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Formulation and Evaluation of Mupirocin Microemulgel for Treatment of Skin Infection

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ABSTRACT
The present study aimed at formulation and evaluation of mupirocin microemulgel for the treatment of skin infections. Standard protocols were followed for the formulation of microemulgel. The formulations exhibited translucency with % transmittance ranging from 95.21±0.8 to 98.02±0.8. pH values ranged from 5.8 to 6.3, and the highest % drug content was observed in E1 at 95.49±1.2. Viscosity was consistent across all formulations (2042 ± 112.54 cps). Particle size and zeta potential were also evaluated, with E4 displaying the lowest particle size at 90.16 and E2 at 92.76. Zeta potential ranged from -20.2 to -29.8 across the formulations. Subsequently, microemulgel was prepared by incorporating microemulsion into carbopol gel and evaluated for various parameters. pH ranged from 5.7 to 6.5 among formulations F1 to F6. Viscosity ranged between 20162 and 42336 mPa.s, with F1 exhibiting the lowest and F6 the highest viscosity. Drug content of all formulations fell within the optimal range of 90-110%, ensuring content uniformity. F1 displayed 99.14% drug release. Antimicrobial activity testing revealed zone of inhibition values of 14±0.5mm, 10±0.74mm, and 7±0.57mm for concentrations of 100µg/ml, 50 µg/ml, and 25 µg/ml, respectively. Stability tests indicated that F1 microemulgel remained stable after three months under accelerated stability conditions. It was concluded that F1 microemulgel holds potential for the effective treatment of skin infections.

Keywords: Skin diseases, Topical drug delivery, Microemulgel, Mupirocin, S. aureus, Bacterial infections

I. INTRODUCTION

The skin plays a crucial role in regulating the passage of substances, maintaining moisture levels, and controlling body temperature to uphold internal equilibrium, known as homeostasis. Skin disorders affect approximately one-third of the global population, ranking as the fourth most prevalent human ailment. Despite their widespread impact, the significance of skin conditions is often underestimated. The considerable prevalence of skin ailments, coupled with their long-term effects on morbidity and disability-adjusted life years, particularly evident in conditions like atopic dermatitis and chronic inflammatory disorders such as psoriasis, along with the substantial expense associated with advanced treatments like biologics, collectively contribute to the burden of skin diseases. The high incidence of skin cancer and its treatment expenses further strain healthcare systems financially. Atopic dermatitis, constituting 15 percent of all nonfatal diseases, stands as a primary contributor to skin-related issues. Additionally, acne, a common inflammatory skin condition prevalent among women and teenagers, underscores the need for effective topical treatments for these disorders.[1-3]

Topical medication delivery involves administering medication through the skin to address various skin issues. Transdermal drug delivery systems (TDDS) are self-contained formulations designed to release medication into the bloodstream at a controlled rate when applied to intact skin. A transdermal patch, also known as a skin patch, adheres to the skin to deliver a specific dose of medication directly into the bloodstream. These methods are commonly used to treat local skin infections such as fungal and microbial infections, or when other routes of drug administration are not suitable. Whether providing local or systemic effects, these preparations offer a safe and efficient means of delivering medication compared to conventional approaches, often requiring smaller doses.[4-5]

Microemulgel is a gel formulation comprising microemulsion droplets with a size range typically between 10 to 100 nm. Microemulsions exhibit thermodynamic stability and offer a unique environment for incorporating both hydrophilic and hydrophobic medications. These systems are composed of multiple components including nonpolar, aqueous, surfactant, and co-surfactant agents. When

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surfactants are introduced into an immiscible mixture of oil and water, they bind to the oil/water interface, reducing surface tension. This property enables the integration of hydrophobic medications, which often face solubility challenges when directly incorporated into gel bases. By incorporating the hydrophobic medication into the oil phase and dispersing it homogeneously within the aqueous phase using a blend of surfactant and co-surfactant, the interfacial tension between the two liquid phases is reduced, promoting their miscibility and facilitating drug release.[6-8]

