RESEARCH PAPER

"Development and Characterization of a Dual Drug Microemulsion System Containing Aceclofenac and Tizanidine"

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ABSTRACT
Background: Combination therapy involving a non-steroidal anti-inflammatory drug (NSAID) and a centrally acting muscle relaxant is widely used for the management of musculoskeletal disorders. However, oral administration of Aceclofenac and Tizanidine is associated with gastrointestinal irritation, first-pass metabolism, and systemic adverse effects. Aceclofenac and Tizanidine belong to BCS class II.
Objective: The present study aimed to develop and characterize a dual drug-loaded microemulsion system containing Aceclofenac and Tizanidine for enhanced topical delivery with improved permeation and reduced systemic exposure.
Methods: Microemulsion formulations were prepared using the phase titration method and formulated using oil, surfactant, and co-surfactant systems selected based on solubility and pseudo-ternary phase diagram studies. Optimized formulations were evaluated for droplet size, zeta potential, pH, viscosity, drug content, in vitro release, and stability. Fourier Transform Infrared Spectroscopy (FTIR) was performed to assess drug–excipient compatibility.
Results: The optimized formulation exhibited a droplet size of 220 nm with low PDI (<0.3), indicating uniform distribution. The optimized formulation showed good viscosity of 104 cps and pH 5.8 ± 0.012 with highest drug content uniformity found to be 89.765%. Stability studies confirmed physical and chemical stability over three months.
Conclusion: The developed dual-drug microemulsion system significantly improved solubility and anti-inflammatory efficacy, indicating its potential as an alternative delivery strategy for the management of inflammatory conditions.
Keywords: Microemulsion, Aceclofenac, Tizanidine, Topical delivery, Dual drug system, Skin permeation, Phase diagram.
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1. Introduction

Inflammation is a complex biological response triggered by tissue injury, infection, or immune dysregulation [1]. It is characterized by redness, swelling, heat, and pain resulting from the release of inflammatory mediators such as prostaglandins and cytokines [2,3]. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the primary therapeutic agents for managing inflammatory disorders; however, their long-term oral administration is frequently associated with gastrointestinal irritation and systemic side effects [4,5].

Aceclofenac, a phenylacetic acid derivative NSAID, exhibits potent anti-inflammatory and analgesic activity by inhibiting cyclooxygenase enzymes [6,7]. Despite its efficacy, aceclofenac is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by poor aqueous solubility and dissolution-limited absorption [8,9]. Similarly, Tizanidine, a centrally acting α2-adrenergic agonist used as a muscle relaxant, undergoes extensive hepatic first-pass metabolism, leading to reduced bioavailability [10,11]

Combination therapy of non-steroidal anti-inflammatory drugs (NSAIDs) with muscle relaxants is commonly employed

in musculoskeletal inflammatory conditions to achieve synergistic therapeutic effects and rapid symptomatic relief [12,13]. Such multidrug regimens are particularly beneficial in conditions involving both inflammation and muscle spasm, including low back pain and osteoarthritis. However, conventional oral dosage forms frequently demonstrate suboptimal bioavailability due to first-pass metabolism and dissolution limitations, while prolonged systemic exposure increases the risk of gastrointestinal, cardiovascular, and central nervous system adverse effects [14–17].

Microemulsions are thermodynamically stable, isotropic dispersions of oil and water stabilized by surfactants and co-surfactants, typically possessing droplet sizes in the nanometer range [18–20]. Their unique architecture enhances drug solubilization and partitioning into the skin, leading to improved permeability [21–23]. The nanoscale droplets provide a large interfacial area and fluidize stratum corneum lipids, facilitating controlled and sustained release of active agents [21,24,25].

