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Original Article

Novel Application of Mixed Solvency Concept for the Development of Topical Emulgel Formulations of Poorly Water-Soluble Drug, Piroxicam, and their Evaluations

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ABSTRACT

Aim: The objective of this research was to investigate the mixed solvency concept as a means to enhance the solubility of Piroxicam and to develop an optimized microemulsion-based gel formulation suitable for topical application. **Materials and Methods:** Piroxicam-loaded microemulsion gel was prepared by using a combination of a pseudo-ternary phase diagram and a D-Optimal mixture design approach. This involved conducting 15 trial runs with three key variables: the percentage of oil blend, water content, and the optimized ratio of surfactant to co-surfactant. The responses assessed were the percentage transmittance and globule size. The Piroxicam microemulsion was formulated using Tween 80 as the surfactant and butanol as the co-surfactant, a combination of Castor oil and Capmul oil as the oil blend, and water. Carbopol 940 was utilized as a gelling agent to formulate the gel for the microemulsion. **Results:** The optimized microemulsion underwent characterization for pH, globule size, transmittance, drug content, viscosity, and texture analysis. Transmission Electron Microscopy (TEM) was employed to investigate the surface morphology of the microemulsion globules. Additionally, an *in vitro* drug release study (flux) was conducted using a Franz diffusion cell fitted with a dialysis membrane. It was observed that the microemulsion gel formulations demonstrated a notably accelerated *in vitro* membrane release rate of Piroxicam in comparison to the marketed formulation. **Conclusion:** Overall, the developed microemulsion gel formulations show promising carriers for the topical delivery of Piroxicam.

Keywords: D-Optimal mixture design, Microemulsion gel, Mixed Solvency, Optimization, Piroxicam, Pseudo ternary phase diagram, Topical drug delivery.

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INTRODUCTION

Improving the solubility of drugs with poor aqueous solubility poses a significant challenge in formulation development. The mix solvency concept of solubilization says that every substance, regardless of its physical state-whether solid, liquid, or gas-exhibits the ability to solubilize other substances.[1] Consequently, concentrated solutions containing a mixture of dissolved substances in any liquid have the potential to improve the solubility of poorly soluble drugs. This innovative technique is versatile and can be employed in a wide range of formulations for such drugs, allowing for a reduction in the concentration of individual solubilizers needed to enhance solubility. This, in turn, helps minimize the toxic effects associated with solubilizers. The mixed solvency concept has emerged as a valuable strategy in formulating numerous poorly soluble drugs. Its application spans various dosage forms, including oily injections, aqueous injections, syrups (in solution form), and topical solutions, showcasing its versatility and efficacy in enhancing drug solubility.[2,3] Furthermore, the mixed solvency concept has found widespread use in the formulation of advanced drug delivery systems such as Self-Emulsifying Drug Delivery Systems (SEDDS), microspheres.[4] nasal gels,[5] liquid-solid systems.[6] solid dispersions, oral films, vaginal films, and other innovative formulations.[7,8]

Piroxicam stands out as a highly potent nonsteroidal anti-inflammatory drug that is widely used in the treatment of conditions like rheumatoid arthritis, osteoarthritis, and various inflammatory diseases.[9] However, oral administration of Piroxicam is associated with several adverse effects such as ulcerative colitis, gastrointestinal irritation, edema, and peptic ulcer.[10] Conversely, the parenteral route of administration leads to significant pain and inflammation at the injection site, causing discomfort for arthritis patients who require daily doses. This study aims to develop an alternative drug delivery system to enhance patient compliance in delivering Piroxicam effectively.[11]

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To address the challenges posed by oral and parenteral routes, the focus is on exploring the topical route for drug delivery, considered a promising approach for drugs like Piroxicam. This method bypasses hepatic first-pass metabolism, allowing for localized drug action in the targeted area.[12] Beyond improving the therapeutic efficacy of the drug, topical delivery helps mitigate adverse effects associated with systemic circulation, offering a potential solution to enhance patient comfort and compliance.[9,10]

Microemulsions are quaternary system consist of oil, water, surfactants, and cosurfactants, forming stable structures with globule sizes typically ranging from 10 to 200 nm.[13] Microemulsions as potential carriers for drug delivery have attracted considerable attention due to their easy preparation, transparency, thermodynamic stability, viscosity, and droplet size. Their small droplet size facilitates efficient incorporation of both hydrophilic and hydrophobic drugs.[14] In contrast, conventional topical agents like ointments, creams, and lotions often suffer from drawbacks. Their sticky nature often causes discomfort to patients upon application, requiring rubbing due to a lower spreading coefficient. Moreover, stability issues are frequently observed. Transparent gels have gained popularity in pharmaceutical preparations as an alternative; however, their effectiveness in delivering water-insoluble drugs is limited. To address this challenge, a microemulsion-based approach is increasingly utilized, allowing the successful incorporation of hydrophobic drugs into a gel-based system. The process involves initially preparing and evaluating an oil-in-water microemulsion, which is then integrated into a gel base, resulting in a dosage form known as a microemulsion-based gel. This approach offers several advantages over conventional topical formulations.[15,16]

Formulating a pharmaceutical microemulsion system is a challenging endeavour that requires validation through rigorous experimental design. Developing a pharmaceutical microemulsion system is a complex process that requires validation through rigorous experimental design. The Quality by Design (QbD) methodology, especially when employing Design of Experiments (DoE), has demonstrated its superiority over conventional approaches in the formulation and optimization processes. Among the various statistical experimental designs, the D-Optimal design stands out as highly compatible for the development of microemulsion systems. This is because a microemulsion consists of three core components: oil, water, and surfactant/co-surfactant. The D-Optimal design is advantageous as it maintains a constant sum of all components (i.e., 100%), allowing flexible modification of each component as needed. This flexibility is illustrated in a pseudo-ternary phase diagram, aiding in the exploration of the microemulsion region.[17,18]

The primary aim of this research was to explore the mixed solvency concept to improve the solubility of Piroxicam and to design and optimize a microemulsion system for Piroxicam using castor oil, Capmul MCM, Tween 80, and n-butanol. Subsequently, the developed microemulsion system was further formulated into a topical gel for convenient, prolonged retention and patient-friendly application on the skin, specifically for arthritis. Solubility assessments and construction of pseudo-ternary phase diagrams were utilized to determine the composition of the Microemulsion (ME) formulation. A D-Optimal mixture design was utilized to systematically evaluate the impact of various formulation factors on the particle size of the Piroxicam-loaded microemulsion.

MATERIALS AND METHODS

Materials

Piroxicam was obtained as a gift sample from Schon Pharmaceutical Limited, Indore, India, Castor oil was from Garima Healthcare Pvt. Ltd., Capmul oil was from Abitech Corporation, Tween 80 was from Sisco Research Laboratories Pvt. Ltd., Propylparaben was from HiMedia Laboratories Pvt. Ltd., Benzoic acid was from Loba Chemie Pvt. Ltd., and Carbopol 940 was from Loba Chemie Pvt. Ltd.

Methods

Determination of the approximate solubility of Piroxicam

The solubility of the drug or solubilizers was determined in oil. In a glass vial, 1 mL of oil was taken, and 5 mg of the drug or solubilizer was added. The mixture was vigorously shaken with slight heating for 20-30 min until a clear solution was achieved. An additional 5 mg of the drug or solubilizer was added, and the process was repeated until a clear solution was obtained. If complete dissolution didn't occur, the amount of oil/blend was increased by 0.5 mL until clarity was achieved. The solution was then left undisturbed for 24 hr to check for precipitation. The approximate solubility was calculated based on the amount of solvent required to completely dissolve the drug.

Development of a solvent system (using the mixed solvency concept) for microemulsion formulation

The solubility of Piroxicam in different oils was less than the desired level. Using a mixed solvency concept to develop a solvent system by dissolving different solid solubilizers in oils at their safe concentration levels, resulting in a strong solvent that could be used to prepare dosage forms. For the development of blends, several solid solubilizers were utilized individually or in combination, and drug solubility experiments were conducted to assess the efficacy of these blends.

