulsion phase. Further water was added progressively to achieve an end formulation consistency (Alaoui *et al.*, 2019).

The resulting formulation was transferred to a shaking incubator at 25±2°C for 24 h in order to achieve thermodynamic equilibrium. Visual examination after incubation was performed to evaluate clarity, homogeneity and phase separation, to ensure the satisfactory drug entrapment and stability of the formulation.

Every set of formulation and its test was performed in triplicate (n = 3) for reproducibility and statistical significance. This sample size was chosen according to standard in formulation research to cover batch-to-batch variation and experimental repeatability.

A pseudo-ternary phase diagram was constructed in the presence of water to determine the appropriate formulation regions using the water titration method. Surfactant and co-surfactant were mixed at different

weight ratios (1:2, 1:1, 2:1, 3:1). Various w/w ratio of oil and surfactant and cosurfactant blend were homogenized (1:9, 7:3, 8:2, 6:4, 5:5). The plot was constructed using TernaryPlot.com and the microemulsion regions were identified. The microemulsion formulation was characterized and the stable microemulsion formulations were screened according to pseudo-ternary phase diagram (Fig. 1).

Characterization

Solubility analysis

Preparation of phosphate buffer at pH 6.8

Potassium dihydrogen phosphate (0.6805g) and disodium hydrogen phosphate (0.184g) were dissolved in approximately 80 mL of distilled water with continuous agitation until a clear solution was obtained. The pH of the solution was assessed and modified to 6.8, utilizing 1N sodium hydroxide or 1N hydrochloric acid, as necessary. The final volume was adjusted to 100 mL with distilled water, yielding a clear and stable phosphate buffer at pH 6.8.

Solubility in buffer solutions

Solubility was evaluated in phosphate buffer solutions with pH values ranging from 1.2 to 7.4. One gram of ibuprofen was agitated in 100 mL of each buffer for 30 minutes. Upon achieving saturation, the solution was filtered and 10 mL of the filtrate was subjected to evaporation. Solubility (mg/mL) was calculated using the formula: $\text{Solubility} = {(W_2 - W_1)}/{10} \; X \; 1000$

Where W_1 represents the weight of the empty dish and W_2 denotes the weight of dish and dried solute. The technique was conducted for each pH value.

Solubility in organic solvents

An excessive quantity of ibuprofen was added into 3 mL of each chosen oils as solvents-vegetable oil, clove oil, castor oil, olive oil and coconut oil. Each combination was constantly stirred for 24 hours to ensure complete interaction, followed by agitating for 10 minutes to improve dispersion. The mixes were thereafter maintained at room temperature for a further 24 hours to facilitate equilibrium. Subsequently, the samples were filtered and the supernatant was examined with a UV-visible spectrophotometer at 282 nm to assess ibuprofen's solubility.

Partition coefficient

The partition coefficient was analysed utilizing the separating funnel technique with water and n-butanol. A 10 mg sample was dissolved in 10 mL of water, subsequently followed by the addition of 10 mL of n-butanol. Following vigorous agitation and phase separation, the concentrations in both layers were quantified spectrophotometrically.

$$Log\ P = \text{Concentration in chloroform}/\text{Concentration in water}$$

Physical evaluation

The visual examination assessed the physical appearance of the ibuprofen-loaded microemulsion. Clarity, transparency and hue were evaluated under standard lighting conditions. The formulation was meticulously assessed for indications of phase separation or drug precipitation.

Globule size and zeta potential determination

The size and distribution of globules were determined using dynamic light scattering (DLS) and a Zetasizer Nano ZS (Malvern Instruments, UK). The sample was diluted with distilled water, placed in a cuvette and inspected at 25°C to measure the average size and polydispersity index.

The morphological assessment was performed using scanning electron microscopy (JEOL JSM-6480LV, Japan). The sample was mounted to a stub, coated with a thin gold layer and analysed to evaluate globule morphology, surface characteristics and overall uniformity.

Microscopic examination

The morphology and distribution of ibuprofen-loaded globules were also visualized under compound microscope. A tiny drop of the sample was placed on a clean glass slide and then covered with a coverslip and analysed under 40x and 100x magnification with a compound microscope (Model: Leica DM500). Photographs were taken to record the morphology and regularity of the droplets (Fig. 2).

pH determination

A digital pH meter was used to measure the pH of ibuprofen-loaded microemulsion. The device was calibrated using standard buffer solutions with pH values of 4.0, 7.0 and 9.0 before use. The electrode was immersed in a sterile beaker containing predetermined volume of the formulation. pH reading was obtained once the results reached a stabilised state at room temperature.

Refractive index

The refractive index of the ibuprofen-containing microemulsion was measured using an Abbe refractometer (ATAGO NAR-1T LO, Japan). After calibration with distilled water, several drops of the formulation were added to the prism surface. Precautions were implemented to guarantee the absence of air bubbles during the measurement, conducted at room temperature.

Drug content determination

The drug content was measured by mixing 1 mL of the microemulsion (ME) with 9 mL of phosphate buffer solution (PBS, pH 6.8) in a test tube. After shaking vigorously for 30 minutes, the solution was left alone for 24 hours. The sample was shaken again and centrifuged at 4000 rpm for 15 minutes. 1 mL of the supernatant was taken and diluted with 9 mL of PBS. The drug content was determined using the UV spectrophotometer.

Calibration curve

A standard calibration curve for ibuprofen was established utilising UV-Visible spectrophotometry. Precisely measured ibuprofen was dissolved in 6.8 pH phosphate buffer to create a stock solution. A serial dilution was performed to achieve concentrations generally 2, 4, 6, 8, 10 and 12µg/mL. The absorbance of each solution was analyzed at 264 nm with a UV spectrophotometer. A graph demonstrating absorbance against concentration was constructed and a linear regression equation was derived to ascertain the drug presence in unknown samples as shown in Fig. 3.

In-vitro dissolution

The Franz diffusion cell apparatus, comprising a donor chamber and a receptor chamber, facilitated the assessment of the permeability of ME. 1g of microemulsion gel was added to the donor compartment, while soaked filter paper in water served as the permeable membrane; parafilm around the apparatus was used to prevent evaporation. The assembly was positioned on magnetic stirrer operating at 60 rpm and 37 °C. Samples were collected at intervals of 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours from the phosphate buffer and were analyzed using a UV Spectrophotometer at 222 nm (Katakam and Katari, 2021).