Mupirocin, previously referred to as pseudomonic acid, stands as a novel antibacterial medication with a unique chemical composition and mechanism of action, setting it apart from conventional antibiotics. This naturally occurring antibiotic demonstrates broad-spectrum efficacy in vitro against numerous gram-positive and gram-negative bacteria. Produced through fermentation utilizing the organism Pseudomonas fluorescens, mupirocin primarily operates by inhibiting bacterial protein synthesis, thus impeding bacterial growth and proliferation.[9]

Mupirocin exhibits a unique mechanism of action by suppressing bacterial isoleucyl-tRNA synthetase, conferring it with a therapeutic advantage and preventing cross-resistance with other antimicrobial drugs. Due to its extensive systemic metabolism, mupirocin is exclusively available in topical formulations. It is commonly utilized to treat impetigo caused by Staphylococcus aureus and Streptococcus pyogenes, along with traumatic skin lesions resulting from secondary skin infections caused by these pathogens.[10] Given the inherent benefits of microemulgel formulations, this study focused on the formulation and evaluation of mupirocin microemulgel for the treatment of skin infections.

II. MATERIALS & METHODS

Chemicals & Reagents

Mupirocin was procured as a gift sample from Bioplus life Sciences Pvt. Ltd. Bangalore. The chemicals including liquid paraffin, methylparaben, propylparaben, carbopol, ethanol, and methanol were procured from Loba Chemie Mumbai. All chemicals and reagents utilized in the study were of standard laboratory grade.

Preparation of microemulsion

The standard method for preparing an emulsion involved several steps. Firstly, the oil phase was prepared by dissolving Span 20 in liquid paraffin in varying ratios.[11] Simultaneously, the aqueous phase was prepared by dissolving Tween 20 in purified water. Mupirocin (1 gram) was dissolved in 5 ml of ethanol, while methylparaben (0.15 g) and propylparaben (0.05 g) were dissolved in 5 gm of propylene glycol, and both were combined with the aqueous phase. Each phase was heated separately to 70-80°C (Table 1). Subsequently, the oil phase was gradually added to the aqueous phase with continuous stirring at 500 rpm until the mixture cooled to room temperature.

Table 1: Formulation composition of MUP microemulsion.

Ingredients	M1	M2	M3	M4
Mupirocin (g)	1	1	1	1
Tween 20 (%)	0.25	0.5	0.75	1
Span 20 (%)	1	0.75	0.5	0.25
Liquid paraffin (%)	5	5	5	5
Purified water (ml) q.s.	25	25	25	25

Characterization of microemulsion

Optical Transparency

The microemulsion was diluted by a factor of 50-100. Optical clarity was evaluated both visually and spectrophotometrically by measuring the percentage of light transmitted at a wavelength range of 400-800 nm using a UV/Visible spectrophotometer.[12]

pH

The pH value serves as an indicator of the suitability of the microemulsion for topical application. To ensure compatibility with human

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skin and enhance acceptability, the pH of the microemulsion was determined using a digital pH meter. The excipients employed in the formulation play a crucial role in determining the final pH of the preparation and the route of administration.[13]

Drug content

A volume of 1 ml of the microemulsion formulations was transferred into a beaker containing 10 ml of phosphate-buffered saline (PBS) adjusted to pH 6.5. The contents of the beaker were stirred for 30 minutes and then allowed to stand for 24 hours. After 24 hours, the contents of the beaker were transferred into a centrifuge tube and centrifuged at 3000 rpm for 10 minutes. The supernatant was carefully separated and filtered. Subsequently, 0.1 ml of the supernatant was appropriately diluted with PBS adjusted to pH 6.5 and assayed spectrophotometrically to determine the drug content.[14]

$$\text{Drug content (\%)} = \frac{\text{Actual amount of drug}}{\text{Theoretical amount of drug}} \times 100$$

