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Formulation and Evaluation of Topical Film Forming Roxithromycin Emulgel

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ABSTRACT

The study aims to develop and evaluate a topical film-forming nano emulgel containing Roxithromycin, an antibiotic targeting Staphylococcus aureus, the cause of impetigo in children. Pre formulation studies determined methanol as the best solvent for Roxithromycin, which has a melting point of 118°C. UV-Visible spectrophotometry identified a maximum absorption at 210 nm with an R^2 value of 0.9991. Solubility studies found Roxithromycin most soluble in black seed oil (43.2 mg/mL), Tween 80 (47.0 mg/mL), and ethanol (40 mg/mL). FTIR confirmed compatibility with excipients. The pseudo-ternary phase diagram indicated that a 1:1 ratio of Smix was optimal, forming a nano emulsion with 40% Smix, 10% oil, and 50% water. Among the formulations, F-II (10% oil, 40% Smix, 50% aqueous phase) was optimized, showing a particle size of 139.7 nm, a zeta potential of -20.2, a PDI of 0.372, drug content of 97.6%, and drug release of 91.2%. Five film-forming emulgels were prepared from this optimized nano emulsion using various polymer concentrations. Formulation FFE-II emerged as optimal, with a pH of 5.98, viscosity of 4079 cps, spread ability of 5.5 cm, extrudability score of 1, drug content of 98.2%, and drug release of 95.5%. Stability studies revealed not much variation in the properties of the emulgel, and release kinetics fit the first-order and Higuchi models with R^2 values of 0.8164 and 0.9725, respectively. Formulation FFE-III displayed clear, adhesive films with excellent properties and long retention time.

Keywords: Emulgel, Roxithromycin, Antibiotic, film forming, nano emulsion

INTRODUCTION

Impetigo primarily affects children and is commonly caused by either group A β-haemolytic streptococci or Staphylococcus aureus. Currently, S. aureus is the predominant pathogen in impetigo cases. Topical antibiotics are preferred for treatment, with roxithromycin emerging as a cost-effective option. [1]

Roxithromycin (ROX), classified as a BCS Class IV drug due to its poor solubility in water, exhibits a 50% absolute oral bioavailability. This acid-stable macrolide antibiotic shares structural similarities with erythromycin and demonstrates a similar antibacterial spectrum, effectively combating pathogens such as Staphylococcus aureus, Streptococcus pneumoniae, and Mycoplasma pneumoniae. Clinical trials confirm its efficacy in treating various infections, including respiratory tract, otolaryngological, genitourinary, and soft tissue infections. Despite its efficacy, conventional oral formulations face

challenges due to ROX's poor solubility and limited residence time in the gastrointestinal tract. To overcome these issues and enhance therapeutic outcomes, topical formulations are preferred, offering targeted treatment with improved drug delivery and reduced systemic side effects. [2,3]

The 2% concentration of roxithromycin produced stable topical drug delivery by effectively encapsulating different solid-state forms (crystalline and amorphous) into vesicle systems. Through comprehensive characterization and comparative release studies, it was demonstrated that vesicles containing roxithromycin in its amorphous forms exhibited improved topical delivery compared to the crystalline form. This targeted delivery ensured effective deposition of roxithromycin in the dermis, where its activity against bacteria. [4]

Topical drug delivery offers advantages over other routes by bypassing first-pass metabolism and avoiding systemic risks, particularly beneficial for treating localized conditions like skin diseases. However, conventional gel formulations face challenges in effectively delivering hydrophobic drugs. Emulgels, combining gel and emulsion properties, overcome this limitation, offering stability and enhanced patient acceptability for both lipophilic and hydrophilic drugs. They act as dual controlled-release systems, providing efficient drug delivery with minimal greasiness and rubbing.

In this context, topical film forming systems represent an innovative approach for treating skin diseases, providing both topical and transdermal treatment. By forming a film on the skin upon evaporation, these systems ensure sustained drug release and improved patient compliance. Utilizing a combination of hydrophilic and hydrophobic polymers, they offer advantages such as ease of application, reduced dosing frequency, and enhanced drug delivery compared to conventional dosage forms. [5, 6]

The study aims to develop and assess a topical film forming emulgel containing 2% roxithromycin, effective against Staphylococcus aureus, for treating impetigo, a common childhood skin infection.

MATERIALS & METHODS

PROCUREMENT OF DRUG AND EXCIPIENTS:

Roxithromycin Purchased from Yarrow Chemicals, Mumbai, India; Methanol, Glycerol Procured from Fisher Scientific, Mumbai; Castor Oil, Tea Tree Oil procured from Purenso Select, MP; Black Seed Oil Procured from Sun Pure Extracts, Delhi; Span 80, Tween 20, Tween 80 Procured from SDFCL Mumbai; Ethanol, Propylene Glycol Procured from Finar, Ahmedabad; Carbopol 934, HPMC, PVP Procured from RP Chemicals, Mumbai; Sodium Hydroxide, PHP Procured from S D Fin Chemicals, Mumbai.