Release kinetics studies

In vitro dissolution modelling analysis was performed using DD Solver. The drug release data was analysed with MS Excel by applying following kinetic models like Zero order, First order, Higuchi Model and Korsmeyer Peppas (Ekenna and Abali, 2022).

Permeation studies

All procedures for animal housing preparation and use were performed in compliance with the institutional guidelines approved by the ethical committee of the University of Veterinary and Animal Health Sciences, Numbered 513 Dated 14/11/2024, following the principles outlined by the Organization for Economy Cooperation and Development guidelines for dermal absorption studies (Hopf *et al.*, 2020). Male Wistar rats (200 to 250g) were purchased and acclimatized for two weeks before the study. The dorsal hair was shaved using an electric clipper. Animals were anesthetized with volatile ether, administered via inhalation through cotton soaked in solvent. Following ethically approved euthanasia full-thick skin samples were excised, cleaned of adhering subcutaneous fat and cut into circular pieces larger than 1.5 cm to match the Franz diffusion cell area. Prepared skin samples were wrapped in aluminium foil and stored at -70° until use. Ibuprofen permeation from the microemulsion gels (F1 to F5) was assessed in vitro using Franz diffusion cell with a diffusion area of 0.64 cm^2 and receptor volume of 5ml. The receptor compartment was filled with water: acetonitrile (40:60) to ensure sink conditions and the system temperature was maintained at 32±1° using a circulating water bath. Frozen skin sections were thawed at 32° placed between the donor and receptor compartments with the stratum corneum facing the donor side. 0.5 ml of each formulation was applied evenly over the skin using a syringe without a needle. At the predetermined intervals (1, 2, 4, 8 and 24 hours) 0.5 ml receptor fluid was sampled and replaced with fresh medium. Samples were filtered and analyzed by HPLC using a C-18 column (4.6 * 250 mm). Mobile phase was water: acetonitrile (40:60) v/v with 4 ml/L chloroacetic acid (pH 3) with flow rate 1ml/min and detected at 254 nm.

The cumulative amount of ibuprofen permitted per cm^2 was plotted against time. Flux (Jss) was calculated from the slope of the linear portion of the curve. The permeability coefficient (Kp) was determined as:

$$Kp = Jss/Cv$$

Where Cv is the ibuprofen concentration in the formulation (Alkrad *et al.*, 2024).

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed using a Perkin Elmer DSC (CT model), calibrated with indium. Accurately measured samples were placed in aluminium pans and were heated from 30°C to 200°C at a rate of 20°C/min under a continuous nitrogen flow. The thermal characteristics and phase transitions of the microemulsion components were analyzed (Ghanbari *et al.*, 2023).

FTIR analysis

FTIR analysis was performed using an Agilent Cary 630 spectrometer over the wave-number range of 4000–400 cm^{-1}, with a velocity of 1 cm/s and a spectral resolution of 4 cm^{-1}. Prior to scanning the test materials, the diamond spectrum was also recorded under identical conditions. Samples were examined to assess molecular structure and detect possible interactions or degradation within the formulation (Boborodea *et al.*, 2025).

RESULTS

The microemulsions were prepared using various permeation enhancer and optimized concentrations of oil to surfactant ratios as shown in Table 1. The solubility analysis of Ibuprofen was performed in simulated GIT buffers and various organic solvents to demonstrate formulation suitability for solvents to disperse and dissolve the drug (Table 2). The physicochemical properties of microemulsion loaded with ibuprofen are summarized in table 3. The linearity of calibration curve demonstrated suitability of UV-Visible Spectrophotometer for dissolution analysis (Fig. 3). The results of release kinetics and permeability are listed in table and figures. The compatibility/stability analysis was performed using FTIR and DSC that are depicted in the figures.

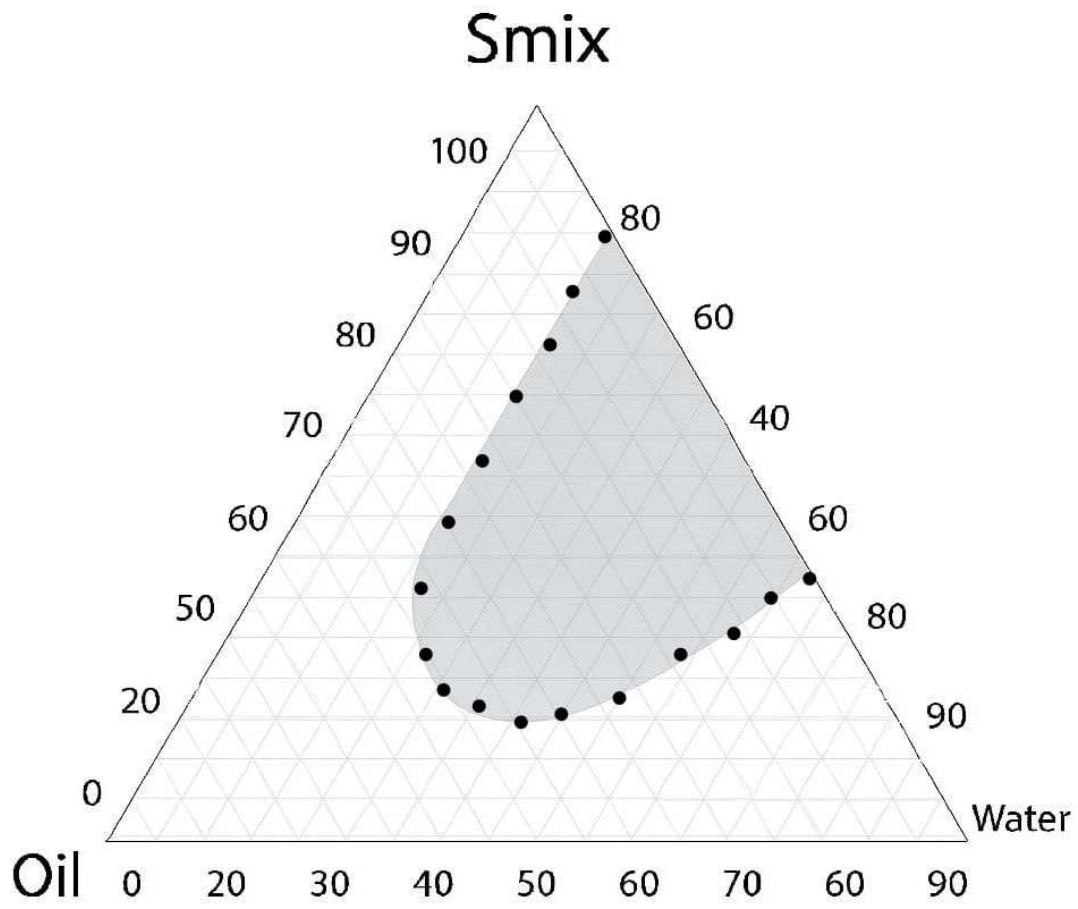

Fig. 1: Pseudo-ternary phase diagram of microemulsion

Table 1: Microemulsion formulations with variable permeation enhancers.

