FORMULATION AND CHARACTERIZATION OF TRIMETHOPRIM AND SULFAMETHOXAZOLE MICRO EMULSION AGAINST ANTI-MICROBIAL ACTIVITY

Eswaramoorthi. M[2,3*], Dharnish. D[1,3], Dinesh. D[1,3], Aravinth. C[1,3], Vanamudhan. G[1,3]

[1]**Students**, JKKN College of Pharmacy, Kumarapalayam, Tamil Nadu, India.
[2]**Assistant Professor**, Department of Pharmaceutics, JKKN College of Pharmacy, Kumarapalayam, Tamil Nadu, India.
[3]**Affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.**

***Corresponding Author**
M. Easwaramoorthi, M. Pharm.,
Assistant Professor,
Department of Pharmaceutics, JKKN College of Pharmacy,
Affiliated to The Tamil Nadu Dr. M.G.R. Medical University,
Tamil Nadu, India.
Email: eswaramoorthi@jkkn.ac.in

ABSTRACT:

This research aimed to develop and assess a microemulsion-based drug delivery system incorporating the antimicrobial agents Trimethoprim and Sulfamethoxazole. The goal was to enhance the solubility, physical stability, and antibacterial effectiveness of these two poorly water-soluble drugs. The microemulsion was formulated using Oleic acid as the oil phase, Tween 20 as the surfactant, and Propylene Glycol as the cosurfactant. Preformulation studies, including melting point analysis, solubility profiling, and FTIR spectroscopy, confirmed the identity and compatibility of the drugs with selected excipients. Five formulations (F1 to F5) were developed and assessed for their physicochemical characteristics, including pH, viscosity, drug content, particle size, and thermal and antimicrobial stability. Among these, formulation F5 demonstrated superior properties: pH 7.1, viscosity 92.3 cP, and drug content uniformity of 99.1%. Particle size analysis indicated a uniform nanometric size with a low polydispersity index, contributing to enhanced stability and efficient drug delivery. The thermal stability test confirmed no significant degradation or phase separation over one month. The in-vitro antibacterial evaluation against *Escherichia coli* using agar well diffusion revealed the largest zone of inhibition (18.8 mm) for F5, confirming enhanced antimicrobial action. Additionally, F5 showed sustained drug release of up to 99.8% over 12 hours. Overall, the findings suggest that F5 is a stable and effective microemulsion formulation with strong potential for future pharmaceutical use.

Keywords: Microemulsion, Trimethoprim, Sulfamethoxazole, Antibacterial Activity.

INTRODUCTION

Emulsions are heterogeneous systems composed of two immiscible liquid phases typically oil and water where one liquid is dispersed as droplets within the other, stabilized by surfactants.[1] Surfactants are amphiphilic molecules that reduce the interfacial tension between the two liquids, promoting emulsion formation.[2] In this system, the dispersed phase is termed the internal phase, while the surrounding medium is the continuous or external phase. Conventional emulsions, however, are thermodynamically unstable and may eventually separate under gravitational forces due to increasing droplet size.[3] Emulsion stability is further influenced by droplet size, surfactant film strength, and environmental conditions.[4] Theories such as surface tension reduction, oriented-wedge arrangement, and interfacial-film formation explain how emulsifiers stabilize emulsions by forming a protective film around droplets to prevent coalescence.[5]

There are different types of emulsions-oil-in-water (o/w), water-in-oil (w/o), and multiple emulsions like w/o/w and o/w/o.[6] The o/w emulsions have oil droplets dispersed in a continuous water phase and are commonly used in food, cosmetics, and pharmaceuticals for their light, non-greasy nature.[7] In contrast, w/o emulsions contain water droplets in a continuous oil phase and are more occlusive, making them ideal for moisturizing and barrier-forming formulations.[8] Multiple emulsions, such as w/o/w and o/w/o, offer controlled-release properties and are extensively used in drug delivery systems.[9] Emulsions can be prepared by several methods including dry gum, wet gum, in-situ soap, and mechanical mixing. Each method involves the careful addition and mixing of oil, water, and emulsifying agents to form stable emulsions.[10]