Approximate solubility of various solubilizers in different oil matrices

Oil-soluble solubilizers are selected based on the solubility of solubilizers in oils.

Approximate solubility of Piroxicam in various blends

The approximate solubility of the drug was determined in prepared oil blends.

Selection of oil blend, surfactant, and co-surfactant

Selection of oil blend

The drug is present in the internal oil phase. The solubility of piroxicam was checked in different blends of solubilizers. The blend which shows the highest solubility enhancement ratio was selected as the oil phase.[19]

Selection of surfactant and cosurfactant (S_{mix})

For the preparation of the microemulsion of Piroxicam, various types of surfactants were explored, and the final selection was done based on their oil accommodation capacity.

Co-surfactant is employed in the formulation when surfactant alone is unable to reduce interfacial tension or achieve the dose of a drug required to form a stable emulsion. The aqueous solution of different co-surfactants with the selected surfactant was prepared in a ratio of 1:1, and oil was slowly added to it.[19]

Construction of a pseudo-ternary phase diagram for the formulation of Piroxicam microemulsion

The concentration range of the microemulsion components was determined using the pseudo-ternary phase diagram, utilizing the oil titration method. Considering drug solubility and the compatibility of surfactant and co-surfactant, the oil phase, surfactant, and co-surfactant were selected. A phase diagram was constructed using water as the aqueous phase, employing Origin 2022 software. Various surfactant and co-surfactant ratios (S_{mix} ratios) were included in the diagram, such as 1:1, 1:2, 1:3, 2:1, and 3:1. Water-S_{mix} mixtures were prepared by vortex mixing, gradually increasing S_{mix} concentration and decreasing water concentration or vice versa, in a ratio ranging from 0.5:9.5 to 9.5:0.5. The resulting water-S_{mix} mixture was titrated with oil using a pipette until the mixture became milky or turbid. Observations were recorded for constructing the phase diagram, maximizing the microemulsion region, and feeding the values into Origin 2022 software. Visually, the turbid emulsions were represented by the black area, while the remaining area indicated the microemulsion region.[13,20,21]

Formulation optimization of ME

The formulation optimization process was conducted using the D-Optimal design within the Design Expert software. Three variables were considered: the percentage of oil blend, the percentage of S_{mix} (surfactant: cosurfactant), and the percentage of water, and two key responses (%transmittance and globule size) for various formulations containing Piroxicam. The experimental design comprised 15 trial runs for Piroxicam formulations as shown in Table 1.[17,22,23]

Statistical model fitting

For determining the optimization of the response variable (R1 and R2) in the direction of an optimal statistical analysis, model selection was the first criterion. To assess the suitability of model fitting, various statistical models, such as linear, quadratic, and special cubic models, were initially evaluated for each response variable (R1 and R2).[24] Analysis of Variance (ANOVA) was conducted to assess the statistical significance of the data, with a p-value threshold of less than 0.05 indicating significance.

Analysis of response variables

Analysis of the response variables was carried out by the recommended 3D response surface plot of the various response variables.

Effect of independent variables on the mean globule size (R1)

The importance of globule size in determining the stability and skin penetration of microemulsions is widely acknowledged. The Design Expert-12 software used the following linear model equation to represent the relationship between the mean globule size (R1) and various degrees of independent variables:

$$R1=488A+45.19B+154.25C$$

Effect of independent variables on % transmittance (R2)

A higher transmittance value consistently signifies favourable emulsification conditions; hence the highest value is considered optimal. The Design Expert-12 software used the following linear model equation to explain the relationship between different values of independent variables and the percent transmittance (R2).

$$R2=90.35A+101.02B+90.61C$$

Preparation of Piroxicam-ME

The final optimized batch Table 1 of Piroxicam microemulsion formulation was prepared through the phase titration method. To achieve this, the recommended quantity of water and S_{mix} were mixed using a vortex mixer. Piroxicam was dissolved in an oil blend. Following that, the internal oil phase (Oil blend) was added to the above mixture and stirred using a vortex mixer to form a homogeneous drug-loaded microemulsion formulation.

Table 1: D -optimal design-based Piroxicam microemulsion formulations and their observed responses.

Sl. No.	Formulation Code	Independent variables (Formulation components) (%)			Response variables (Evaluation parameter)	
		Oil blend	S_{mix}	Water	Globule size (nm)	Transmittance (%)
1.	PXM/ME/01	20	55	25	89.1	98.6
2.	PXM/ME/02	44	35	21	450.1	91.1
3.	PXM/ME/03	44	48	8	293.8	94.9
4.	PXM/ME/04	25	67	8	137	97.9
5.	PXM/ME/05	36	35	29	166.9	93.2
6.	PXM/ME/06	30.166	49.166	20.66	143.8	96.8
7.	PXM/ME/07	44	48	8	268.6	92.8
8.	PXM/ME/08	44	35	21	537.7	88.9
9.	PXM/ME/09	34.5	57.5	8	168.5	97.6
10.	PXM/ME/10	20	67	13	117	98.2
11.	PXM/ME/11	25.08	46.083	28.83	181.6	94.9
12.	PXM/ME/12	20	43	37	147.5	93.3
13.	PXM/ME/13	20	43	37	142.5	92.9
14.	PXM/ME/14	28	35	37	190	85.6
15.	PXM/ME/15	26.3	58.08	15.58	152.1	96.7

Composition of optimized formulation of Piroxicam microemulsion.		
Sl. No.	Components	Quantity (%)
1.	Oil Blend	22
2.	S_{mix}	44
3.	Poly ethylene glycol 400	6
4.	Water	28

PXM=Piroxicam, ME=Microemulsion.

Characterization of Piroxicam-ME

Visual examination

The evaluation of the microemulsion system is based on criteria such as optical clarity, homogeneity, and absence of phase separation.

Determination of pH

The topical formulation should have a pH compatible with skin pH. There may be chances of disruption or irritation if any changes occur in pH. The pH of the optimized formulation of Piroxicam microemulsion was determined by a digital pH meter (Cyberscan 510).[25]

Drug content

The drug content of the optimized formulation of Piroxicam microemulsion was determined by a UV-visible spectrophotometer. For this 1 mL of optimized microemulsion was accurately measured and dissolved in 10 mL of 0.01M methanolic HCl, and then further diluted with 0.01M methanolic HCl, and this solution was analyzed by UV-visible spectrophotometer (Shimadzu® 1700) at 334 nm.[25]

Determination of % transmittance

A UV-visible spectrophotometer was used to determine the percent transmittance at a specific wavelength of 600 nm after the optimized formulation of Piroxicam.[26]

Determination of globule size

The Malvern Zeta Sizer particle size analyzer was used to evaluate the globule size of the optimized formulation of the microemulsion loaded with Piroxicam. Approximately 3 mL of the microemulsion was transferred into the sample cell for globule size analysis.[26]

Transmission electron microscopy of Piroxicam microemulsion

Transmission Electron Microscopy (TEM-Talos L120C) is the crucial technique for studying the microstructures of microemulsions because this method directly generates high-resolution images, enabling the observation of co-existent structures and micro-structural transitions with precision. The morphology and structure of the microemulsion were studied using TEM.[13,27,28] A drop of drug-loaded microemulsion formulation was loaded onto the copper grid and allowed to dry. It was then negatively stained with a drop of 2% phosphotungstic acid.

Development of topical gel formulation of Piroxicam-loaded microemulsion

Gelling agents play a crucial role in enhancing the viscosity of microemulsions, thereby extending their retention time on the skin. The gel base is prepared by soaking various polymers, including Carbopol 940 (2%, 2.5%, 3%), and xanthan gum in water for 1-2 hr. In the preparation of the microemulsion gel formulation, 2% of the water content within the microemulsion was replaced with an equivalent quantity of thickener.[29] To formulate a microemulsion-loaded gel, the optimized piroxicam-loaded microemulsion formulation is integrated into the gel base.