Ingredients	F1	F2	F3	F4	F5
Ibuprofen	2.5g	0.4g	0.24g	0.30g	0.40g
Vegetable oil	4.5ml	4ml	0.9ml	1ml	3ml
Tween 80	30.5ml	6ml	0.4ml	0.5ml	7ml
Butanol	10.2ml	-	0.5ml	0.6ml	-
Ethanol	-	8ml	-	-	6ml
Carbopol 940	2g	2g	2g	2g	2g
Distilled water	q.s	q.s	q.s	q.s	q.s.

Table 2: Solubility analysis of ibuprofen in different pH buffers and various solvents

pH & Solvents	Solubility (mg/mL)	Pharmacopeial classification
1.2	8.5	Sparingly soluble
5.4	10.5	Sparingly Soluble
6.8	9.5	Sparingly Soluble
7.0	15.5	Freely Soluble
7.4	23.5	Freely Soluble
Vegetable oil	18.2	Freely Soluble
Clove oil	15.0	Freely Soluble
Castor oil	10.8	Sparingly Soluble
Olive oil	12.3	Sparingly Soluble
Coconut oil	9.7	Sparingly Soluble

Table 3: Physical characterization of Ibuprofen loaded microemulsion (n=3, mean ± S.D.)

Tests	Results
Clarity	Clear
pH	5.1 ± 0.20
Globule size	117.5 ± 2.3nm
Zeta potential	-6.47 ± 0.15mV
Refractive Index	1.439 ± 0.002
Drug Content	90.30 ± 1.8%

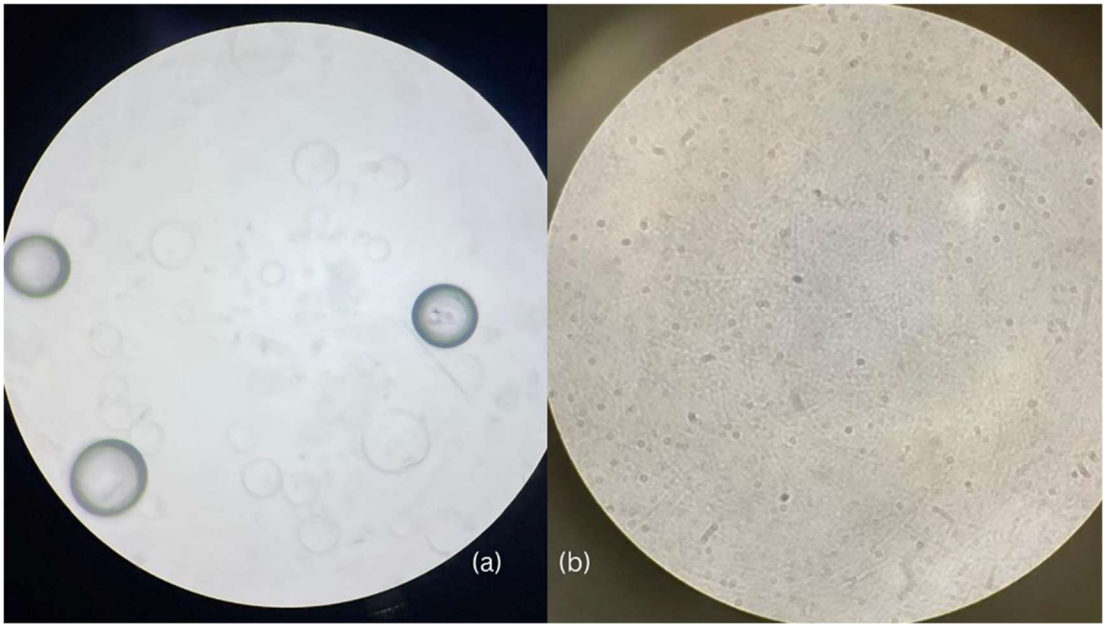

Fig. 2: a) Microscopic examination of ibuprofen-loaded microemulsion at 40x and b) Microscopic examination of ibuprofen-loaded microemulsion at 100x

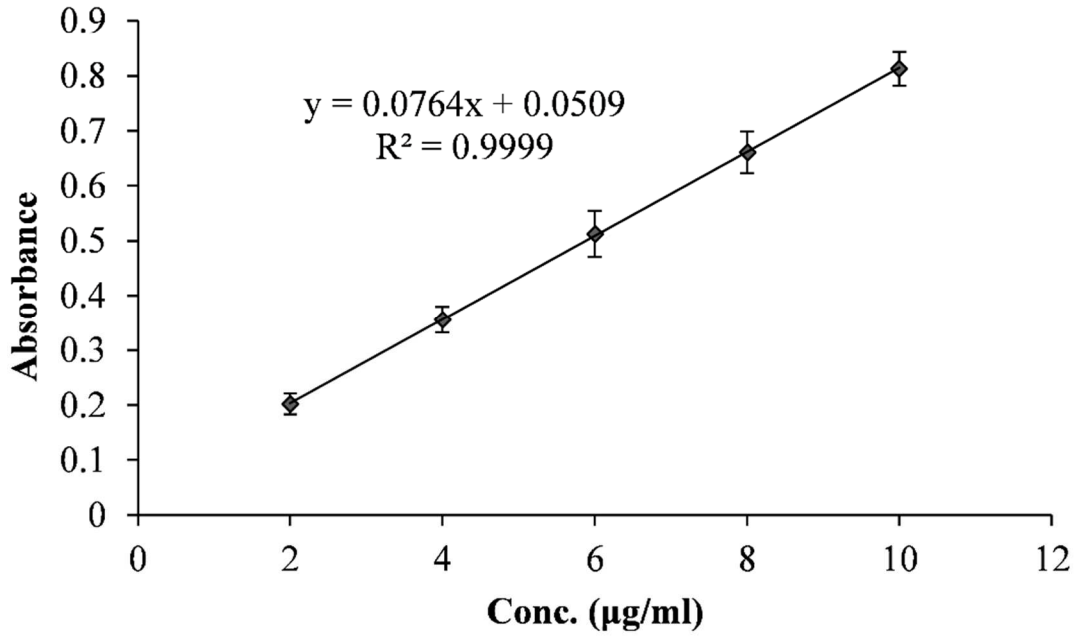

Fig. 3: Standard calibration curve of ibuprofen (n=6)