Despite extensive research on single-drug microemulsion systems for topical delivery of non-steroidal anti-inflammatory drugs and other therapeutic agents, there are currently no reported studies specifically exploring dual-drug microemulsion systems incorporating both Aceclofenac and Tizanidine for enhanced anti-inflammatory and muscle-relaxant activity [26–28]. Previous analytical studies have described simultaneous determination of Aceclofenac and Tizanidine in combined oral dosage forms, but these focus on quantification techniques rather than formulation development [29]. Separate microemulsion formulations have been developed for individual drugs such as Aceclofenac to improve skin permeation and efficacy [30] and microemulsion-based gels have been optimized for Tizanidine delivery [31], indicating the potential of microemulsion platforms for topical/transdermal systems. However, the absence of reported dual-drug microemulsion research underscores the need to develop and characterize a novel dual-drug microemulsion system and evaluate its anti-inflammatory performance.

2. Materials and Methods

2.1Materials

Aceclofenac and Tizanidine were procured as gift samples from a certified pharmaceutical manufacturer. The selected oil phase, Isopropyl Myristate, along with the surfactant Tween 80 and co-surfactant Propylene Glycol, were of analytical grade. All other chemicals and solvents employed in the study were of pharmaceutical grade.

2.2 Solubility Studies

Solubility studies were carried out by adding an excess quantity of each drug separately into various oils, surfactants, and co-surfactants. The mixtures were vortexed and subsequently shaken at a controlled temperature of 25 ± 1°C to attain equilibrium. Afterward, the samples were centrifuged and filtered, and the supernatant was analyzed spectrophotometrically following appropriate dilution.

2.3 Construction of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were developed using the water titration method by employing different surfactant to co-surfactant (Smix) ratios of 1:1, 2:1, and 3:1. The microemulsion regions were identified through visual observation and subsequently plotted on triangular coordinate graphs.

Table 1-Ratio of Oil and Smix-A (1:1) for pseudoternary phase diagram

Oil	Smix	Water	Tizanidine:Aceclofenac
9	1	0.4	20:100
8	2	0.7	20:100
7	3	1.2	20:100
6	4	1.6	20:100
5	5	1.9	20:100

4	6	2.4	20:100
3	7	2.3	20:100
2	8	3.1	20:100
1	9	2.9	20:100

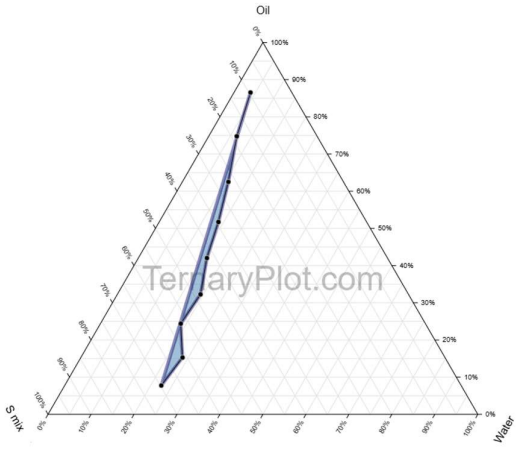


Figure No. 1- Pseudoternary phase diagrams of microemulsion composed of oil phase, surfactant (Tween 80) and cosurfactant (Propylene glycol) and water

Table 2- Ratio of Oil and Smix-B (1:2) for pseudoternary phase diagram

Oil	Smix	Water	Tizanidine:Aceclofenac
9	1	0.6	20:100
8	2	0.9	20:100
7	3	1.5	20:100
6	4	1.8	20:100
5	5	2.4	20:100
4	6	2.6	20:100
3	7	2.3	20:100
2	8	3.5	20:100
1	9	3.7	20:100

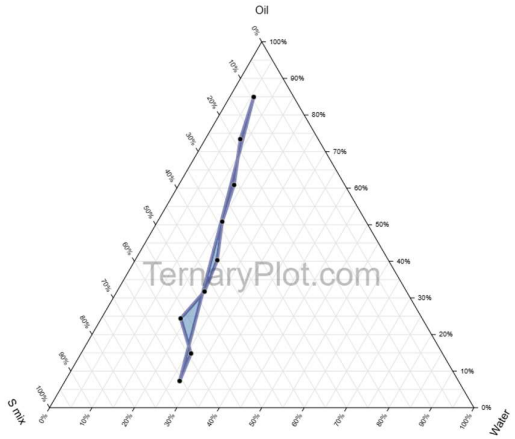


Figure No. 2- Pseudoternary phase diagrams of microemulsion composed of oil phase, surfactant (Tween 80) and cosurfactant (Propylene glycol) and water