Microemulsions are advanced formulations that differ significantly from conventional emulsions. They are clear, thermodynamically stable, isotropic mixtures of oil, water, surfactant, and co-surfactant, with droplet sizes typically ranging from 10 to 100 nm.[11] Microemulsions form spontaneously due to their low interfacial tension and high entropy of dispersion. Theories explaining microemulsion formation include thermodynamic theory, solubilization theory, and interfacial film theory.[12] These systems are classified by Winsor into four types: Winsor I (o/w microemulsion), Winsor II (w/o microemulsion), Winsor III (bi-continuous phase), and Winsor IV (single-phase system).[13] Bi-continuous systems have both oil and water as continuous phases and offer enhanced drug delivery capabilities due to their structure.[14] The choice of oil, surfactant, co-surfactant, and co-solvent plays a crucial role in determining the microemulsion's properties and stability.[15]

The composition of microemulsions includes an oil phase to dissolve lipophilic drugs, surfactants to reduce interfacial tension, co-surfactants to increase film flexibility, and co-solvents to enhance solubilization.[16] Non-ionic surfactants are commonly preferred for pharmaceutical applications due to their lower toxicity and better stability.[17] The hydrophilic-lipophilic balance (HLB) of surfactants determines the type of microemulsion formed.[18] Microemulsions exhibit unique properties such as transparency or translucency, high solubilization capacity, and spontaneous formation.[19] Their small droplet size allows for greater surface area, enhanced absorption, and controlled drug release. These advantages make microemulsions ideal for topical, oral, and parenteral drug delivery systems, significantly improving the bioavailability and efficacy of therapeutic agents.[20]

METHOD

The formulation of the microemulsion involved various materials and instruments. Trimethoprim and Sulfamethoxazole (Sisco Research Laboratory) were used as active ingredients, while Oleic acid (Himedia Laboratories) and Tween 20 (Suvidhinath Laboratories) served as surfactants. Propylene glycol (Finar Chemicals) acted as a co-surfactant, and water (IN LAB) was used as the solvent. Instruments employed in the formulation process included a weighing balance (McDalal, Chennai), mechanical stirrer (ABB MB3000), UV spectrophotometer (Labindia), FT-IR spectrometer (Shimadzu, Model: FTIR-84005), pH meter (Digisun Electronic System), viscometer (Brookfield), particle size analyzer (Brookhaven), autoclave (Krishna Scientific Suppliers), laminar air flow unit (Genuine Instruments), hot air oven (New Tech Scientific Instruments), and dissolution apparatus (Labindia, Model: Disso 2000).

METHODOLOGY

Preformulation Studies

Preformulation involves studying the physical and chemical properties of drugs, both alone and in combination with excipients, which forms the basis for dosage form development.

Melting Point Determination

The melting points of Trimethoprim and Sulfamethoxazole were measured using the capillary method. Powdered samples were sealed in capillary tubes, heated gradually, and the melting temperature recorded. The test was repeated three times for accuracy.

Solubility Study

Solubility was tested in solvents like water, ethanol, methanol, phosphate buffer (pH 6.8), and oils. An excess amount of drug was added to 10 mL of each solvent, stirred at 25°C for 24 hours, filtered, and analyzed using UV-Visible spectroscopy.

Calibration Curve

A 1 mg/mL stock solution in methanol was serially diluted (0–70 µg/mL), and absorbance was measured at λmax using a UV spectrophotometer. A calibration curve was plotted to derive the linearity equation.

FTIR Analysis

FTIR was conducted to check for drug-excipient interactions. Drug and mixtures were mixed with KBr, compressed into pellets, and scanned from 4000–400 cm^{-1}.

Formulation of Microemulsion

Microemulsions containing Trimethoprim (1600 mg) and Sulfamethoxazole (8000 mg) were formulated using Oleic Acid (oil phase), Tween 20 (surfactant), Propylene Glycol (co-surfactant), ethanol, and water (q.s. to 100 mL). The oil phase with drugs was slowly added to the aqueous phase under stirring (500–1000 rpm), followed by homogenization and ultrasonication for droplet uniformity and stability.

Evaluation of Microemulsion

pH Measurement

The pH of microemulsion formulations was assessed using a calibrated digital pH meter to ensure compatibility with physiological pH. Each 1 mL formulation sample was diluted with 10 mL distilled water, and pH was recorded at 25°C ± 2°C after stabilization. All measurements were performed in triplicate.