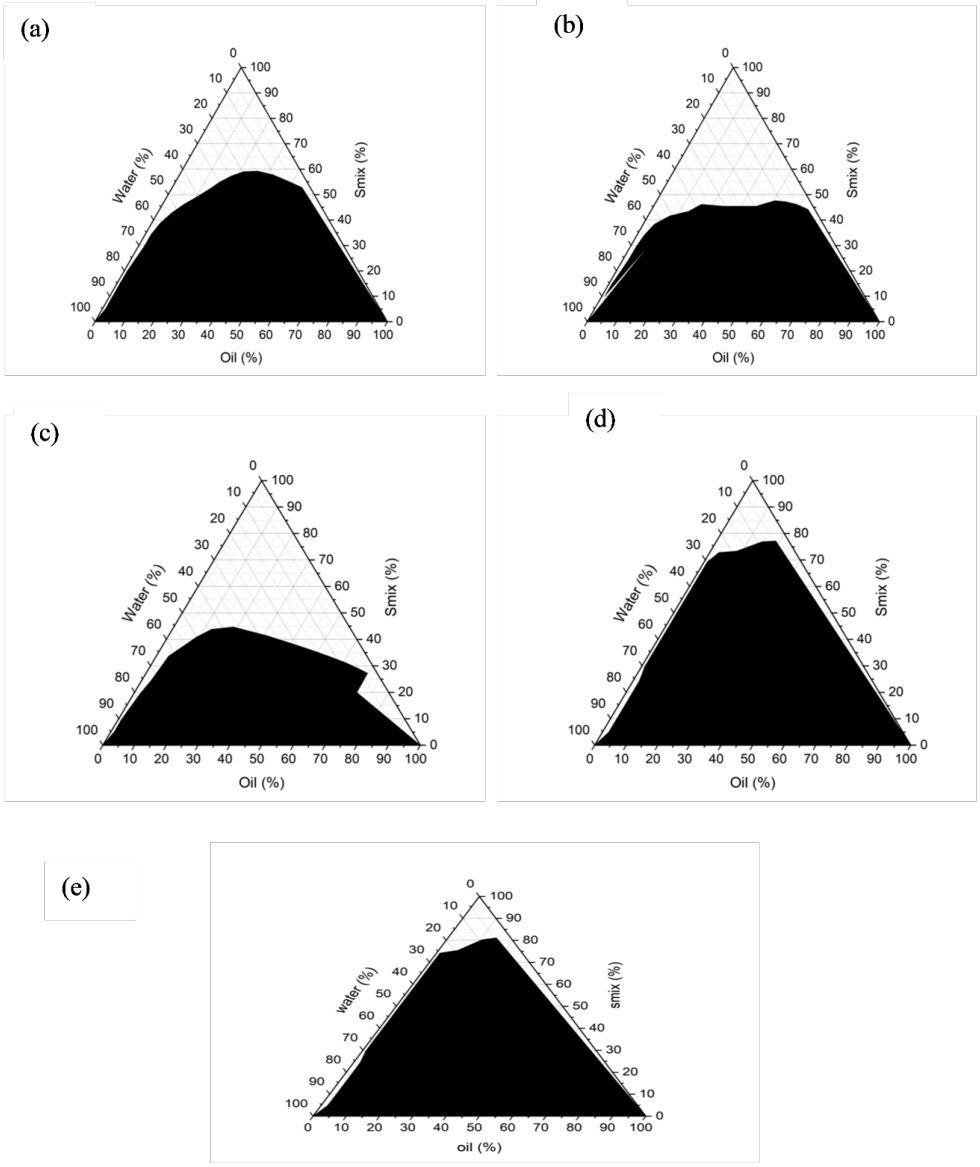


Figure 1: Pseudo ternary phase diagram of microemulsion using (a) S_{mix} in 1:1 ratio (b) S_{mix} in 2:1 ratio (c) S_{mix} in 3:1 ratio (d) S_{mix} in 1:2 ratio (e) S_{mix} in 1:3 ratio.

Evaluation of the developed gel formulation of Piroxicam-loaded microemulsion

The physical appearance

Visual inspection was conducted under bright light to assess the appearance and homogeneity of the gel loaded with Piroxicam microemulsion.

pH determination

A digital pH meter (Cyberscan 510) was used to determine the 1% aqueous solution of the gel of Piroxicam microemulsion. The pH of the topical gel should be similar to that of the skin.

Determination of viscosity

The viscosity of the Piroxicam microemulsion gel was assessed using a Brookfield viscometer, specifically the model DV-II+Pro, under ambient conditions. For viscosity measurement, Spindle 64 was utilized at a rotation speed of 100 rpm.

Table 2: Approximate solubility of Piroxicam in various oils.

Sl. No.	Oils	Approximate solubility
1.	Sesame oil	1.4 mg/mL
2.	Coconut oil	2.5 mg/mL
3.	Castor oil	3.3 mg/mL
4.	Capmul MCM	6 mg/mL
5.	Castor + Capmul MCM (1:1)	9.5 mg/mL

Results indicating the approximate solubility of Piroxicam in different blends of sesame oil.

Sl. No.	Solvent	Blend	Blend Composition		Solubility (mg/mL)	Enhancement solubility
			Solubilizer	Concentration		
1.	Sesame Oil	A1	BHA BHT Menthol Camphor	5% 5% 5% 5%	5	3.5
2.		A2	BHA BHT Thymol	5% 5% 5%	3.5	2.5
3.		A3	BHA BHT Benzoic acid Methylparaben Propyl paraben	5% 5% 1.5% 1% 1%	6	4.2
4.		A4	BHA BHT Thymol Menthol Camphor Methyl paraben Propyl paraben	3% 3% 3% 3% 3% 1% 1%	4.5	3.2
5.		A5	BHA BHT Menthol Thymol	10% 10% 5% 5%	7	5

Results indicating the approximate solubility of Piroxicam in different blends of coconut oil.

Sl. No.	Solvent	Blend	Blend Composition		Solubility (mg/mL)	Enhancement solubility
			Solubilizer	Concentration		

Sl. No.	Oils				Approximate solubility	
1.	Coconut oil	B1	BHA BHT Menthol	10% 10% 10%	7.5	3
2.		B2	BHA BHT Camphor Menthol Benzoic acid Propyl paraben	5% 5% 5% 5% 3% 2%	10	4
3.		B3	BHA BHT Camphor Menthol Benzoic acid Propyl paraben	7.5% 7.5% 5% 5% 2% 2%	10	4

Results indicating the approximate solubility of Piroxicam in different blends of castor and capmul oil.

Sl. No.	Solvent	Blend	Blend Composition		Solubility (mg/mL)	Enhancement solubility
			Solubilizer	Concentration		
1.	Castor Oil	C1	Propyl paraben Methyl paraben Benzoic acid	5% 5% 5%	20	3.3
2.		C2	Propyl paraben Methyl paraben Benzoic acid BHT BHA	3% 3% 3% 3% 3%	12.5	2.08
3.		C3	Propylparaben Methyl paraben Benzoic acid Menthol Thymol BHT	3% 3% 3% 3% 3% 3%	12.5	2.08
4.		C4	BHT BHA Menthol Thymol	5% 5% 5% 5%	10	1.66
5.		C5	Propylparaben Methyl paraben Benzoic acid	7.5% 7.5% 5%	25	4.16
6.		C6	Propylparaben Methyl paraben Benzoic acid BHT Thymol Menthol	5% 5% 5% 3% 3% 3%	17.5	2.91

Sl. No.	Oils				Approximate solubility	
7.		C7	Propylparaben Methyl paraben Benzoic acid Menthol+ BHT	3% 3% 3% 3%+3%	17.5	2.91
8.		C8	Propylparaben Methyl paraben Benzoic acid Thymol BHA	3% 3% 3% 3% 3%	17.5	2.91
9.		C9	Propylparaben Methyl paraben Benzoic acid BHT+BHA Menthol Thymol	5% 5% 5% 3%+3% 2% 2%	20	3.33
10.		C10	Propylparaben Methylparaben Benzoic acid	7.5% 2.5% 1%	20	3.33
11.	Castor and capmul oil	C11	Propyl paraben Benzoic acid	10% 1.25%	27.5	2.84

BHT=Butylated hydroxy toluene, BHA=Butylated hydroxy anisole.