Viscosity Measurements

Viscosity measurements were conducted using a Brookfield digital viscometer. The sample holder was filled with the samples and then placed into a flow jacket mounted on the viscometer. A spindle adaptor (spindle no. 2) was utilized, rotating at an optimal speed, to measure the viscosity of the preparation. Measurements were taken across the entire range of speed settings, ranging from 10 rpm to 100 rpm, with a duration of 30 seconds each.[15]

Particle size

Particle size distribution is a critical parameter for assessing the efficacy of the topical route. The measurement of particle size and size distribution of the microemulsion was conducted using dynamic light scattering with a Zetasizer 3000 particle size analyzer from Malvern Instruments, Malvern, UK. The size of the microemulsion droplets plays a significant role in percutaneous absorption of the drug. When the droplet size is minimized, it increases the likelihood of interaction with a fixed area of the stratum corneum, thus enhancing efficiency in percutaneous uptake. Permeation studies indicate that the permeation rate escalates as the concentration of both the oil and the surfactant/co-surfactant (S/CoS) mixture decreases. Samples were placed in square glass cuvettes, and droplet size analysis was conducted at a temperature of 25°C.[16]

Zeta potential of the microemulsion

The zeta potential of formulations was assessed using the Malvern Zetasizer. Samples were introduced into clear disposable zeta cells, and the results were recorded. Prior to introducing a fresh sample, cuvettes were cleaned with methanol and rinsed with the sample to be measured before each experiment. The measurement relied on the electrophoretic mobility (expressed in micrometers per second) of the particles, which was then converted to the zeta potential using the built-in software of the mastersizer 2000.[17]

Preparation of carbopol gel

Fifty grams (50 g) of carbopol gel were prepared by dispersing 1 gram of carbopol powder in 50 ml of purified water with the assistance of a moderate-speed stirrer set at 50 rpm. Subsequently, the pH was adjusted to the range of 6.5-6.8 using 0.5 N sodium hydroxide.[18]

Formulation of Mupirocin microemulgel

Six formulations of Mupirocin were formulated by blending the obtained emulsions with the gel in a 1:1 ratio, employing gentle stirring until a homogeneous microemulgel was achieved (Table 2). This mixing process was conducted within an ultrasonic cell crusher noise isolating chamber, facilitated by Labman.

Table 2: Composition of microemulgel of Mupirocin

Ingredients (mg)	Formulation code (%w/w)					
	F1	F2	F3	F4	F5	F6
Microemulsion Equivalent to Mupirocin	1	1	1	1	1	1
Carbapol 940	0.5	1.0	1.5	0.5	1.0	1.5
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s
Propylene glycol	5.0	5.0	5.0	5.0	5.0	5.0
Methyl parabene	0.03	0.03	0.03	0.03	0.03	0.03

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Ethyl parabene	0.01	0.01	0.01	0.01	0.01	0.01
Water (q.s.)	100	100	100	100	100	100

Evaluation of microemulgel

Physical characteristic

The physical characteristics of the microemulgel formulations, including color, clogging, homogeneity, and texture, were examined, and detailed observations were recorded.[19]

Determination of pH

The pH of the microemulgel was determined using a digital pH meter.[20] One gram of the gel was dissolved in 25 ml of distilled water, and the electrode was subsequently immersed into the gel formulation for 30 minutes until a constant reading was obtained. The pH measurements for each formulation were replicated twice, and the constant readings were noted.

Washability

The formulations were applied to the skin, and subsequently, the ease and extent of washing with water were manually assessed. Observations regarding the ease of washing off and the extent to which the formulation was removed were recorded.[21]

Extrudability study

The microemulgel formulations were filled into collapsible metal tubes or aluminum collapsible tubes.[22] The tubes were then compressed to extrude the material, and the extrudability of the formulation was evaluated.