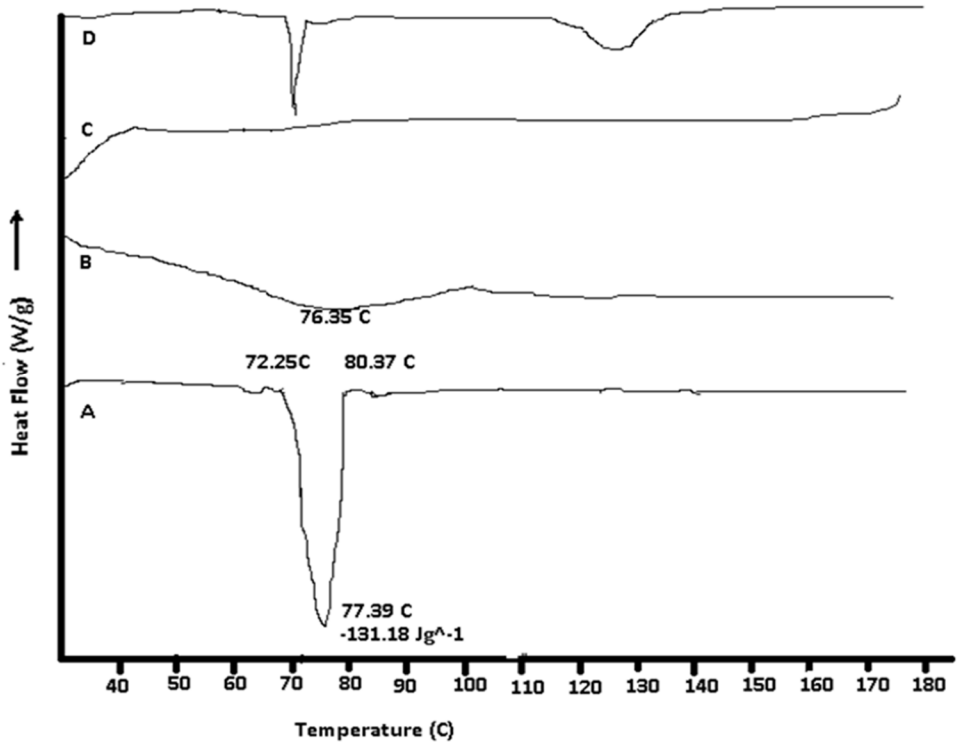

Fig. 4: DSC analysis results of A) Ibuprofen B) Carbopol C) Tween 20 D) Formulation

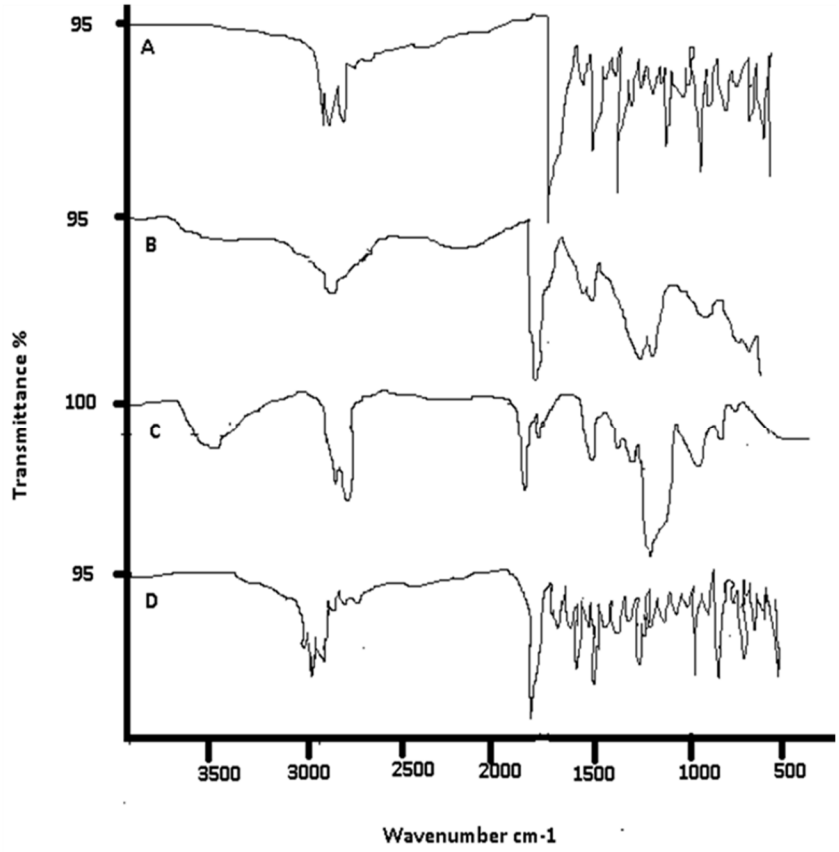

Fig. 5: FTIR of A) Ibuprofen B) Carbopol C) Tween 20 D) Formulation

Table 4: Kinetic analysis of five formulation based on application of release kinetic models

	F1	F2	F3	F4	F5
Zero order					
k_0	13.84	12.73	12.05	14.24	12.82
R^2	0.97	0.72	0.86	0.65	0.86
AIC	34.14	43.52	39.96	45.94	40.54
MSC	3.24	0.96	1.65	0.72	1.67
First order					
k_1	0.27	0.26	0.23	0.34	0.25
R^2	0.94	0.90	0.99	0.89	0.97
AIC	37.99	36.89	21.20	38.88	30.81
MSC	2.60	2.06	4.77	1.89	3.29
Higuchi model					
k_H	32.40	30.93	28.97	34.75	30.80
R^2	0.88	0.97	0.97	0.96	0.96
AIC	42.42	29.95	30.67	31.89	32.17
MSC	1.86	3.22	3.19	3.06	3.06
Korsmeyer Peppas model					
k_{KP}	19.10	28.95	23.66	34.13	25.05
n	0.82	0.54	0.62	0.51	0.62
R^2	0.9874	0.9688	0.9967	0.9585	0.9920
AIC	30.00	31.13	18.19	33.84	24.29
MSC	3.92	3.02	5.27	2.74	4.38