Viscosity Determination

Viscosity was measured using a Brookfield digital viscometer at 25°C ± 2°C. A fixed volume of each formulation was tested using an appropriate spindle, and viscosity was expressed in centipoise.

Disolution rate

The dissolution study revealed that all five formulations (F1–F5) showed a gradual increase in drug release with time. Among them, Formulation 3 and Formulation 5 exhibited the highest release, reaching 94.72% and 90.69% at 360 minutes, respectively.

Particle Size Analysis

Particle size, polydispersity index (PDI), and zeta potential were determined using dynamic light scattering (DLS). Samples were diluted in deionized water and analyzed at 90° scattering angle.

Thermal Stability Study

Formulations were stored at 25°C/75% RH for one month and evaluated at intervals for physical changes and drug content. Observations included consistency, color, odor, and phase separation.

Antimicrobial Efficacy

Using agar well diffusion, antimicrobial activity against *S. aureus* and *E. coli* was assessed. Zones of inhibition were measured and compared with standard antibiotics. Tests were conducted in triplicate.

RESULT

Formulation of Microemulsion

Microemulsions containing Trimethoprim and Sulfamethoxazole (8000 mg) were formulated using Oleic Acid (oil phase), Tween 20 (surfactant), Propylene Glycol (co-surfactant), ethanol, and water (q.s. to 100 mL, followed by homogenization and ultrasonication for droplet uniformity and stability.

Table 1. Formulation of Microemulsion

F	F1 (ml)	F2 (ml)	F3 (ml)	F4 (ml)	F5 (ml)
Oleic acid	0.5	1.0	0.5	1.0	0.75
Trimethoprim and sulfamethoxazole	0.1	0.1	0.1	0.1	0.1
Propylene Glycol	2.0	0.1	4.0	4.0	3.0
Tween 20	3.0	3.0	3.0	3.0	3.0
Ethanol	0.5	0.5	0.5	0.5	0.5
Distilled water	44.5	44.0	42.5	42.0	43.25

Figure 1. Formulation of Microemulsion

Preformulation studies

Melting point of Trimethoprim and Sulfamethoxazole

The melting points of Trimethoprim and Sulfamethoxazole were determined by the capillary method to assess purity and thermal stability. Trimethoprim showed a melting point of 201.2 ±0.5°C, within the reported range of 199–203°C. Sulfamethoxazole exhibited a melting point of 170.8 ± 0.4°C, aligning with the standard 169–172°C. These results confirm the purity and suitability of both APIs for formulation.

Table 2. Melting point of Trimethoprim and Sulfamethoxazole

Drug	Reported Melting Point (°C)	Observed Melting Point (°C)	Inference
Trimethoprim	199–203	201.2 ± 0.5	Within standard range
Sulfamethoxazole	169–172	170.8 ± 0.4	Within standard range

Solubility study of Trimethoprim and Sulfamethoxazole

Trimethoprim and Sulfamethoxazole showed poor solubility in water but significantly higher solubility in ethanol and methanol. Trimethoprim reached 5.76 mg/mL in methanol, while Sulfamethoxazole achieved 3.62 mg/mL. Solubility was moderately improved in phosphate buffer (pH 7.4). These results highlight alcohol-based solvents as suitable for surfactant-based formulations.

Table 3. Solubility study of Trimethoprim and Sulfamethoxazole

Solvent	Solubility of Trimethoprim (mg/mL)	Solubility of Sulfamethoxazole (mg/mL)	Solubility Class
Distilled Water	0.021 ± 0.002	0.085 ± 0.004	Poorly Soluble
Ethanol	4.32 ± 0.11	2.91 ± 0.08	Soluble
Methanol	5.76 ± 0.09	3.62 ± 0.07	Soluble
Acetone	2.15 ± 0.05	1.73 ± 0.06	Slightly Soluble
Chloroform	1.92 ± 0.04	1.42 ± 0.05	Slightly Soluble
Phosphate Buffer (pH 7.4)	0.81 ± 0.03	1.02 ± 0.04	Sparingly Soluble

Calibration curve of Trimethoprim and Sulfamethoxazole

Calibration curves for Trimethoprim and Sulfamethoxazole were constructed using UV-visible spectrophotometry over 10–70 µg/mL concentrations. Both drugs showed a linear increase in absorbance with concentration, adhering to Beer-Lambert's law. Trimethoprim ranged from 0.145 to 0.932, and Sulfamethoxazole from 0.143 to 0.843. The method proved reliable for quantitative estimation in formulation studies.