Spreadability determination

Spreadability, a crucial parameter for assessing the uniformity and ease of application of topical formulations, denotes the ability of a gel to uniformly spread when administered onto the skin or targeted areas. This characteristic is inversely correlated with hardness, which signifies the force necessary for a specific deformation, consequently affecting spreadability. The TA-XT plus Texture Analyzer (Stable Microsystem, Surrey, UK) was used to measure the spreadability of the Piroxicam microemulsion gel, with a focus on its significance in gel application. A higher spreadability value is desirable for optimal gel performance.[30]

Cohesiveness and adhesiveness determination

The cohesiveness and adhesiveness of the gel containing a Piroxicam microemulsion were determined using the TA-XT plus (stable micro system, Surrey, UK) Texture Analyzer. Cohesiveness refers to the capacity of a substance to maintain its integrity and stick together. The cohesiveness of a material is an intermolecular attraction that binds a molecule together. Adhesiveness pertains to the energy required to surpass the force of attraction between the surface of the sample and the surface of the probe. Enhanced physical crosslinking within a polymer facilitates its ability to sustain contact with the skin over an extended duration.[31]

In vitro drug release study of the developed gel containing Piroxicam microemulsion

Piroxicam's *in vitro* drug release was assessed using a Franz diffusion cell setup, where a dialysis membrane separated the donor and receptor compartments. The microemulsion gel and a commercially available gel, each containing an equivalent of 2.5 mg of Piroxicam, were placed in contact with a dialysis membrane within the donor compartment. Meanwhile, the receptor compartment was filled with 15 mL of phosphate buffer at pH 7.4. A magnetic stirrer ensured continuous stirring of the buffer solution throughout the duration of the experiment. The temperature was maintained at 37±2°C. Samples were withdrawn at 15 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 10 hr from the receptor compartment and was replaced by the fresh media (phosphate buffer saline (pH 7.4)). The samples were analyzed using a UV-visible spectrophotometer (Shimadzu® 1700) at a wavelength of 358 nm.[32]

Drug release kinetics of the developed gel of Piroxicam-loaded microemulsion

To explore the release kinetics of Piroxicam from the microemulsion, data from the *in vitro* release study were subjected to analysis using various kinetic models. Five models were applied, including zero order, first order, Hixon-Crowel, Korsmeyer-Peppas, and Higuchi models (4).

RESULTS AND DISCUSSION

Determination of the approximate solubility of Piroxicam

The findings presented in Table 2 provide a comprehensive overview of the successful determination of Piroxicam's approximate solubility in various oils. Through systematic experimentation, the solubilization capacity of different oils for Piroxicam has been effectively elucidated.

Development of a solvent system (using the mixed solvency concept) for microemulsion formulation

Approximate solubility of Piroxicam in various blends

The following Table 2 shows the estimated solubility of Piroxicam in various blends of oils.

Selection of oil blend, surfactant, and co-surfactant

Selection of oil blend

The blend code C11, characterized by the maximum solubility of Piroxicam, was chosen as the internal oil phase. This blend consists of propylparaben and benzoic acid, combined in a 1:1 ratio with castor and Capmul oil to achieve a solution.

Selection of surfactant and co-surfactant

Tween 80 was finally selected as the surfactant as it showed the highest oil accommodation capacity for the oil blend. It is a non-irritating and non-ionic surfactant and is widely used for the preparation of o/w emulsions.

Butanol was opted for as the cosurfactant in a 1:1 proportion with Tween 80 because of its exceptional capacity to accommodate oil, surpassing other alternatives in this aspect.

Construction of a pseudo-ternary phase diagram for the formulation of Piroxicam microemulsion

A pseudo-ternary diagram was constructed by varying the ratios of surfactant to cosurfactant, including ratios such as 1:1, 1:2, 1:3, 2:1, and 3:1. Microemulsion with a 3:1 ratio of S_{mix} exhibited the largest microemulsion region area, but in the 3:1 ratio of S_{mix} concentration of individual surfactant is high which may cause irritation that's why 2:1 ratio of S_{mix} was selected. The area of the microemulsion region under the pseudo-ternary phase diagram is shown in the following Table 3, Figure 1 depicts a pseudo-ternary diagram illustrating various combinations denoted as (a), (b), (c), (d), and (e).

D-optimal mixture design to optimize the formulation of Piroxicam-loaded microemulsion.

The experimental design comprised 15 trial run responses for Piroxicam formulations, as detailed in Table 1.

Statistical model fitting

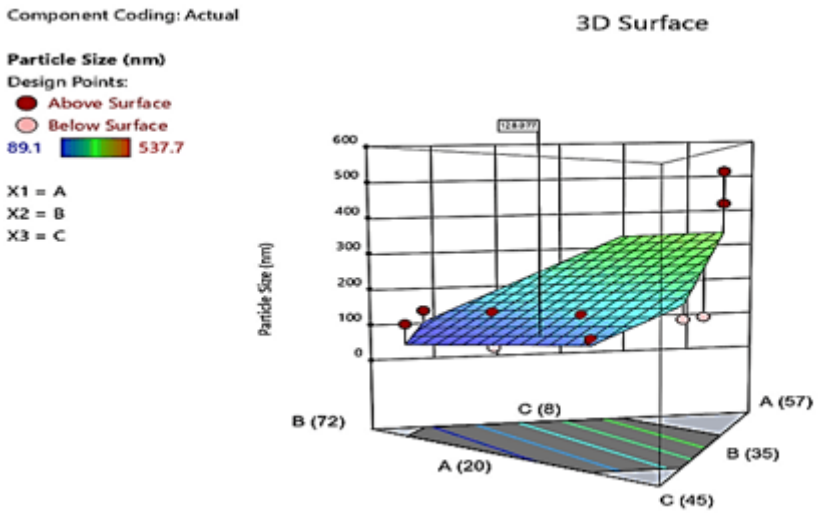
The statistical summary of the response variable is shown in Table 4.

Analysis of response variables

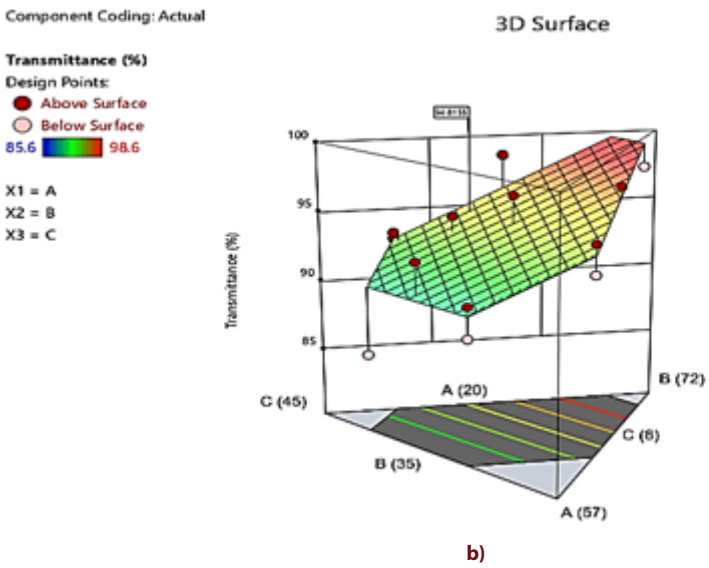
Analysis of the response variables was carried out by the recommended 3D response surface plot of the various response variables, as illustrated in Figures 2a, 2b. The formulation was optimized based on its globule size and transmittance.

The optimized composition of the Piroxicam microemulsion formulation predicted by the D-optimal mixture design

The prepared 15 microemulsion formulation batches' results and all 2 response variables of formulation were fed into the D-optimal



a)



b)

Figure 2: 3D plots showing the effect of independent variables on (a) Globule Size (nm), (b) Transmittance (%).

Table 3: Area of the microemulsion region under the pseudo-ternary phase diagram.