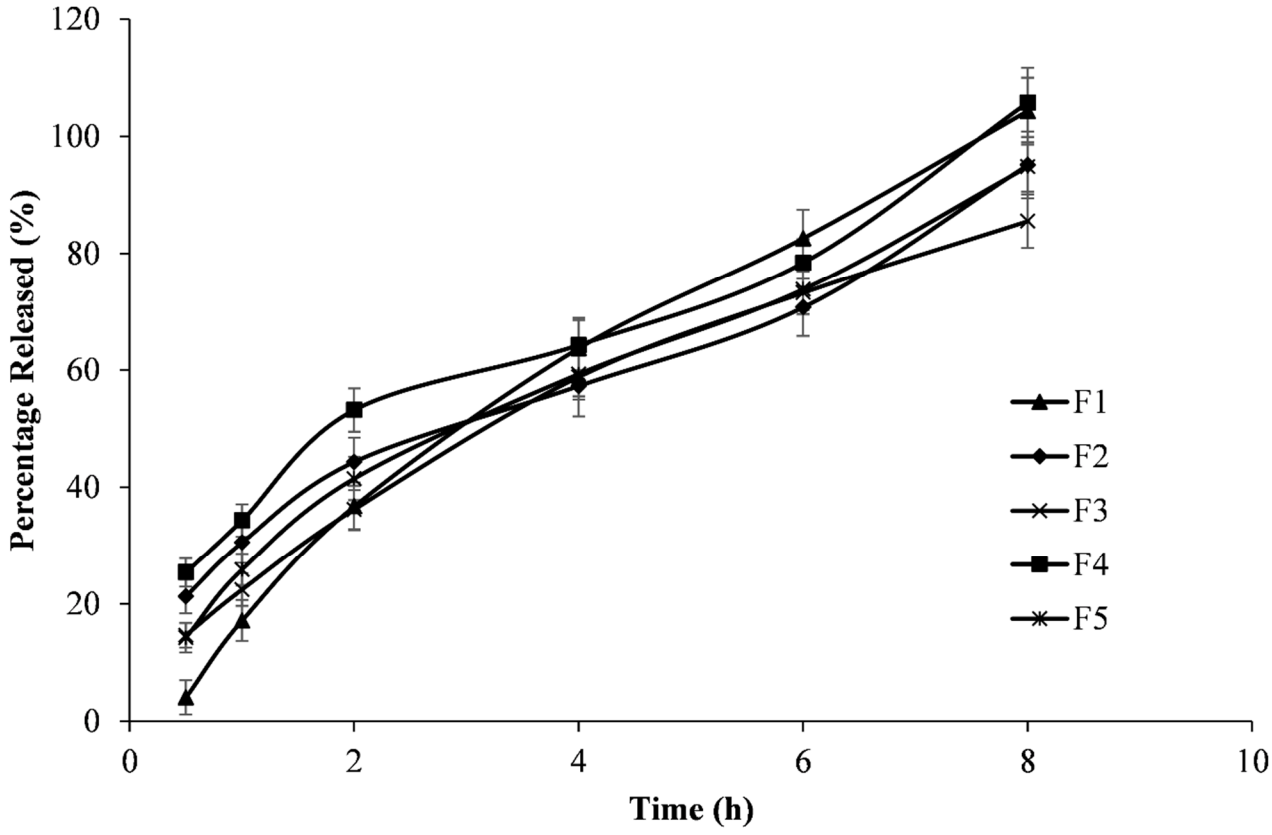

Fig. 6: Drug release of F1, F2, F3, F4, F5 microemulsion formulations of ibuprofen (n=6)

Table 5: Flux and permeability coefficient of ibuprofen microemulsion gels (mean ± SD, n = 3)

Formulation	Flux (Jss) (µg/cm²/h)	Kp (cm/h ×10⁻³)
F1	1.40 ± 0.19	0.028 ± 0.001
F2	2.45 ± 0.29	0.049 ± 0.002
F3 (Best)	4.20 ± 0.64	0.084 ± 0.005
F4	2.25 ± 0.18	0.045 ± 0.004
F5	1.98 ± 0.14	0.040 ± 0.004