PREFORMULATION STUDIES:

PHYSICOCHEMICAL PROPERTIES OF DRUG

Organoleptic properties:

Take a little quantity of the drug substance and spread it on a white surface. Examine it closely to see its color, smell it to check for its odor, and feel it to understand its texture. [7]

Solubility:

Test roxithromycin solubility by adding excess drug to 5 ml of water, ethanol, and methanol in conical flasks. Shake, filter, dilute, and analyze the concentrations using UV spectroscopy. [7]

Melting Point:

To determine the melting point of roxithromycin capillary tube method is used as per usp, noting the temperature at which the drug transitions from its original state to liquid. [7]

Determination Of Absorption Maxima (λmax):

A stock solution of roxithromycin at a concentration of 100 µg/ml in methanol was

prepared. This stock solution was then diluted with methanol to achieve the required concentrations. The uv spectra were recorded over the range of 200-400 nm spectrophotometrically, and the wavelength of maximum absorption was identified.

Calibration Curve Of Roxithromycin

Stock solution: (1000µg/ml) – dissolve 100 mg of roxithromycin in 100 ml of methanol.
Working standard solution: (100µg/ml) – pipette 5 ml from the 1000 µg/ml stock solution and dilute it to 10 ml with methanol Aliquots of 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml from the stock solution were pipetted into 10 ml volumetric flasks and diluted with methanol to yield concentrations of 5, 10, 15, 20, and 25 µg/ml, respectively. The absorbance at the λmax for each concentration was measured.

SOLUBILITY STUDIES:

Screening of Oil Phase, Surfactant & Cosurfactant: For screening, an excessive quantity of drug was mixed with 10 ml of various oils (olive oil, tea tree oil, black seed oil), surfactants (Span 80, Tween 20, Tween 80), and co-surfactants (glycerol, ethanol, propylene glycol) in 10 ml vials. After mixing with a cyclomixer, the solutions were centrifuged at 3000 rpm for 10 minutes, filtered, and analysed for UV absorbance at 210 nm following dilution with buffer. [8]

Emulsification Study of Oil by Surfactants: Water and surfactant were taken in equal ratio of 5:5. Subsequently, 2.5 mL of this solution was dispensed into individual glass vials. The oil phase, (i.e. the selected oil), was gradually added drop by drop to each vial while vigorously vertexing until the solution turned cloudy. The surfactant that successfully incorporated the highest quantity of oil was identified as most effective emulsifying agent. [8]

FTIR: DRUG – EXCIPIENT COMPATIBILITY STUDY:

FTIR analysis of pure drug Roxithromycin & excipients: FTIR analysis of pure Roxithromycin was performed using the K-Br pellet method, analyzing between 3500 and 500 cm^{-1}. Excipients, including black seed oil, Tween 80, and ethanol, were analyzed using the liquid spectra method between 5000 and 500 cm^{-1}.

FTIR analysis of pure roxithromycin drug along excipients - Black seed oil, Tween 80 & Ethanol: For the drug-excipient mixture, the FTIR analysis also used the liquid spectra method over the same range of wave numbers.[9]

CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM:

In this study, we employed the water titration method. Co surfactant and Surfactant are mixed in an equal ratio 1:1 ratio (Smix) and vortexed for 5 minutes. Various oil-to-Smix ratios (e.g., 1:9, 2:8) were tested by slowly adding water drop by drop until cloudiness or gel formation occurred, indicating the endpoint. The collected data was then analyzed using TernaryPlot.com to determine the "area of emulsification." [10]

PREPERATION OF EMULSION:

For the preparation of emulsion, concentrations of oil, water, surfactant, and cosurfactant were systematically varied as given in Table 1, maintaining a constant drug concentration. Weighed quantity of the roxithromycin was dissolved in black seed oil at a temperature of 60°C in a beaker, further the oily phase solution was cooled. The Smix was added to the distilled water respectively and *aqueous phase* was prepared. Oily phase was added to aqueous phase at 1000 rpm at 400 -500 C temperature. The final mixture was mixed by vertexing. To formulate nano emulsion the coarse emulsion was subjected to sonication by using probe sonuicator for 30 minutes to reduce the particle size.[8]

Table 1: Formulation Table Of 2% Roxithromycin Film Forming Emulsion

FORMULATION	*S Mix (ml)*	*Oil (ml)*	*Water (ml)*	*Drug (mg)*
I	16.12	1.72	5.16	200
II	9.85	2.35	10.80	200
III	10.17	4.22	8.60	200
IV	8.59	5.75	8.66	200
V	7.22	7.22	8.57	200
VI	5.21	7.15	10.64	200

Figure 1: Roxithromycin Emulsion Formulated

CHARACTERIZATION OF PREPARED ROXITHROMYCIN NANOEMULSION:

Particle Size, Polydispersity Index and Zeta Potential Analysis: The samples were measured using photon correlation spectroscopy with a ZetaSizer. Samples (1 ml) were analysed at 25°C with a 90° angle of scatter. Samples were further diluted & placed in cuvettes with electrodes for triplicate analysis. [8]

Drug Content: 1 ml of the emulsion was diluted with methanol in a volumetric flask and measured spectrophotometrically at 210 nm. A blank drug-free emulsion was used for calibration. [8]