Sl. No.	The ratio of oil and surfactant co-surfactant mixture	Area of microemulsion region (%)
1.	1:1	22.71
2.	2:1	23.52
3.	3:1	33.89
4.	1:2	6.76
5.	1:3	5.34

mixture design, which suggests one optimum microemulsion composition and its properties. The final batch was selected based on the highest desirability value i.e., 0.897. Figure 3a shows the suggested composition and maximum desirability of the optimized microemulsion formulation. Overlay plot for the optimized formulation of Piroxicam is shown in Figure 3b. as suggested by the design, following the optimization process, the microemulsion formulations recommended by the design were analyzed, as mentioned in Table 4.

Evaluation of optimized final formulation of Piroxicam microemulsion

Visual examination

The optimized formulation of the Piroxicam microemulsion exhibited transparency, clarity, and homogeneity, with no observable phase separation phenomenon.

Determination of pH

The optimized formulation of Piroxicam-loaded microemulsion was found to have a pH of 5.4.

Drug content

The drug content of the optimized formulation of Piroxicam-loaded microemulsion was found to be 98.67±0.45%.

Determination of % transmittance

The higher value of transmittance shows a better and more stable microemulsion formulation. The % transmittance of the optimized formulation was found to be 96.5±.24%.

Determination of globule size

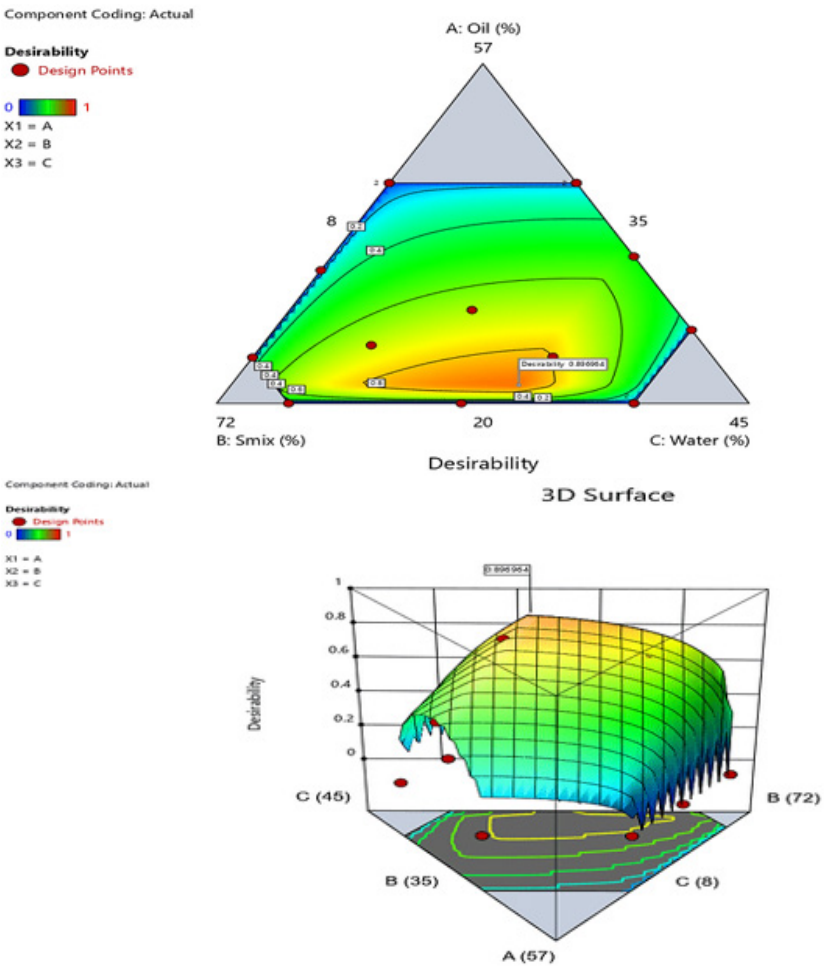
Decreasing the globule size may enhance the contact area between the micro-emulsion system and the skin, thereby aiding the transportation of the drug through the skin. The optimized Piroxicam microemulsion formulation had a particle size of 147.1 nm, as shown in Figure 4.

Transmission electron microscopy of Piroxicam microemulsion

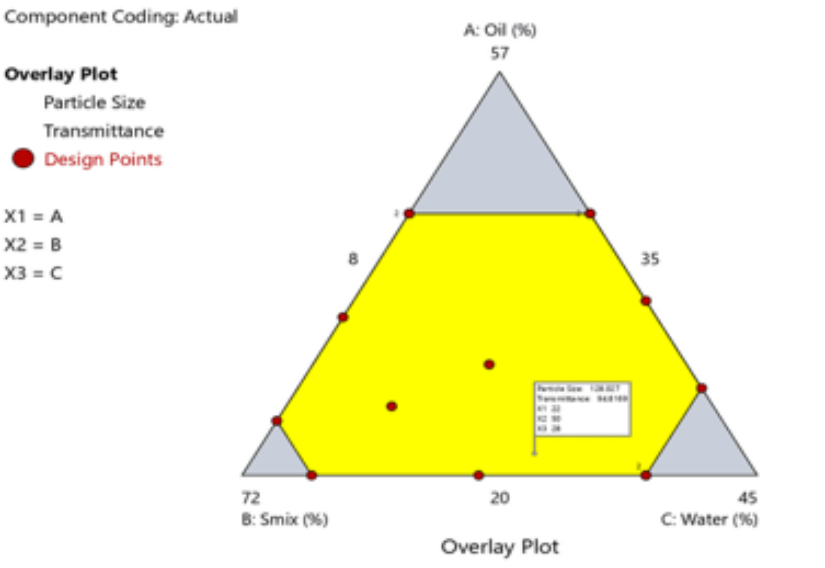
The TEM micrographs showed nano-sized, nearly spherical droplets of the developed microemulsion formulation, as shown in Figure 5.

Development of a topical gel formulation of Piroxicam-loaded microemulsion

A 2% concentration of Carbopol 940 successfully formed a suitable gel with the microemulsion, exhibiting the desired homogeneity and consistency. As a result, Carbopol 940 was selected to formulate the gel for the microemulsion.



a)



b)

Figure 3: (a) The optimized formulation of Piroxicam-loaded microemulsion having the highest desirability shown in 2D contour plots and 3D response surface, (b) Overlay plot for optimized formulation of Piroxicam as suggested by the design.

Evaluation of the developed gel formulation of Piroxicam-loaded microemulsion

The physical appearance

Visual inspection of the Piroxicam microemulsion gel was carried out in bright light, which shows the homogeneity and clarity, and there were no lumps formed in the gel.

pH determination

The formulated product is safe and does not induce any skin irritation or discomfort because its pH values are close to skin pH. Piroxicam microemulsion gel pH was found to be approximately 6.4.

Table 4: Model fitting and ANOVA analysis of measured response variables for software-designed Piroxicam-loaded microemulsion formulations.

Response variable	Model	Sequential *p*-value	Lack of fit p-value	Adjusted R2 value	Predicted R2 value	Remarks
Mean particle size (R1)	Linear	0.0009	0.1002	0.6390	0.5013	Suggested
	Quadratic	0.0911	0.1545	0.7571	0.5910	
	Special cubic	0.2755	0.1545	0.7667	0.4919	
Transmittance (R2)	Linear	0.0006	0.1622	0.6658	0.5476	Suggested
	Quadratic	0.1010	0.2397	0.7695	0.5558	
	Special cubic	0.2391	0.2496	0.7843	0.4832	

Software predicted and experimentally observed response variable data of the optimized formulation of Piroxicam microemulsion.

Composition of optimized batch		Measured response		
Components	Quantity (%)	Response variable	Software predicted value	Experimentally observed value
A (oil blend)	22	Mean particle size (nm)	128.077	147.1
B (S_{mix})	50	Transmittance (%)	94.8155	96.5
C (Water)	28			

Table 5: Comparative *in vitro* release of Piroxicam-loaded microemulsion gel.