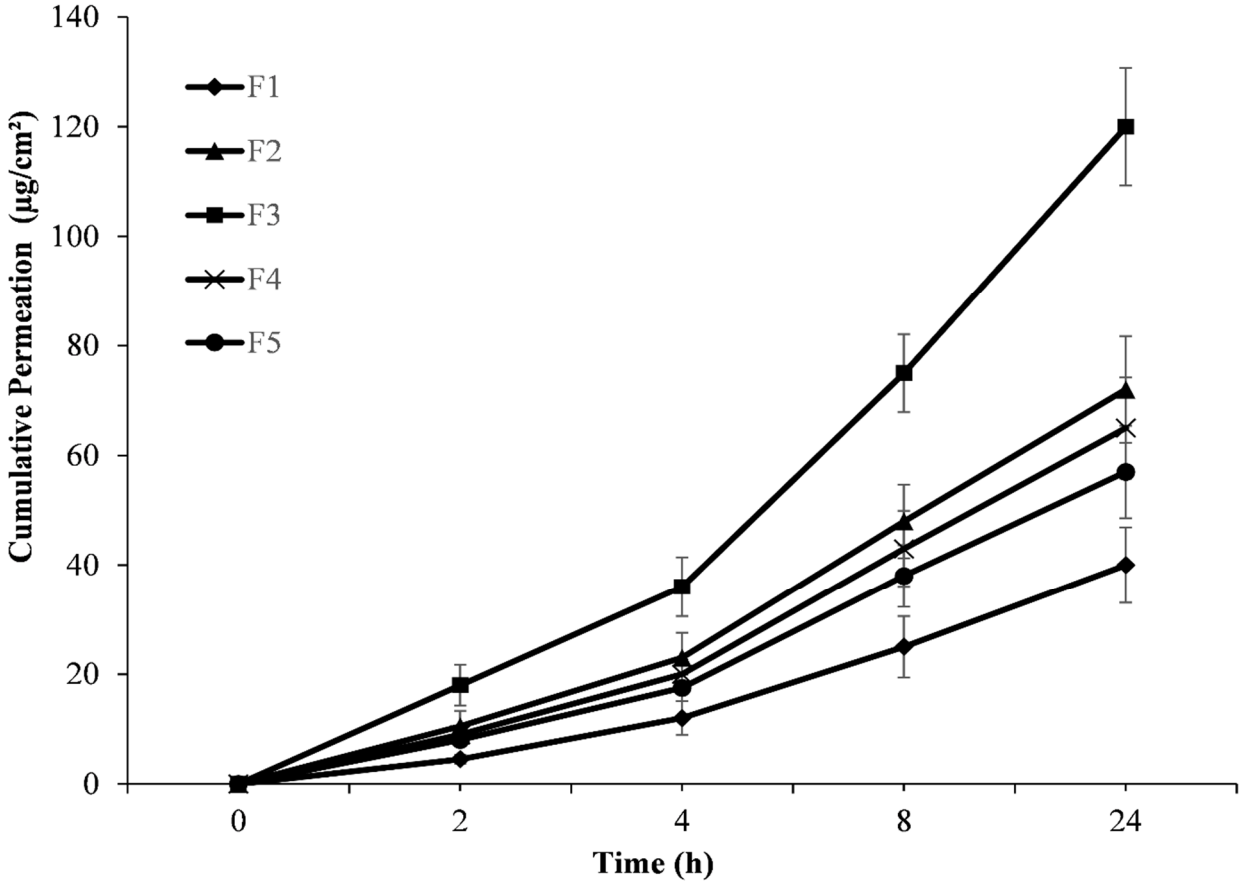

Fig. 7: Cumulative permeation of ibuprofen from formulation F1, F2, F3, F4, F5 (n=6)

DISCUSSION

Solubility of ibuprofen increased with ascending pH, 8.5 mg/mL at pH 1.2 to 23.5 mg/mL at pH 7.4. The ionization of carboxylic acid group held responsible for such behaviour. A log P of 2.48 for the partition coefficient evaluated by shake flask method estimated using UV-visible spectrophotometry indicated significant lipophilicity, consistent with recent experimental findings and important to ibuprofen's absorption and distribution in biological systems (Czyrski, 2019).

The ibuprofen-loaded microemulsion exhibited translucency with a mild yellow hue, signifying excellent clarity, homogeneity and physical stability, with no observable phase separation or drug precipitation (Alaoui *et al.*, 2019). This corresponds with prior research indicating that polymer-free microemulsions are uniform and stable, with the incorporation of xanthan gum enhancing viscosity while maintaining clarity (Djekic *et al.*, 2016). The microemulsion exhibited a polydispersity index (PDI) of 0.253, indicating a narrow size distribution, with an average globule size of 117.5 nm. The zeta potential measured -6.47 mV, signifying a substantially negative surface charge, in accordance with previous observations.

The pH measured was pH 5.1 ± 0.2, falling within the skin's physiological range (4.5-6.5), therefore rendering it appropriate for topical use and reducing the risk of irritation (Jain *et al.*, 2023). The refractive index measured 1.439 ± 0.002, confirming the formulation's transparency, isotropy and stability, consistent with previously documented values for stable microemulsion systems (Agboola *et al.*, 2023).

Drug content analysis employing UV-visible spectrophotometry at 220 nm demonstrated high precision (R^2 = 0.9995). The yield was 90.30%, within the USP limit of 85%–115%. Handling faults, equipment discrepancies and drug degradation may cause minor variances. Optimizing formulation factors and controlling ambient conditions are stressed in previous studies. Handling, process and equipment calibration should be improved to meet pharmacopeial requirements (Hamed *et al.*, 2019). Various solvents including vegetable oil, clove oil, castor oil, olive oil and coconut oil were used to evaluate the solubility of Ibuprofen. Vegetable oil demonstrated highest solubility of Ibuprofen in it therefore ibuprofen was classified as freely soluble in the vegetable oil and sparingly soluble in all other oils. Thus, vegetable oil was selected as oil phase for the formulation due to its improved solubility (Wen *et al.*, 2021).

The microscopic image in fig. 2 revealed smooth, spherical droplets with consistent shape, signifying the effective formation of the microemulsion gel. The particles demonstrated a uniform nanoscale dimension with negligible aggregation, indicating effective dispersion and stability of the system. The polished surface and distinct form, validate the successful integration of ibuprofen into the microemulsion matrix stabilized by Carbopol. Maximum uniform distribution was also consistent with the results of DLS for the size of globules. No merging or clustering was observed visually. The lack of abnormalities or structural failures further signifies a stable and well-structured composition appropriate for topical administration (Hafizah Aulia Ul, 2024).

The thermogram of pure ibuprofen in Fig.4 showed a clear endothermic peak Tm around 75-78°C (Amirinejad *et al.*, 2020). While tween 20 displayed no clear melting peak but a broad endothermic transition connected to molecular relaxation (Ibrahim *et al.*, 2018). By contrast, the DSC thermogram of the ibuprofen-loaded formulation showed greatly diminished intensity of the sharp melting peak of pure ibuprofen which was strong evidence of effective entrapment of the ibuprofen inside the matrix generated by Carbopol 940 and Tween 20.

FTIR spectrum of pure Ibuprofen in Fig.5 showed characteristic peaks around 3000 cm^{-1} (C-H stretching), 1707 cm^{-1} (C=O stretching of carboxylic group) conforming its structure (Nistor *et al.*, 2025). Carbopol 940 exhibited a broad O-H stretching band around 3400 cm^{-1} and a sharp C=O stretching peak near 1700 cm^{-1}, typical of its polymeric nature (Bhatti *et al.*, 2022). Tween 20 showed distinct peaks at 3476 cm^{-1} (O-H stretching), 2920–2860 cm^{-1} (C-H stretching), 1734 cm^{-1} (ester C=O stretching) and 1095 cm^{-1} (C-O-C ether stretching), matching its known profile (Ortiz-Tafoya and Tecante, 2018). The formulation some less intense C=O stretching of carboxylic group of ibuprofen with presence of C-H stretching confirmed good compatibility and stability of the formulation.