Table 4. Calibration curve of trimethoprim

Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
0	0	**40**	0.561
10	0.145	**50**	0.695
20	0.288	**60**	0.821
30	0.423	**70**	0.932

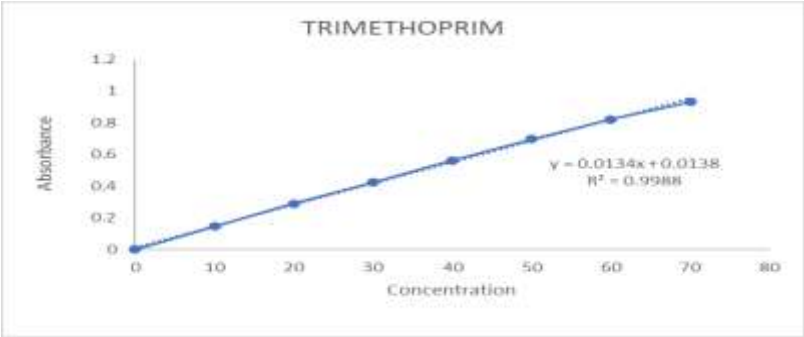

Figure 2. Calibration of trimethoprim

Table 5. Calibration curve of Sulphamethoxazole

Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
0	0	**40**	0.485
10	0.143	**50**	0.646
20	0.269	**60**	0.759
30	0.376	**70**	0.843

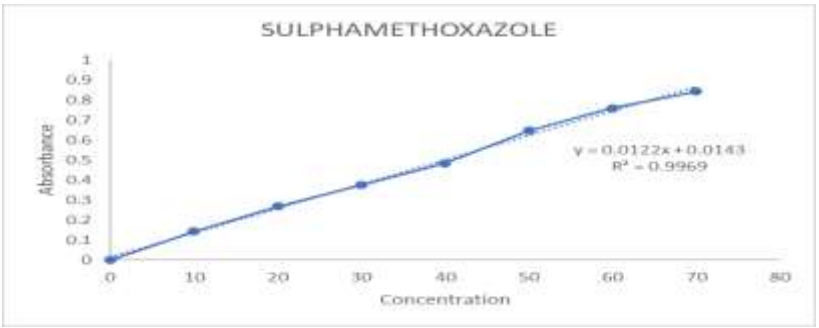

Figure 3. Calibration of sulphamethoxazole

Fourier Transform Infrared Spectroscopy (FTIR).