Table 3- Ratio of Oil and Smix-C (2:1) for pseudoternary phase diagram

Oil	Smix	Water	Tizanidine:Aceclofenac
9	1	0.3	20:100
8	2	0.7	20:100
7	3	1.2	20:100
6	4	1.4	20:100
5	5	1.3	20:100
4	6	2.1	20:100
3	7	2.6	20:100
2	8	3.2	20:100
1	9	3.6	20:100

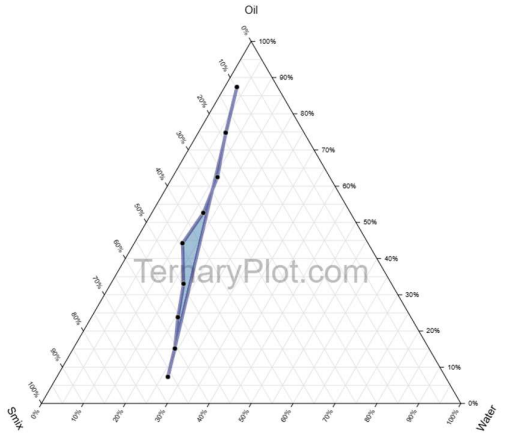


Figure No. 3- Pseudoternary phase diagrams of microemulsion composed of oil phase, surfactant (Tween 80) and

cosurfactant (Propylene glycol) and water

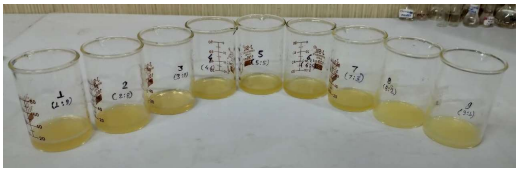


Figure No. 4 - Mixture of oil, Smix and water for pseudo ternary phase diagram

3. Preparation of Microemulsion

Tizanidine and Aceclofenac were incorporated into mixtures of oil, surfactant, and co-surfactant in varying ratios, as specified in Table 4. Subsequently, an appropriate quantity of water was added dropwise to each mixture under continuous stirring using a magnetic stirrer. The microemulsions containing Tizanidine and Aceclofenac were formed spontaneously upon stirring. All prepared microemulsion formulations were stored at ambient temperature for further evaluation.

Table 4Composition of Microemulsion

Formulation	A: Oil %	B: Smix %	C: Stirring speed Rpm	Tizanidine: Aceclofenac (mg)
ME 1	40	50	2000	20:100
ME 2	45	40	2500	20:100
ME 3	40	40	3000	20:100
ME 4	40	45	2500	20:100
ME 5	40	50	3000	20:100
ME 6	45	45	3000	20:100
ME 7	35	45	3000	20:100
ME 8	40	40	2000	20:100
ME 9	35	40	2500	20:100
ME 10	35	50	2500	20:100
ME 11	35	45	2000	20:100
ME 12	45	45	2000	20:100
ME 13	45	50	2500	20:100

3.1 Experiment design

The optimization of the microemulsion formulation was carried out using Response Surface Methodology (RSM) with Design-Expert® software (Version 12.0.1.0). The software was employed to evaluate the quadratic response surface and to develop second-order polynomial models based on a three-factor, three-level Box–Behnken experimental design.

3.2 Optimization of microemulsion

Based on the pseudo-ternary phase diagram, appropriate weight ratios of oil and Smix (low, medium, and high levels) were selected. Formulation compositions were then proposed within the identified microemulsion region of the phase diagram.