The drug release profile of five formulations demonstrated gradual and rapid release in first two hours describing initial adjustment in diffusion with the drug present in outmost portion of gel had to travel least distance to bathing medium (Fig. 6). The steady release after first phase depicted controlled release from the microemulsion gel. The drug release kinetics of five formulations (F1-F5) were analyzed using DDSolver software (Table 4). After testing, formulation F1, F2, F3, F4 and F5 did not followed the zero order and first order model as R^2, AIC and MSC values were out of the acceptable range. F2 and F4 showed best fit with Higuchi model. Higuchi model describes drug release as diffusion process based on modified Fick's law of diffusion which is proportional to square root of time. It depict concentration independency and follows nearly zero order (Ozturk and GÜVEN, 2019). F2 showed a linear and diffusion-activated release based on square root of time with R^2 of 0.9714. While F4 with R^2 value of 0.9665 displayed a classical diffusion profile with high initial burst followed by slower release. F1 followed Korsmeyer Peppas Model which describes drug release from polymeric systems, with R^2 of 0.9874, AIC=30.00 and MSC=3.9296. The release exponent n=0.823 further supported Non-Fickian (anomalous) diffusion i.e. combination of diffusion and erosion which suggests the drug is released both by diffusion through the matrix and erosion of the polymer. Drug release is thus steady and moderately controlled (Öztürk *et al.*, 2018). Similarly, F5 showed adherence to Korsmeyer Peppas Model with R^2 value of 0.9920 and n =0.628, proving its suitability for controlled release. While F3 exhibited outstanding release behavior following Korsmeyer Peppas Model with lowest AIC (18.19), highest MSC (5.2791) and best R^2 value (0.9967) supporting its suitability for controlled and sustained release from the microemulsion gel (Payyal *et al.*, 2020). The n value (0.626) for F3 further confirmed its anomalous transport behavior.

Table 5 demonstrate flux and permeability coefficient of ibuprofen microemulsion gels. The cumulative permeation profile clearly demonstrated that F3 microemulsion gel outperformed all the formulations achieving the highest ibuprofen penetration across the rat skin over 24 hours. F3 showed a cumulative permeation of approximately 120 µg/cm^2 at 24 h in Fig.7. The performance of F3 was attributed to its balanced composition of Tween 80, vegetable oil and small quantities of n-butanol. Such a composition was likely responsible for optimizing the microemulsion droplet size and facilitating better solubilization of ibuprofen leading to enhanced penetration. Microemulgel with co-surfactants can effectively disrupt the lipid architecture of the stratum corneum thus promoting transparent drug delivery (Wen *et al.*, 2021). The lower flux observed in F1

may have been due to its higher surfactant and oil content, which likely increased viscosity of formulation and reduced the diffusion rate of drug. In contrast, F2 containing ethanol showed good permeation consistent with the known role of ethanol as a skin penetration enhancer. Additionally, microemulsion system designed with an optimal oil to surfactant ratio provides a high degree of drug solubilization and skin penetration which aligns well with the findings for F3 in this study (Ait-Touchente *et al.*, 2023).

Among all formulations, F3 is thus the most successful formulation since it provides a well-balanced release profile perfect for long-term therapeutic effect along with highest cumulative drug permeation.

CONCLUSION

The optimized ibuprofen microemulgel exhibited superior skin delivery, prolonged release and increased permeability. It provides a reliable and efficient alternative to traditional formulations, reducing systemic adverse effects and enhancing therapeutic results.

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Authors' contributions
1. Amna Nosheen Jaweria: Methodology and writing.
2. Maiza Mubashaar: Result and discussion writing.
3. Aqsa Ashraf: Microemulsion Formulation, Post-formulation Studies.
4. Sehar Khalid: Data Analysis, Post-formulation studies.
5. Iqra A. Majeed: Pre-formulation Studies, Formulation Design.
6. Quratulain Shoaib: Revision and Writing.
7. Talib Hussain*: Conceptualization, Designing, Supervising, Writing and Editing.

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The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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The authors report no conflict of interest and are sole responsible for the data provided.

REFERENCES

Agboola AA, Nowak A, Duchnik W, Kucharski L, Story A, Story G, Struk L, Antosik AK and Ossowicz-Rupniewska P (2023). Emulsion-based gel loaded with ibuprofen and its derivatives. *Gels,* **9**(5): 391.

Ait-Touchente Z, Zine N, Jaffrezic-Renault N, Errachid A, Lebaz N, Fessi H and Elaissari A (2023). Exploring the versatility of microemulsions in cutaneous drug delivery: Opportunities and challenges. *Nanomaterials* **13**(10): 1688.

Alaoui Y, Fahry A, Rahali Y, Cherkaoui N, Bensouda Y and Laatiris A (2019). Formulation, optimization and characterization of ibuprofen loaded microemulsion system using D-optimal mixture design. *Int. J. Appl. Pharm.,* **11**(4): 304-312.

Alkrad JA, Sayeh WN, Sijari A, Naser A, Neubert RH and Dahmash EZ (2024). *In-vivo* and *in-vitro* transdermal availability of Ibuprofen using novel solubility enhancing fluid nanosized carrier systems. *Int. J. Pharm.,* **650**: 123684.

Amirinejad M, Davoodi J, Abbaspour MR, Akhgari A, Hadizadeh F and Badiee A (2020). Preparation, characterization and improved release profile of ibuprofen-phospholipid association. *J. Drug Deliv. Sci. Technol.,* **60**: 101951.

Anuar N, Sabri AH, Effendi TJB and Hamid KA (2020). Development and characterisation of ibuprofen-loaded nanoemulsion with enhanced oral bioavailability. *Heliyon,* **6**(7): e04570.

Bhatti MHT, Sohail S, Aslam MU, Ather H, Hussain T and Kashif M (2022). Formulation, development and characterization of ibuprofen microemulgel for arthritis. *J. Contemp. Pharm.,* **6**(2): 57-64.

Boborodea A, O'Donohue S, Brookes A, Zieschang F and Boborodea A (2025). Improved flow cell design for a more performant gel permeation chromatography-fourier transform infrared (GPC-FTIR) analysis. *Int. J. Polym. Anal. Charact.,* 1-12.