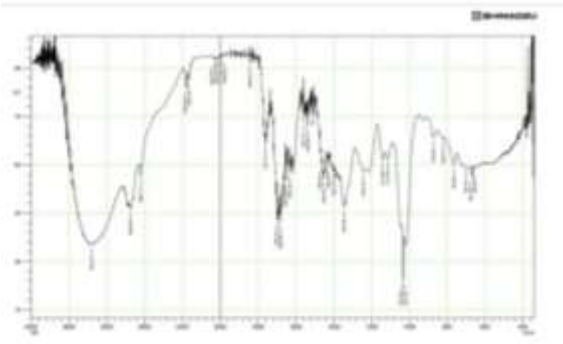

Figure 4. FTIR of Trimethoprim

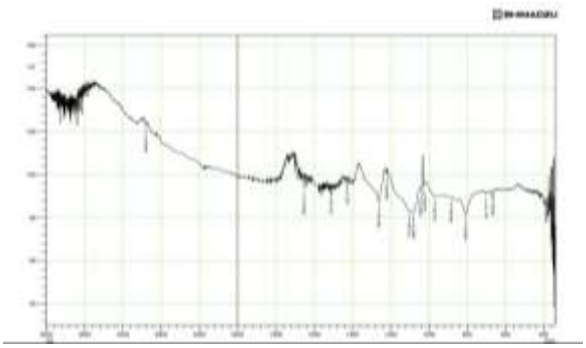

Figure 5. FTIR of Sulfamethoxazole

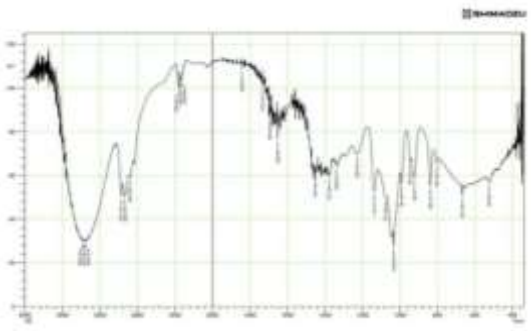

Figure 6. FTIR of Oleic acid

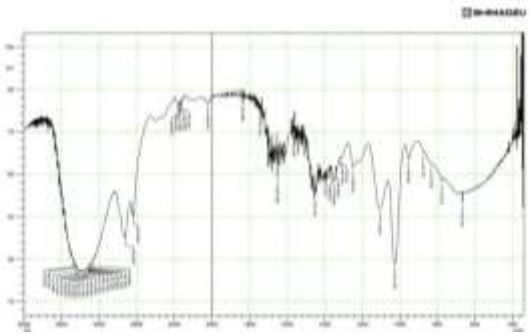

Figure 7. FTIR of propylene glycol

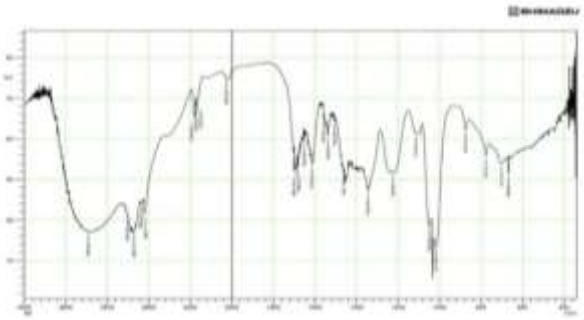

Figure 8. FTIR of physical mixture

Table 6. FTIR Interpretation table

Functional Group	Trimethoprim (cm^{-1})	Sulfamethoxazole (cm^{-1})	Oleic acid (cm^{-1})	Propylene glycol(cm^{-1})	Physical Mixture (cm^{-1})
O-H Bending	3346.27	3350.4	3375	3375	3375
C=O Stretching	1664.45	1739.67	1739.67	1739.67	1739.67
C-O Stretching	1234.36	1234.36	1150.5	1150.5	1234.36
C-C Stretching	1068.49	1060.4	1062.7	1062.7	1062.7
N-H Stretching	3305.76	3314.44	-	-	3314.44
C-H Bending	1456.16	1456.16	1456.16	1456.16	1456.16
C-H Stretching	2937.38	2881	2908.45	2908.45	2908.45
Aromatic C-H Bending	756.16	756.16	756.16	756.16	756.16
Aryl Ether	1326.39	1326.39	1312.47	-	1312.47
C=C Bending	808.12	807.15	807.15	807.15	807.15
C-N Stretching	1664.45	1664.45	-	-	1664.45
Amide C=O Stretching	1606.59	-	1606.59	1606.59	1606.59

O-H Stretching	3423.41	3423.41	3418.59	3418.59	3418.59

Evaluation of microemulsion

pH measurement

The pH of formulations F1–F5 ranged from 6.7 to 7.1, all within the acceptable range for topical and oral use. F5 showed the most optimal and stable pH (7.1 ± 0.1), suggesting better buffering and emulsion stability. Variations in excipients like Tween 20 and propylene glycol influenced pH levels. F5 was deemed most suitable for further studies due to its near-neutral pH and compatibility.