Sl. No.	Time (hr)	Cumulative % drug release of a marketed product	Cumulative % drug release of a microemulsion gel (mean±SD)	Flux ($mg/cm^2.h$)
1.	0	0	0	Microemulsion gel 0.5702
2.	0.25	5.37	5.60±0.103	
3.	0.5	11.78	13.11±0.273	
4.	1	21.21	23.07±0.377	
5.	2	37.18	43.06±0.249	
6.	3	45.42	49.91±0.717	Marketed gel 0.5202
7.	4	53.01	58.82±1.167	
8.	6	60.64	68.35±1.310	
10.	8	68.86	75.33±0.717	
11.	10	72.94	79.23±1.354	

Drug release kinetic data and model fitting of developed Piroxicam loaded microemulsion gel.

Sl. No.	Drug release kinetic model	Equation	K	R2
1.	Zero-order	Q_0-Qt=k_0t	0.130	0.8573
2.	First order	log Q=logQ_0-kt/2.303	-0.001	0.9641
3.	Hixson-Crowell	$Q_0$1/3-Qt1/3=kt	-0.003	0.9341
4.	Korsmeyer-Peppas	Log (Q_0-Qt)=log k + n log t	31.952	0.8481
5.	Higuchi	Q_0-Qt=kt1/2	3.603	0.9724

(k is rate constant; tis the time; Q_0 is the initial drug amount; Qt is the drug amount remaining at time t).

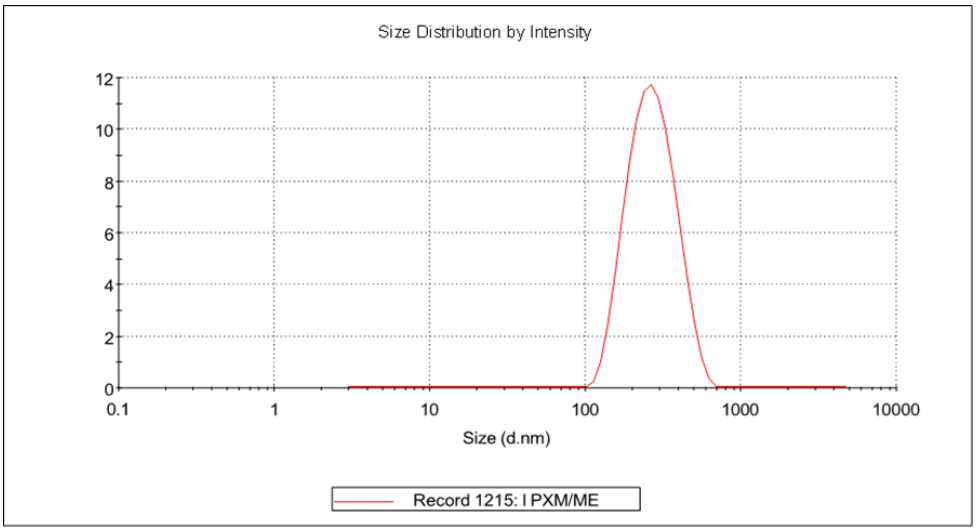


Figure 4: Particle size distribution of optimized formulation of Piroxicam.

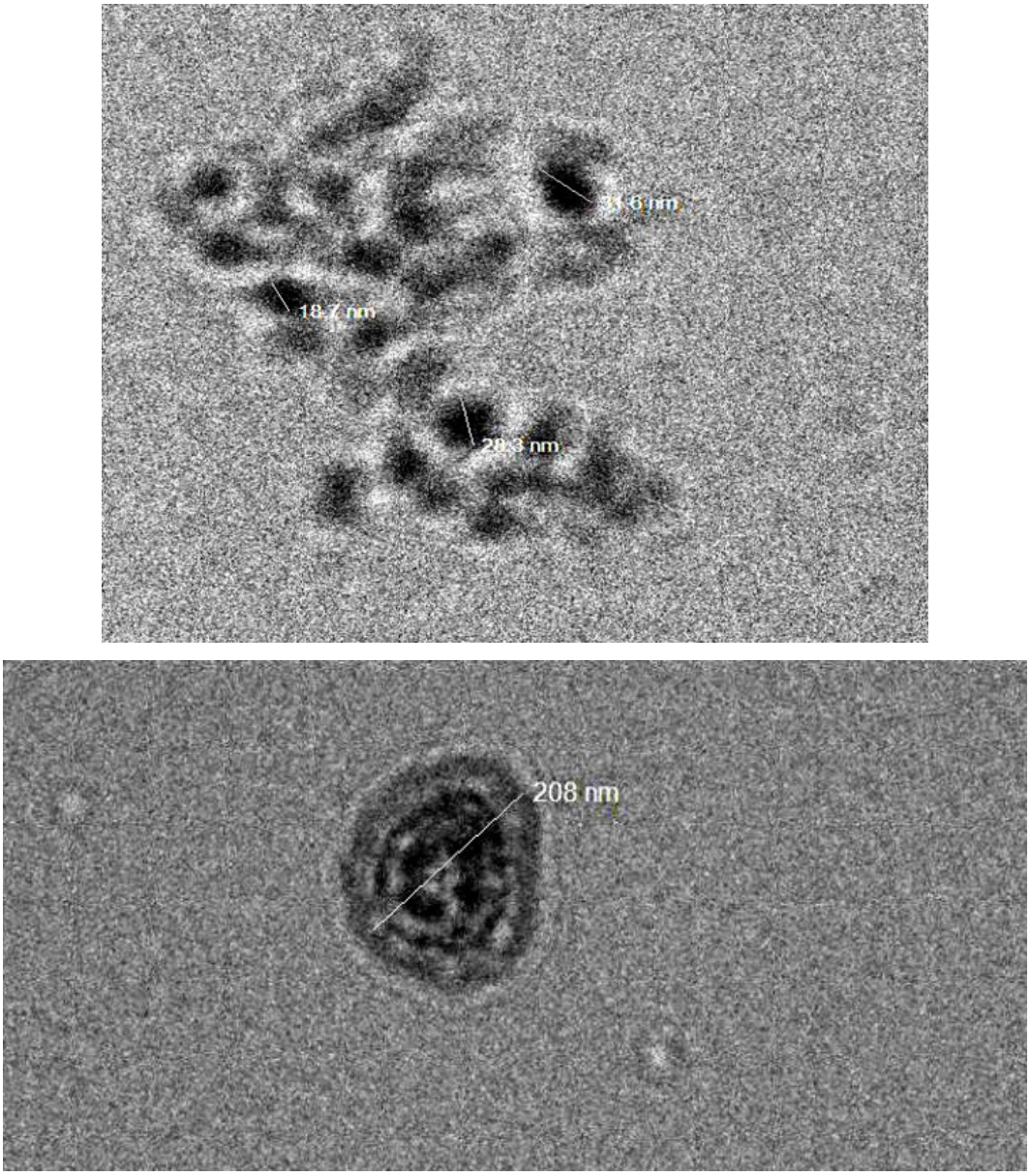
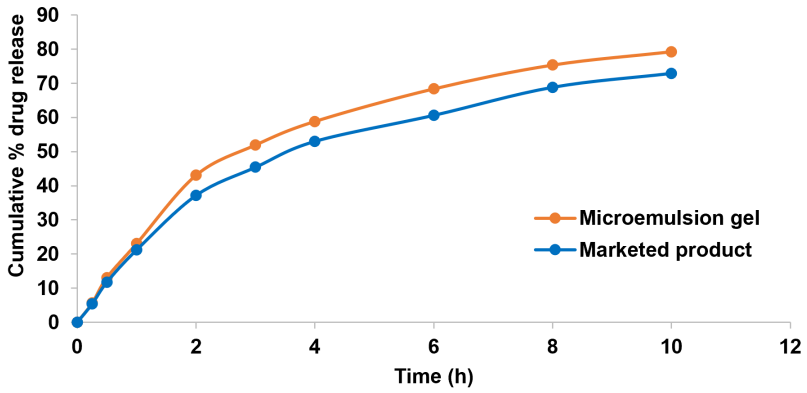
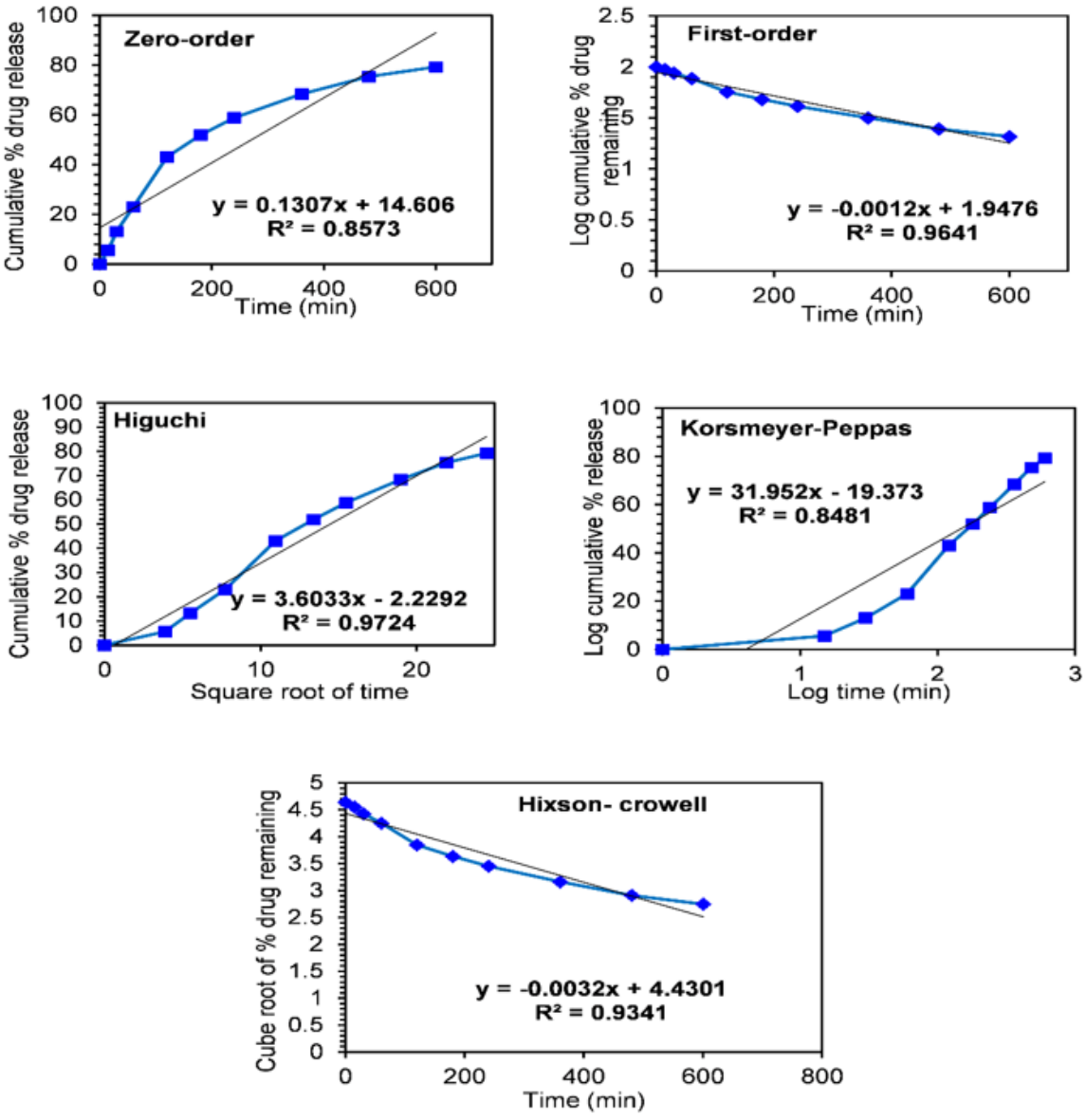