Spreadability

To determine the spreadability of the microemulgel formulation, two glass slides of standard dimensions (6×2) were selected. The microemulgel formulation to be evaluated was applied onto one of the slides. The second slide was then placed over the first slide, sandwiching the formulation between them along a length of 6 cm. A weight of 100 grams was placed on the upper slide to ensure uniform spreading of the microemulgel formulation to form a thin layer. After removing the weight, any excess formulation adhering to the slides was carefully removed. The lower slide was then secured onto the apparatus, while one end of the upper slide was attached to a string connected to a 20-gram load via a simple pulley mechanism. The time taken for the upper slide, under the influence of the weight, to travel a distance of 6 cm and separate from the lower slide was recorded as a measure of spreadability.[23]

Viscosity

The viscosity of the prepared gel was determined using a Brookfield digital viscometer. Spindle no. 6 was utilized at a rotational speed of 10 rpm and a temperature of 25°C. An ample quantity of gel was filled into a suitable wide-mouth container, ensuring that the gel level was adequate to allow for the immersion of the viscometer spindle.[23] Prior to measurements, the gel samples were allowed to settle for 30 minutes at a constant temperature of 25 ± 1°C. This settling period ensured uniformity and stability of the gel before viscosity measurements were taken.

Drug content

To determine the drug content, 1 gram of the prepared gel was mixed with 100 ml of ethanol. From this solution, aliquots of different concentrations were prepared through suitable dilutions after filtering the stock solution. The absorbance of these diluted solutions was measured at 222 nm using a spectrophotometer. The drug content was calculated using linear regression analysis of the calibration curve obtained from plotting the absorbance values against the known concentrations of the drug in the solutions. This allowed for accurate quantification of the drug content in the gel formulation.

Preparation of cellophane membrane for the diffusion studies:

A cellophane membrane of approximately 25 cm x 2 cm dimensions was selected and washed thoroughly under running water.[24] Subsequently, it was soaked in distilled water for 24 hours prior to its utilization in diffusion studies. This soaking period aimed to remove any residual glycerin present on the membrane. Once prepared, the membrane was mounted onto the diffusion cell for further experimentation.

Diffusion Studies:

The in-vitro diffusion of the drug from various gel preparations was investigated using a classical cylindrical tube designed in the laboratory, with a simple modification using a glass tube measuring 15 mm in internal diameter and 100 mm in height. In this setup, the diffusion cell

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membrane was coated with 1 gram of the formulation and securely fastened to one end of the tube, while the other end remained open to ambient conditions, serving as the donor compartment.

The diffusion cell was inverted and partially immersed in a 250 ml beaker containing freshly prepared neutralizing phosphate buffer with a pH of 7.4, acting as the receptor base. This system was maintained for 2 hours at a temperature of 37±0.5°C, with the media being stirred using a magnetic stirrer. At predetermined time intervals, aliquots of 5 ml volume were withdrawn and replaced with an equal volume of the receptor medium. These withdrawn aliquots were suitably diluted with the receptor medium and analyzed using a UV-Vis spectrophotometer at a wavelength of 222.0nm, with neutralizing phosphate buffer at pH 7.4 serving as the blank solution.[25]

Drug release kinetics study is a crucial aspect of pharmaceutical research and development that involves analyzing the release behavior of a drug from a dosage form over time. Various mathematical models are employed to describe and understand the drug release pattern.

Antimicrobial activity of microemulgel

The agar well diffusion method was employed for this investigation, focusing on Staphylococcus aureus as the target organism. Sterilized petri dishes were filled with the growth media and left undisturbed until solidification occurred. Following this, bacterial cultures were evenly spread across the media surface. Using a sterile cork borer, wells of 6mm diameter were carefully created in the petri dishes. Subsequently, the prepared formulations were introduced into the wells, allowing the drug to disperse within the media.