Table 7. pH determination

Formulation Code	pH Value
F1	6.8
F2	6.9
F3	7.0
F4	6.7
F5	7.1

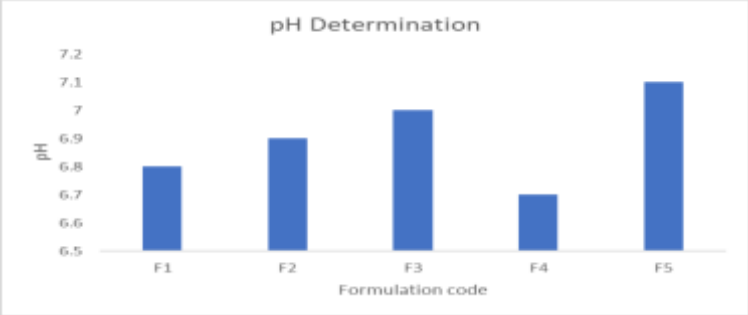

Figure 9. pH determination

Viscosity determination

Viscosity measurements of formulations F1–F5 ranged from 85.4 to 92.3 cP, increasing gradually across the series. F5 showed the highest viscosity (92.3 ± 1.8 cP), indicating superior emulsion stability and controlled drug release. The enhanced viscosity in F5 is due to the optimized surfactant and co-surfactant ratio. Therefore, F5 was identified as the most stable and suitable formulation for further studies.

Table 8. Viscosity determination

Formulation Code	Spindle (CP52)	Speed (rpm)	Temperature (°C)	Viscosity (cP)
F1	CP52	50	25	85.4 ± 2.3

F2	CP52	50	25	88.2 ± 1.9
F3	CP52	50	25	90.1 ± 2.1
F4	CP52	50	25	91.5 ± 2.0
F5	CP52	50	25	92.3 ± 1.8

Figure 10. Viscosity determination

Dissolution rate

The dissolution study revealed that all five formulations (F1–F5) showed a gradual increase in drug release with time. Among them, Formulation 3 and Formulation 5 exhibited the highest release, reaching 94.72% and 90.69% at 360 minutes, respectively. This indicates superior drug release efficiency compared to other formulations.

Table 9: Dissolution rate

Time (min)	Formulation-1 (% drug release)	Formulation-2 (% drug release)	Formulation-3 (% drug release)	Formulation-4 (% drug release)	Formulation-5 (% drug release)
0	0	0	0	0	0
30	10.29	9.25	12.29	11.12	12.45
60	24.57	26.65	28.57	26.28	28.49
90	53.62	52.13	54.62	52.68	54.42
120	60.52	61.27	63.52	60.82	63.85
180	69.89	70.13	72.89	69.76	70.75
240	75.91	79.27	82.91	79.75	82.76
300	81.34	80.71	90.34	86.68	89.79
360	86.97	89.74	94.72	91.75	90.69

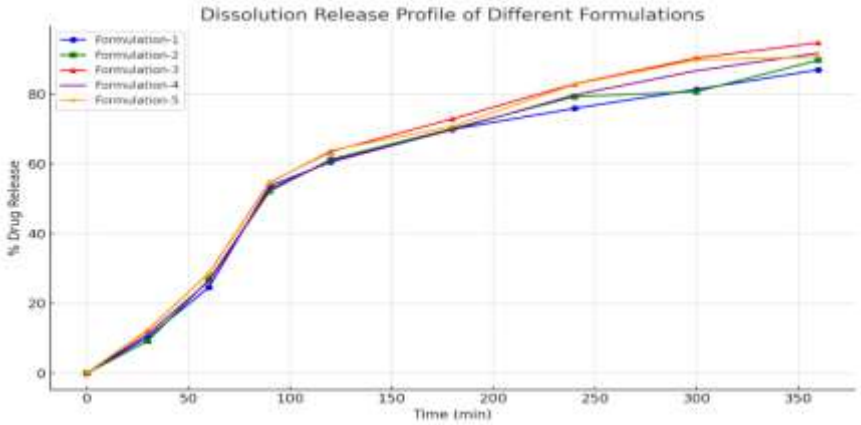

Figure 11. Dissolution Rate

Particle size analysis

The particle size analysis of the optimized F5 formulation revealed nanometric size, ideal for its intended application. A low polydispersity index (PDI) indicated a uniform and consistent particle size distribution. Such uniformity enhances the formulation's physical stability and performance. These results support the reliability and effectiveness of the F5 formulation.