Figure 5: TEM of the optimized microemulsion.



(a)



(b)

Figure 6: (a) Comparative in vitro release of Piroxicam- loaded microemulsion gel with marketed gel of Piroxicam. (b) The drug release kinetic model plots of the developed microemulsion gel of Piroxicam

Determination of viscosity

The viscosity of the Piroxicam microemulsion gel was determined to be 3791 cps at room temperature, which indicates the good consistency of the formulation.

Determination of spreadability

The spreadability of the microemulsion gel was found to be 41.479 g. The result indicates that the microemulsion gel has good spreadability and low spread over time.

Determination of cohesiveness and adhesiveness

The microemulsion gel formulation adhesiveness and cohesiveness were found to be 34.585 g and -116.230 g, respectively. The result indicates polymer would increase skin retention.

In vitro drug release study and release kinetics of the developed gel of Piroxicam microemulsion

The *in vitro* release of the microemulsion gel of Piroxicam and the marketed gel of Piroxicam was found to be 79.23±1.354% and 72.94% at 10 hr as shown in Figure 6a and Table 5. It was concluded that the microemulsion gel shows better drug release than the marketed product.

The drug release kinetics of the developed microemulsion gel of Piroxicam is depicted in Figure 6b and were described using a variety of kinetic models. According to Table 5, the R2 values for the various kinetic models were found to be in the range of zero-order (0.8573), first-order (0.9641), Hixson-Crowel (0.9341), Korsmeyer-Peppas (0.8481), and Higuchi (0.9724). It is clear from Figure 6b that the drug release of Piroxicam from the microemulsion-based gel properly complies with the Higuchi drug release model because the drug release profile is close to the regression line, and the highest value coefficient of correlation value (R2) was 0.9724

CONCLUSION

The results obtained from this study suggest that the solubility of a poorly oil-soluble drug such as Piroxicam can be significantly enhanced by employing a combination of solid solubilizers (Benzoic acid and propylparaben). This approach may be applicable for formulating an oil-in-water microemulsion system of Piroxicam, achieved through the phase titration method and subsequent evaluation. The initial step involved preparing a pseudo- ternary phase diagram, assessing various ratios (1:1, 2:1, 3:1, 1:2, and 1:3) of surfactant to co-surfactant. And it was found to be 2:1 ratio was selected for the further step. The formulation was optimized using the D-optimal design, considering three variables (the percentage of oil phase, S_{mix}, and aqueous phase) and two response variables (globule size and 5 transmittance). The optimal microemulsion formulation of Piroxicam comprised 50% surfactant to cosurfactant ratio (Tween 80 and butanol), 22% oil blend (a combination of Castor oil and Capmul oil), and 28% water. Additionally, 2% carbopol 940 was used as a gelling agent to formulate the microemulsion gel. The *in vitro* release rate of the microemulsion gel containing Piroxicam was significantly higher compared to the conventional formulation. The prepared formulation has shown all the necessary attributes and can be a better alternative to the conventional formulation.

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ABBREVIATIONS

ME: Microemulsion; **TEM:** Transmission Electron Microscope; **nm:** Nano Meter; **ºC:** Degree Centigrade.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study aimed to improve the solubility of Piroxicam and develop an optimized microemulsion-based gel for topical application using a novel approach known as the mixed solvency concept. The preparation of Piroxicam-loaded microemulsion gel involved a series of experiments guided by a combination of pseudo-ternary phase diagrams and D-Optimal mixture design. Key variables such as the percentage of oil blend, water content, and the ratio of surfactant to co-surfactant were varied in 15 trial runs. The resulting microemulsion formulation included Tween 80 as the surfactant, butanol as the co-surfactant, and a blend of Castor oil and Capmul oil as the oil phase, along with water. Carbopol 940 was utilized as a gelling agent to formulate the gel. The optimized microemulsion underwent thorough characterization, including pH determination, measurement of globule size and transmittance, assessment of drug content, viscosity evaluation, and texture analysis. Additionally, Transmission Electron Microscopy (TEM) was employed to examine the surface morphology of microemulsion globules. *In vitro* drug release studies were conducted using a Franz diffusion cell equipped with a dialysis membrane. The results revealed a significantly enhanced release rate of Piroxicam from the microemulsion gel formulations compared to the commercially available formulation. This research underscores the potential of mixed solvency concept-based microemulsion gels as promising platforms for efficient drug delivery.