The petri dishes were then incubated for 24 hours at 37°C to facilitate bacterial growth and drug action. After incubation, the diameter of the zones of inhibition was visually assessed and measured using a ruler (in millimeters). The antibacterial activity of each formulation was evaluated in triplicate, and the mean value was recorded for analysis.[26]

Stability Studies

Stability studies were conducted in adherence to the guidelines set forth by the International Conference on Harmonisation (ICH). The optimal formulation (F1) was chosen for evaluation and stored in glass vials under three different conditions: 5°C, 25°C with 60% relative humidity (RH), and 40°C with 75% RH, for a duration of 3 months. Subsequently, the samples underwent physical examination, including visual inspection, and the pH of each sample was measured. Additionally, the drug content assay was performed to assess the stability of the formulation under the specified storage conditions.[27]

III. RESULTS & DISCUSSION

Initially, the prepared microemulsions underwent evaluation for various parameters. The four microemulsions exhibited translucency, with %Transmittance values ranging from 95.21±0.8 in E3 to 98.02±0.8 in E1. The pH ranged between 5.8 to 6.3 across the formulations. The highest % Drug content was observed in E1, at 95.49±1.2. Viscosity remained consistent across all formulations, with a value of 2042 ± 112.54 cps (Table 3).

Table 3: Characterization of microemulsion (A6)

Parameters	E1	E2	E3	E4
Visual observation	Translucent	Translucent	Translucent	Translucent
%Transmittance value	98.02±0.8	96.45±1.2	95.21±0.8	97.86±1.0 %
pH	6.3	5.8	6.0	6.2
% Drug content	95.49±1.2	88.82±1.4	93.45±0.8	94.62±1.2
Viscosity (cps)	2042 ± 112.54	2042 ± 112.54	2042 ± 112.54	2042 ± 112.54

Particle size and zeta potential analysis of the microemulsion revealed the lowest particle size in E4 at 90.16, whereas E2 exhibited a size of 92.76. Zeta potential ranged from -20.2 to -29.8 among the four formulations (Table 4).

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Table 4: Particle size and zeta potential of microemulsion

Parameters	E1	E2	E3	E4
Particle size (nm)	90.25	92.76	91.45	90.16
Zeta potential (mV)	-29.8	-20.2	-21.6	-29.8

Subsequently, the microemulgel formulations, obtained by incorporating the microemulsion into gel, were evaluated. The pH ranged from 5.7 to 6.5 among formulations F1 to F6 (Table 5). Viscosity varied significantly, with values ranging between 20162 and 42336 mPa.s. Notably, microemulgels containing 0.5% w/w carbopol exhibited the lowest viscosity, while those with 1.5% w/w concentration had the highest (Table 5 and figure 1). This observation aligns with literature, indicating an increase in viscosity with higher polymer concentrations, assuming other factors remain constant.

Table 5: pH and Viscosity of MUP microemulgel formulations

Formulation	pH	Viscosity (mPa)
F1	6.2	20162
F2	6.5	33140
F3	5.7	35987
F4	6.1	31560
F5	6.2	36311
F6	6.4	42336