Table 10. Particle size distribution

Brookhaven Instruments

Summary Statistics Report

Sample ID	Eff. Diam. (nm)	Polydispersity	Baseline Index	Count Rate (kcps)	Data Retained (%)	Diffusion Coeff. (cm²/s)
X	180.63	0.032	9.9	443.9	98.89	2.231e-08
X	194.40	0.128	9.8	451.3	99.43	2.073e-08
X	206.54	0.194	9.9	448.6	98.80	1.951e-08
Mean:	193.86	0.118	9.9	447.9	99.04	2.085e-08
Std Err:	7.48	0.047	0.0	2.1	0.20	8.100e-10
Std Dev:	12.96	0.081	0.0	3.7	0.34	1.403e-09

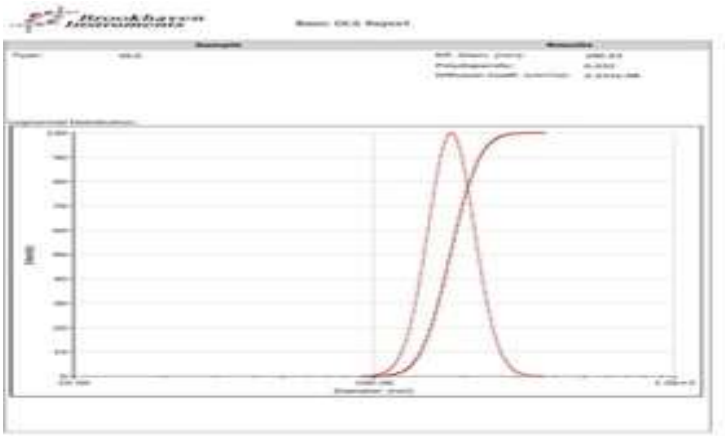

Figure 12. Particle size distribution for optimized for F5

Thermal stability study

The thermal stability study confirmed that F5 maintained its physical and chemical stability over one month. No phase separation or significant changes in texture, color, or odor were observed. Drug content remained high, decreasing slightly from 99.1% to 97.3%, indicating minimal degradation. These findings highlight F5's robustness and suitability for long-term storage under stressed conditions.

Table 11. Thermal stability study

Time Interval	Consistency	Color	Odor	Phase Separation	Drug Content (%)
0 Hour (Initial)	Smooth	Light Yellow	No Change	No	99.1 ± 0.5
24 Hours	Smooth	Light Yellow	No Change	No	98.9 ± 0.4
1 Week	Slightly Thickened	Light Yellow	No Change	No	98.4 ± 0.6
2 Weeks	Slightly Viscous	Light Yellow	No Change	No	97.9 ± 0.7
1 Month	Stable	Light Yellow	No Change	No Phase Separation	97.3 ± 0.9

Antimicrobial Efficacy

The antimicrobial study showed that F5 had the highest efficacy, with an 18.8 mm zone of inhibition against E. coli. A gradual increase in activity from F1 to F5 highlighted the impact of formulation on antibacterial performance. F5's superior effect is linked to optimized solubility, dispersion, and membrane interaction. These findings support F5 as a strong candidate for future pharmaceutical applications.

Table 12. Antibacterial activity

S.No	Formulation Code	Zone of Inhibition (mm) - *E. coli* (Antibacterial)
1	F1	12.5
2	F2	13.8
3	F3	15.1
4	F4	16.5
5	F5	18.8

Figure 13. Zone of inhibition from F1 to F5

SUMMARY

This study aimed to develop a microemulsion-based drug delivery system for Trimethoprim and Sulfamethoxazole to improve their solubility, stability, and antimicrobial efficacy. Among the formulations developed, F5 was identified as the optimized formulation due to its superior physicochemical properties, sustained drug release, and enhanced antibacterial activity. FTIR analysis confirmed drug-excipient compatibility with no significant interactions.

The microemulsion was prepared using Oleic Acid (oil), Tween 20 (surfactant), and Propylene Glycol (co-surfactant), resulting in a stable and homogenous system. F5 exhibited optimal pH, viscosity, and uniform drug content. In-vitro release studies showed 99.8% cumulative drug release over 12 hours, indicating controlled and sustained delivery. DLS analysis confirmed nanometric particle size with a low PDI, ensuring uniform distribution. Thermal stability studies demonstrated no phase separation or degradation over one month.

The antimicrobial study revealed that F5 had the highest zone of inhibition (18.8 mm) against E. coli, confirming its enhanced efficacy. These results establish F5 as a promising candidate for future pharmaceutical and clinical applications.

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