REFERENCES

1. Ludhiani Simran Maheshwari RK. A Review Article: Mixed Solvency Concept in Formulation and Extraction. International Journal of Pharmacy & Pharmaceutical Research. 2021; 21.
2. Maheshwari RK, Shilpkar R. Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept. International Journal of Pharma and Biosciences. 2012;3(1):179-89.

3. Solanki SS, Soni LK, Maheshwari RK. Study on Mixed Solvency Concept in Formulation Development of Aqueous Injection of Poorly Water Soluble Drug. Journal of Pharmaceutics. 2013; 2013:678132.
4. Rathod Megha, Agrawal Sikha. Development and Evaluation of Furosemide Microspheres Made by Mixed Solvency Concept. International Journal of Pharmaceutical erudition. 2013: 10.
5. Agrawal A, Maheshwari R. Formulation development and evaluation of *in situ* nasal gel of poorly water soluble drug using mixed solvency concept. Asian Journal of Pharmaceutics (AJP). 2011;5(3).
6. Agrawal R, Maheshwari RK. Novel application of mixed solvency concept in the development of oral liquisolid system of a poorly soluble drug, cefixime and its evaluation. Journal of Drug Delivery and Therapeutics. 2018;8:5-8.
7. Ludhiani Simran Maheshwari RK. Novel Application of Mixed Solvency Concept to Develop and Formulate Liquisolid System of a Poorly Water Soluble Drug, Furosemide and Their Evaluations. Der Pharm Lett. (2021);13:146-52.
8. Thakur Y, Maheshwari RK. Novel Application of Mixed Solvency Concept to Develop and Formulate Dry Powder Injection for Reconstitution of a Poorly Water Soluble Drug, Amlodipine Besylate and their Evaluations. Journal of Drug Delivery and Therapeutics. 2021;11:101-8.
9. Mohammadi-Samani S, Zojaji S, Entezar-Almahdi E. Piroxicam loaded solid lipid nanoparticles for topical delivery: Preparation, characterization and *in vitro* permeation assessment. Journal of Drug Delivery Science and Technology. 2018;47:427-33.
10. Garg V, Singh H, Bhatia A, Raza K, Singh SK, Singh B, *et al.* Systematic Development of Transethosomal Gel System of Piroxicam: Formulation Optimization, *In vitro* Evaluation, and *ex vivo* Assessment. AAPS PharmSciTech. 2017;18(1):58-71. Epub 20160211.
11. Singh S, Patel J, Kare S. Estimation of Piroxicam in Tablet Dosage Form by using UV-vis. Spectrophotometer. Asian Journal of Research in Chemistry. 2016;9:82.
12. Tasneem R, Khan HMS, Zaka HS, Khan P. Development and cosmeceutical evaluation of topical emulgel containing Albizia lebbeck bark extract. Journal of Cosmetic Dermatology. 2022;21(4):1588-95.
13. Chauhan L, Muzaffar F, Lohia S. Design, development and evaluation of topical microemulsion. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(2):605-10.
14. Sharma G, Wilson K, van der Walle CF, Sattar N, Petrie JR, Ravi Kumar MNV. Microemulsions for oral delivery of insulin: Design, development and evaluation in streptozotocin induced diabetic rats. European Journal of Pharmaceutics and Biopharmaceutics. 2010;76(2):159-69.
15. Fonseca V, Bhide P, Joshi M. Formulation, Development and Evaluation of Etoricoxib Nanosize Microemulsion Based Gel for Topical Drug Delivery. Indian Journal of Pharmaceutical Education and Research. 2019;53:s571-s9.
16. Abdulkarim MF, Abdullah GZ, Chitneni M, Salman IM, Ameer OZ, Yam MF, *et al.* Topical piroxicam *in vitro* release and *in vivo* anti-inflammatory and analgesic effects from palm oil esters-based nanocream. Int J Nanomedicine. 2010;5:915-24. Epub 20101104.
17. Shukla T, Pandey SP, Khare P, Upmanyu N. Development of ketorolac tromethamine loaded microemulsion for topical delivery using D-optimal experimental approach: Characterization and evaluation of analgesic and anti-inflammatory efficacy. Journal of Drug Delivery Science and Technology. 2021;64:102632.
18. Jeirani Z, Mohamed Jan B, Si Ali B, Mohd. Noor I, Chun Hwa S, Saphanuchart W. The optimal mixture design of experiments: Alternative method in optimizing the aqueous phase composition of a microemulsion. Chemometrics and Intelligent Laboratory Systems. 2012;112:1-7.
19. Patel V, Kukadiya H, Mashru R, Surti N, Mandal S. Development of microemulsion for solubility enhancement of clopidogrel. Iran J Pharm Res. 2010;9(4):327-34. PubMed PMID: 24381597; PubMed Central PMCID: PMC3870056.
20. Ahmad J, Amin S, Kohli K, Mir SR. Construction of Pseudoternary Phase Diagram and its Evaluation: Development of Self-dispersible Oral Formulation. International Journal of Drug Development and Research. 2013;5:84-90.
21. Gannu R, Palem CR, Yamsani VV, Yamsani SK, Yamsani MR. Enhanced bioavailability of lacidipine via microemulsion based transdermal gels: Formulation optimization, *ex vivo* and *in vivo* characterization. International Journal of Pharmaceutics. 2010;388(1):231-41. doi: https://doi.org/10.1016/j.ijpharm.2009.12.050.
22. Jain P, Soni R, Paswan SK, Soni PK. Ketoconazole Laden Microemulsion Based Gel Formulation Against Skin Fungal Infection. International Journal of Applied Pharmaceutics. 2023.
23. Hu Q, Fu XL, Dong YY, Ma J, Hua J, Li JT, *et al.* D-Optimal Design and Development of a Koumine-Loaded Microemulsion for Rheumatoid Arthritis Treatment: *In vivo* and *in vitro* Evaluation. Int J Nanomedicine. 2023;18:2973-88. Epub 20230605.
24. Chouhan P, Saini T. D-optimal design and development of microemulsion based transungual drug delivery formulation of ciclopirox olamine for treatment of onychomycosis. Indian J Pharm Sci. 2016;78(4):498-511.
25. Gohil R, Patel A, Pandya T, Dharamsi A. Optimization of brinzolamide loaded microemulsion using formulation by design approach: characterization and *in vitro* evaluation. Current Drug Therapy. 2020;15(1):37-52.
26. Kumar N, Shishu. D-optimal experimental approach for designing topical microemulsion of itraconazole: Characterization and evaluation of antifungal efficacy against a standardized Tinea pedis infection model in Wistar rats. European Journal of Pharmaceutical Sciences. 2015;67:97-112.
27. Ita K. Chapter 6 - Microemulsions. In: Ita K, editor. Transdermal Drug Delivery: Academic Press; 2020. p. 97-122.
28. Acharya DP, Hartley PG. Progress in microemulsion characterization. Current Opinion in Colloid & Interface Science. 2012;17(5):274-80. doi: https://doi.org/10.1016/j.cocis.2012.07.002.
29. Das S, Lee SH, Chia VD, Chow PS, Macbeath C, Liu Y, *et al.* Development of microemulsion based topical ivermectin formulations: Pre-formulation and formulation studies. Colloids Surf B Biointerfaces. 2020;189:110823. Epub 20200123.
30. Lacalendola Tundisi L, Artem Ataide J, Lopes JH, Silvério L, Lancellotti M, Paiva-Santos AC, *et al.* Terbinafine Nanohybrid: Proposing a Hydrogel Carrying Nanoparticles for Topical Release. Pharmaceutics. 2023;15:841.
31. Rahman SS, Ahmed AB. Development and evaluation of mucoadhesive nanogel of nevirapine for vaginal application. Int J Appl Pharm. 2019;11(3):144-9.
32. Güngör S, Bergišadi N. *In vitro* release studies on topical gel formulations of nimesulide. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2003;58(2):155-6.

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