Czyrski A (2019). Determination of the lipophilicity of ibuprofen, naproxen, ketoprofen and flurbiprofen with thin-layer chromatography. *J. Chem.,* **2019**(1): 3407091.

Dhepe S, Veer V, Kasabe A and Awatade P (2022). Formulation and evaluation of microemulsion containing ketoprofen. *Int. J. Health Sci.,* **6**(S2): 14679-14687.

Djekic L, Martinovic M, Stepanovic-Petrovic R, Micov A, Tomic M and Primorac M (2016). Formulation of hydrogel-thickened nonionic microemulsions with enhanced percutaneous delivery of ibuprofen assessed *in-vivo* in rats. *Eur. J. Pharm. Sci.,* **92**: 255-265.

Ekenna IC and Abali SO (2022). Comparison of the use of kinetic model plots and DD solver software to evaluate the drug release from griseofulvin tablets. *J. Drug Deliv. Ther.,* **12**(2-S): 5-13.

Ghanbari E, Picken SJ and van Esch JH (2023). Analysis of differential scanning calorimetry (DSC): Determining the transition temperatures and enthalpy and heat capacity changes in multicomponent systems by analytical model fitting. *J. Therm. Anal. Calorim.,* **148**(22): 12393-12409.

Hafizah Aulia Ul SP, Khotib Mohammad, Cahyaningsih Umi and Sadiah Siti (2024). Ibuprofen injectable microemulsion preparation coated by chitosan: Formulation, characterization, in-vitro performance, anti-inflammation activity and hematology assessment. *Int. J. App. Pharm.,* **16**(3): 159-166.

Hamed R, Al-Adhami Y and Abu-Huwaij R (2019). Concentration of a microemulsion influences the mechanical properties of ibuprofen in situ microgels. *Int. J. Pharm.,* **570**: 118684.

Hopf NB, Champmartin C, Schenk L, Berthet A, Chedik L, Du Plessis JL, Franken A, Frasch F, Gaskin S, Johanson G, Julander A, Kasting G, Kilo S, Larese Filon F, Marquet F, Midander K, Reale E and Bunge AL (2020). Reflections on the OECD guidelines for *in-vitro* skin absorption studies. *Regul. Toxicol. Pharmacol.,* **117**: 104752.

Ibrahim TM, Abdallah MH, El-Megrab NA and El-Nahas HM (2018). Upgrading of dissolution and anti-hypertensive effect of Carvedilol via two combined approaches: self-emulsification and liquisolid techniques. *Drug Dev. Ind. Pharm.,* **44**(6): 873-885.

Jain P, Soni R, Paswan SK and Soni PK (2023). Ketoconazole laden microemulsion based gel formulation against skin fungal infection. *Int. J. App. Pharm.,* **15**: 49-60.

Katakam LNR and Katari NK (2021). Development of in-vitro release testing method for permethrin cream formulation using Franz Vertical Diffusion Cell apparatus by HPLC. *Talanta Open,* **4**: 100056.

Mancini G, Gonçalves LMD, Marto J, Carvalho FA, Simoes S, Ribeiro HM and Almeida AJ (2021). Increased therapeutic efficacy of SLN containing etofenamate and ibuprofen in topical treatment of inflammation. *Pharmaceutics,* **13**(3): 328.

Meraj M, Khalid N, Hamid M, Adnan F, Ali S and Naseer M (2025). Prevalence of osteoarthritis in Nawab Shah, Pakistan: A cross-sectional study. *Rawal Med. J.,* **49**: 476.

Naeem M, Iqbal T, Nawaz Z, Hussain S, Ahmer A, Kumar H, Yousuf M, Irshad I, Ahmad A and Parkash O (2020). Optimization of ibuprofen therapeutic system for enhanced transdermal delivery: A quality by design approach. *Lat. Am. J. Pharm.,* **39**: 2241-2249.

Nistor M, Nicolescu A, Amarandi RM, Pui A, Stiufiuc RI and Dragoi B (2025). Multi spectroscopic investigation of maisine-based microemulsions as convenient carriers for co-delivery of anticancer and anti-inflammatory drugs. *Sci. Rep.,* **15**(1): 5175.

Ortiz-Tafoya MC and Tecante A (2018). Physicochemical characterization of sodium stearoyl lactylate (SSL), polyoxyethylene sorbitan monolaurate (Tween 20) and κ-carrageenan. *Data in Brief,* **19**: 642-650.

Ozturk A and Guven U (2019). Cefaclor monohydrate loaded microemulsion formulation for topical application: Characterization with new developed UPLC method and stability study. *J. Res. Pharm.,* **23**(3): 426-440.

Ozturk A, Guven U and Yenilmez E (2018). Flurbiprofen loaded gel based topical delivery system: Formulation and in vitro characterization with new developed UPLC method. *ACTA Pharm. Sci.,* **56**(4): 81-105.

Payyal SP, Rompicherla NC, Sathyanarayana SD, Shriram RG and Vadakkepushpakath AN (2020). Microemulsion based gel of sulconazole nitrate for topical application. *Turk. J. Pharm. Sci.,* **17**(3): 259.

Rathore LS, Patidar MS, Pagare MA and Dubey PK (2023). Microemulgel: As a novel vehicle for antimicrobial drugs. *Int. J. Pharm. Drug Res.,* **11**: 177-188.

Theochari I, Mitsou E, Nikolic I, Ilic T, Dobricic V, Pletsa V, Savic S, Xenakis A and Papadimitriou V (2021). Colloidal nanodispersions for the topical delivery of Ibuprofen: Structure, dynamics and bioperformances. *J. Mol. Liq.,* **334**: 116021.

Wen MM, Ismail NIK, Nasra MMA and El-Kamel AH (2021). Repurposing ibuprofen-loaded microemulsion for the management of Alzheimer's disease: Evidence of potential intranasal brain targeting. *Drug Deliv.,* **28**(1): 1188-1203.

Zalavadia B PK (2025). Investigation of microemulsion system for topical delivery of Halobetasol propionate. *Int. J. Pharm. Sci. Drug Res.,* **17**(2): 110-118.

Zhang Y, Cao Y, Meng X, Li C, Wang H and Zhang S (2020). Enhancement of transdermal delivery of artemisinin using microemulsion vehicle based on ionic liquid and lidocaine ibuprofen. *Colloids Surf B: Biointerfaces,* **189**: 110886.