Figure No. 5 Trial formulations as per Box–Behnken design

Figure No. 6 Trial formulations as per Box–Behnken design after 24 hrs

Table 5 Final Composition of Optimized formulations

S. No	Formulation code	Oil (%)	Smix (%)	Water (%)	Stirring speed (rpm)	Tizanidine: Aceclofenac (mg)	Temperature (^{0}C)
1.	ME	35	45	20	3000	20:100	32.0

Figure No.6 Optimized Microemulsion

4 Evaluation of Optimized Microemulsion-

4.1 Particle size analysis

The particle size of the prepared microemulsion formulation was determined using Dynamic Light Scattering (DLS) with a particle size analyzer. Prior to analysis, a small aliquot of the formulation was suitably diluted with distilled water to ensure appropriate scattering intensity. The diluted sample was then transferred into a clean, dust-free cuvette and analyzed at room temperature. The instrument provided measurements of the mean particle size and polydispersity index (PDI), which reflect the uniformity of particle size distribution. These parameters are critical for assessing the stability of the formulation and its suitability for oral or transdermal drug delivery applications.


Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	228.6 nm	61.1 nm	206.5 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	228.6 nm	61.1 nm	206.5 nm

Cumulant Operations
Z-Average : 203.3 nm
PI : 0.517
Molecular weight measurement
Molecular weight : ---
Mark-Houwink-Sakurada parameters : ---

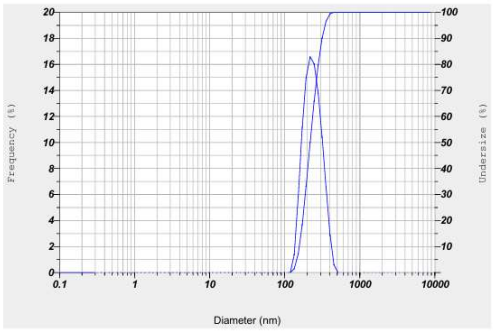


Figure 71 Particle size of optimized formulation

Table 6 Particle size of microemulsion formulation

S. No	Formulation	Particle size
1.	ME	203.3

The particle size of the optimized microemulsion formulation (ME) was found to be **203.3 nm**, indicating the formation of a nanosized system. Such a particle size is desirable as it suggests good dispersion and stability of the microemulsion.

4.2 Zeta potential analysis

The zeta potential of the microemulsion formulation was determined using a Horiba Zetasizer to assess surface charge and predict colloidal stability. Prior to analysis, a small quantity of the formulation was suitably diluted with distilled water to optimize conductivity and minimize particle aggregation. The diluted sample was then transferred into a specialized zeta potential cell and analyzed at room temperature. The instrument measured the electrophoretic mobility of the dispersed droplets and calculated the corresponding zeta potential, providing insight into the electrostatic interactions within the system. Higher absolute values of zeta potential, whether positive or negative, indicate stronger repulsive forces between particles, thereby reducing aggregation and enhancing the physical stability and shelf life of the microemulsion formulation.

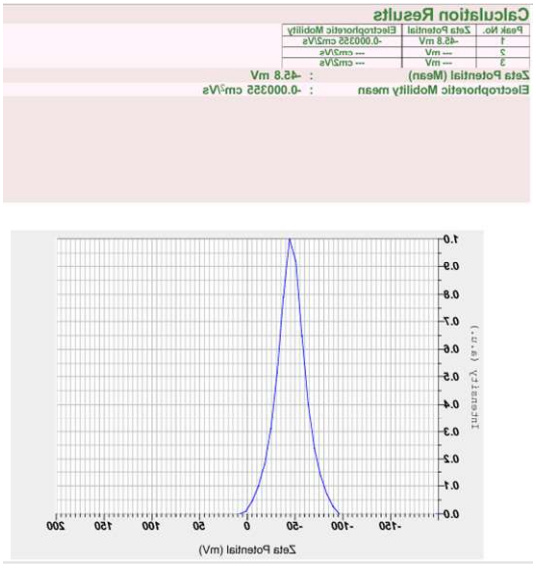


Figure No. 8Zeta potential of microemulsion

Table 7 Zeta potential of microemulsion formulation

S. No	Formulation	Zeta potential
1.	ME	-45.8 mV

The zeta potential of the microemulsion formulation (ME) was found to be **−45.8 mV**, which is more negative than the predicted value (−25.499 mV). A high magnitude of negative zeta potential indicates strong electrostatic repulsion between droplets, contributing to good physical stability of the system.