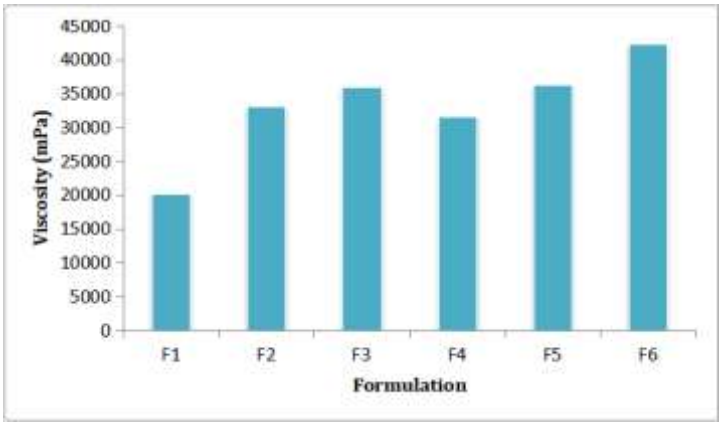

Figure 1: Viscosity of the formulated Microemulgels

The spreadability of Formulations F2, F4, F5, and F6 measured approximately 8.0 cm, a characteristic largely influenced by their polymer concentration. Spreadability was observed to be contingent upon both polymer concentration and viscosity. With an increase in polymer concentration, the viscosity of the formulations rose, leading to a reduction in spreadability. Enhanced spreadability of emulgels facilitates ease of application, consequently augmenting the available surface area for drug permeation (Table 6 and figure 2).

The average drug content of all formulations fell within the optimal range of 90-110%, as per regulatory guidelines. This range signifies the acceptable content uniformity for topical semi-solid dosage forms. Hence, the values obtained for Formulations F1 to F6 indicate satisfactory content uniformity (Table 6).

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Table 6: Spreadability of MUP microemulgel formulations

Formulation	Diameter (cm)	% Drug content
F1	8.5	98.12
F2	8.0	97.75
F3	7.0	96.74
F4	8.2	96.45
F5	7.8	95.67
F6	7.1	95.88

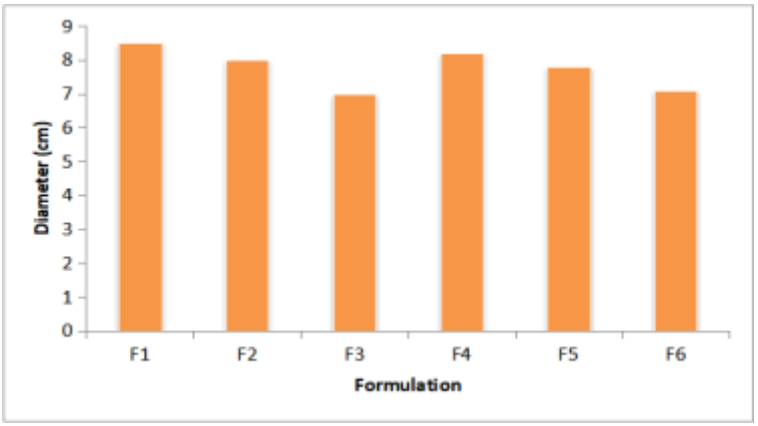

Figure 2: Spreadability of the formulated microemulgels of MUP

The release of the drug from its emulsified gel formulation followed the descending order: F1 > F2 > F4 > F3 > F5 > F6, respectively. Notably, Formulation F1, containing 0.5% w/w carbopol, exhibited the highest drug permeation after 4 hours, while Formulation F6, with 1.5% w/w carbopol, showed the lowest drug permeation. The concentration of carbopol in the formulation directly impacted drug permeation, with lower concentrations leading to higher permeation (Table 7 and Figure 3).

Table 7: Cumulative percentage of drug permeated

Time (min)	% Cumulative drug release						Marketed Formulation (Mupicip Ointment)
	F1	F2	F3	F4	F5	F6	
0	0	0	0	0	0	0	0
15	28.85	24.45	22.25	18.85	22.15	20.23	42.25
30	38.85	33.36	36.65	32.25	29.98	29.98	65.58
45	55.65	52.23	45.85	42.25	48.85	35.45	97.78
60	72.25	63.32	55.65	59.98	59.96	48.85	-
120	89.98	74.85	66.58	76.65	69.98	63.32	-
240	99.14	89.98	82.23	88.74	82.23	77.85	-