4.3 Viscosity

The viscosity of the freshly prepared microemulsion was measured using a digital viscometer. The appropriate spindle (No. 2) along with the guard leg was immersed in the sample, ensuring proper positioning within the fluid. The measurement was carried out at a rotational speed of 60 revolutions per minute (rpm). The viscosity of the microemulsion was recorded in poise.

Table 8 Viscosity of microemulsion formulation

S. No	Formulation	Viscosity (Actual value)
1.	ME	104 cP

Figure No.9 Viscosity determination of microemulsion

4.4 Drug Content

The drug content of the microemulsion formulation was determined by dissolving 1 mL of the formulation (equivalent to 10 mg of drug) in 10 mL of methanol. The resulting solution was further diluted appropriately with methanol, and the absorbance was measured using a UV–Visible spectrophotometer at a wavelength of 294 nm, with a blank microemulsion serving as the control. All measurements were performed in triplicate to ensure accuracy and reproducibility.

The drug content of the microemulsion formulation was found to be 89.765% as determined by UV–Visible spectroscopic analysis.

4.5 pH

The apparent pH of all micro emulsions was determined at 25°C by immersing the electrode directly into the micro emulsion using a digital pH meter.

The pH value of microemulsion was found to be 5.8 ± 0.012 by using pH meter.

4.6 SEM

An optimized formulation was selected and analyzed for superficial morphology and shape using a SEM (ZEISS). For surface morphology, microphotographs were obtained at a greater magnification (200X).

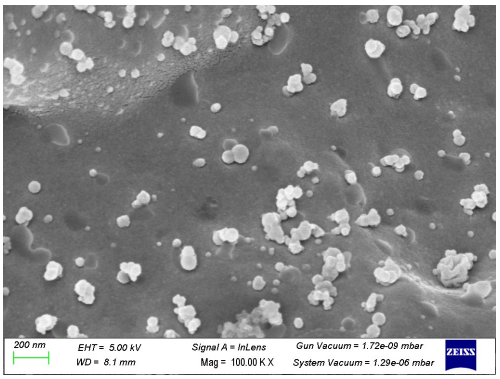


Figure No. 10 SEM image of micro emulsion formulation

The SEM micrograph shows the surface morphology of the prepared microemulsion at a magnification of 100,000× with a scale bar of 220 nm. The particles appear mostly spherical to quasi-spherical in shape and are distributed across the surface. The particle size appears to be in the nanometer range, indicating successful formation of nanosized carriers.

4.7 TEM

Morphology and structure of the micro emulsion were studied using transmission electron microscopy (TEM) (Technai 20, Philips, Holland) at an acceleration voltage of 200KV. In order to perform the TEM observations, a drop of the micro emulsion was directly deposited on the holey film grid and observed after drying.

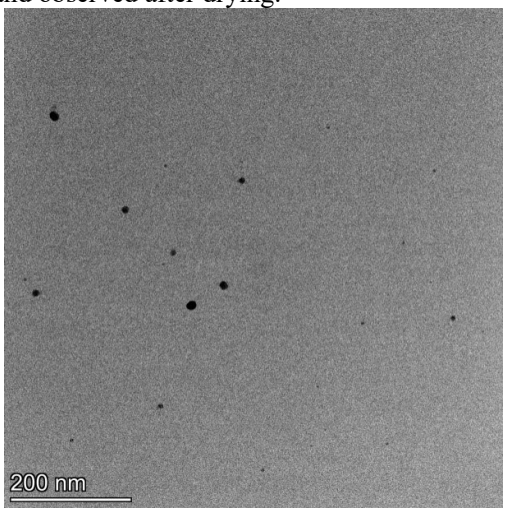


Figure No 11 TEM image of Microemulsion

The TEM image shows discrete, well-dispersed nanosized droplets with predominantly spherical morphology. The particles appear uniformly distributed without significant aggregation, indicating good stability of the microemulsion system. Based on the scale bar (200 nm), the droplet size is observed to be in the nanometer range, suggesting successful formation of a nano-sized microemulsion.

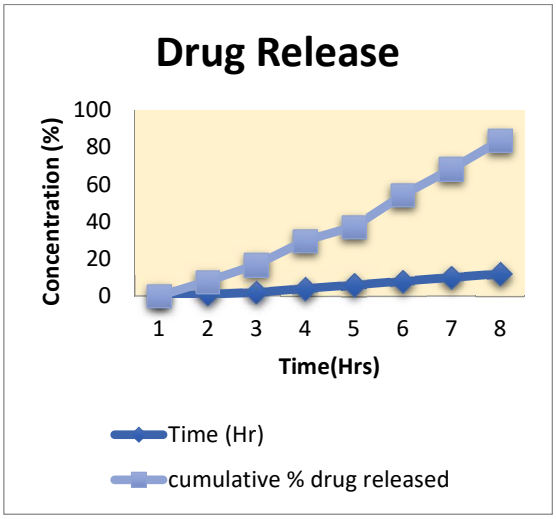
4.8*In vitro* release study by dialysis method

Drug release was determined by dialysis method; two ml of microemulsion formulation was poured into dialysis bags and put into a 25 ml phosphate buffer (pH 7.4) and stirred (100 rpm, room temperature). At predetermined time intervals, 2 ml of phosphate buffer was taken and then substituted with fresh

phosphate buffer. Finally, the amounts released in the phosphate buffer were measured by a spectrophotometer at 294 nm. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 294 nm using a UV-visible spectrophotometer by keeping phosphate buffer pH 7.4 blank and the amount of released drug was estimated by the standard curve.

Table 9. *In vitro* release study

Time (hrs)	Cumulative % drug released	% drug remaining/ drug present	Square root time	Log cumulative % drug remaining	Log time	Log cumulative % drug released	% drug released	Cube root of % drug remaining (wt)	Wo-Wt
0	0	100	0.0000	2.000	0.0000	0.0000	100	4.642	0.0000
0	0	100	0.0000	2.000	0.0000	0.0000	100	4.642	0.0000
1	7.87	92.14	1.00	1.964	0.00	0.895	7.86	4.517	0.12
			0		0				5
2	16.85	83.25	1.414	1.920	0.301	1.224	8.89	4.366	0.276
4	30.76	70.24	2.0000	1.847	0.602	1.4744	13.01	4.126	0.516
6	37.3	62.7	2.449	1.797	0.778	1.5558	7.54	3.973	0.669
8	56.32	45.68	2.828	1.660	0.903	1.7355	17.02	3.575	1.0067
10	68.43	31.57	3.162	1.499	1.000	1.8355	14.111	3.161	1.4811
12	85.56	16.44	3.464	1.216	1.079	1.8999	15.13	2.543	2.099



Graph 1. In-vitro drug release for micro emulsion prepared by optimization

5. Conclusion and Discussion-

The present study successfully developed and optimized a microemulsion system containing Tizanidine and Aceclofenac using pseudo-ternary phase diagram and Response Surface Methodology (RSM). The optimized formulation (ME) consisting of Isopropyl Myristate (35%), Tween 80 and Propylene Glycol (45%, 2:1 ratio), and water (20%) exhibited desirable physicochemical characteristics.

The formulation showed appropriate particle size with a low polydispersity index, indicating uniform distribution of droplets. The zeta potential values suggested good physical stability of the system. Additionally, the viscosity and drug content (87.765%) confirmed the suitability and uniformity of the formulation.

Overall, the developed microemulsion system demonstrated promising potential as an effective drug delivery system for Tizanidine and Aceclofenac, which may enhance drug solubility, stability, and bioavailability. Hence, it can be considered a suitable candidate for further in vivo studies and therapeutic applications.

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