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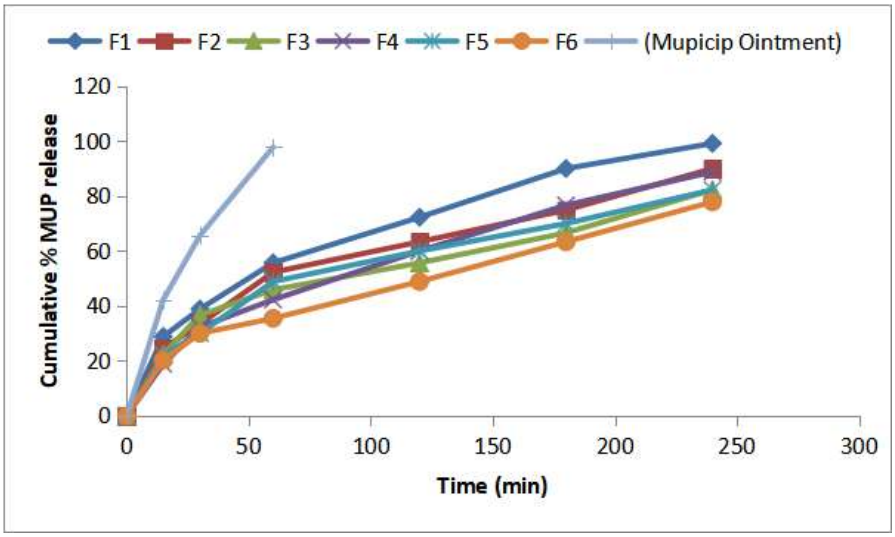

Figure 3: Cumulative percentage drug permeated as a function of time.

Furthermore, the formulated microemulgel demonstrated potent antimicrobial activity, as evidenced by zone of inhibition measurements of 14±0.5 mm, 10±0.74 mm, and 7±0.57 mm for concentrations of 100 µg/ml, 50 µg/ml, and 25 µg/ml, respectively (Table 8).

Table 8: Antimicrobial activity of microemulgel (Optimized formulation F1) against Staphylococcus aureus

Formulation	**Zone of inhibition (mm)**		
	100µg/ml	**50 µg/ml**	**25 µg/ml**
Microemulgel	14±0.5	10±0.74	7±0.57

Stability studies conducted on the best-selected formulation, F1, over a three-month period in accelerated stability conditions revealed promising results. Upon physical examination, Formulation F1 maintained its cream to off-white color, exhibiting translucency and homogeneity without any observable grittiness or phase separation. Importantly, there was no significant difference in % drug content between the initial and 3-month stability samples, indicating the stability of the formulated emulgels under accelerated conditions (Table 9).

Table 9: Stability studies at different conditions (F1)

Storage Conditions	**Formulation (F1)**	**Observations on storage for Drug content (%)**			
		Initial	**1 month**	**2 months**	**3 months**
4±1^{o}C	% Drug Content	100%	100%	99.82±0.41%	99.61±0.34%
	Appearance	Cream white	No change	No change	No change
	pH	6.5	6.5	6.5	6.5
25±2^{0}C and 60±5% RH	% Drug Content	100%	100%	99.73±1.6	99.54±1.3%
	Appearance	Cream white	No change	No change	No change
	pH	6.5	6.5	6.5	6.4
40±2^{o}C and 75±5% RH	% Drug Content	100%	99.65±2.7	99.38±3.1	99.14±1.6%
	Appearance	Cream white	No change	No change	No change
	pH	6.5	6.5	6.4	6.4

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IV. CONCLUSION

The current study found that the spontaneous emulsification approach can be employed to prepare micronized formulations. When characterized for physical appearance and drug release, an optimized formulation of microemulgel appeared to be superior to marketed mupirocin ointment. Based on in vitro and the created microemulgel enhanced the bioavailability of mupirocin, a poorly water soluble medication. Thus, our investigation confirmed that the microemulgel formulation can be employed for mupirocin topical formulation. Currently, there are just a few marketed microemulgel formulations on the market; nonetheless, it offers a huge arena for development and research. Microemulgels will have a wide range of applications in skin care in the future.

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