In Vitro Diffusion Studies: In vitro diffusion studies were performed using a Franz Diffusion cell with a 6.8 pH receptor compartment and 10 mL of nano emulsion in the donor compartment. The temperature was maintained at 37 ± 0.5°C with stirring at 100 rpm. Aliquots (1 mL) were withdrawn at intervals, replaced with fresh buffer, and analyzed spectrophotometrically at 210 nm to calculate the cumulative drug release percentage.[8]

PREPARATION OF FILM FORMING EMULGEL

Gel solution: The gelling agent i.e. Carbopol was dispersed in water under constant magnetic stirring for about 30 minutes. The polymer solution the film-forming agents was dissolved in water with constant stirring. The prepared roxithromycin emulsion was poured into the gel solution with constant stirring, and to this the prepared polymer solution was added gradually in order to produce a homogenous solution. The emulsification was performed at 60°C. [11]

The details about amount of gelling agent & film forming agent used in each formulation are given in Table 2.

Table 2: Formulation Table Of 2% Optimized F - II Roxithromycin Film Forming Emulgel for Different Polymer Concentration

FORMULATION	**FFE - I**	**FFE - II**	**FFE - III**	**FFE - IV**	**FFE - V**
Roxithromycin optimized nano emulsion	2 %	2 %	2 %	2 %	2 %
Carbopol 934	2 %	2 %	2 %	2 %	2 %
HPMC E15	1 %	1.5 %	2%	2.5 %	3 %
PVP 30	1 %	1.5 %	2 %	2 %	2.5 %
Methyl Paraben	0.3 %	0.3 %	0.3 %	0.3 %	0.3 %
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.

EVALUATION OF ROXITHROMYCIN FILM FORMING EMULGEL

Physical Appearance: The prepared formulation was evaluated based on visual observations to determine its appearance, which was categorized as clear, opaque, or white. [11]

pH: 1 g of emulgel was dissolved in 100ml of distilled water in order to produce a clear solution, and this is measured for pH by utilizing digital pH meter. [11]

Viscosity: Viscosity was determined by using a Brookfield Viscometer by employing T-shaped spindle. [11]

Spreadability: The spread ability was assessed by using two glass slides. 0.5 g of the emulgel was placed in-between the slides, and initial diameter was measured. A 5 kg weight was then applied for 1 minute, and the resulting increase in diameter was recorded. [11]

Extrudability: The tubes were sealed, and the extruded emulgel strand was evaluated for continuity. A continuous strand was rated as 1, intermittent breaks as 2, and complete discontinuity as 3. [11]

Drug Content: 0.5 g of nanoemulgel was dissolved in phosphate buffer pH 6.8 i.e. 50ml and sonicate it for 10 minutes. The solution was filtered & measured spectrophotometrically at 210 nm using buffer as a blank. [11]

In Vitro Diffusion Studies: The studies were conducted using a Franz Diffusion cell with a cellophane membrane. 1g of emulgel was applied to the membrane between donor and receptor compartments filled with 25 mL of phosphate buffer (pH 6.8). The system was maintained at 37 ± 0.5°C with stirring at 100 rpm for 8 hours. Aliquots (1 mL) were taken at intervals, replaced with fresh buffer, and analyzed at 210 nm to determine the cumulative drug release percentage. [11]

Drug Release Kinetics: To understand the release mechanism of pharmaceutical dosage forms we estimate drug release kinetic. Four common models used to analyse drug release mechanisms are zero order, first order, Higuchi and Peppas equations. [11]

Zero Order Kinetics: The fraction of drug released (Q) is linearly related to time (t): $\mathbf{Q = k_0 t}$. A linear plot of drug release fraction versus time is plotted.

First Order Kinetics: Wagner's model suggests drug release from slow-release tablets follows apparent first-order kinetics, described by**:** $\mathbf{\ln(1 - Q) = -k_1 t}$ A linear plot of logarithm of remaining drug versus time indicates first-order kinetics.

Peppas-Korsemeyer Equation: This model refines the fit for drug release data: $\mathbf{Mt/ M \infty = k\ t^n}$. A linear plot of logarithm of drug release fraction versus the logarithm of time indicates the Peppas-Korsemeyer.

Higuchi Equation: This model shows a linear relation between drug released per unit surface area (Q) and square root of time: $\mathbf{Q = k_2 t^{1/2}}$. A linear plot of drug release versus square root of time indicates the Higuchi equation.

Stability Studies: Optimized formulations of roxithromycin emulgel underwent stability studies as per guidelines issued by ICH. Various parameters such as viscosity, spread ability, pH and drug content release were assessed before and after 30, 60, and 90 days. [11]

EVALUATION OF FILM FORMED FROM ROXITHROMYCIN FFE

Film Forming Time: To determine the film-forming time, 0.5 g of the emulgel was applied as a patch on the forearm of volunteer. The duration required for the emulgel to dry completely and form a film was recorded. Dryness was confirmed by placing a glass slide on the film without applying pressure; the film was considered

dry when no residue remained on the slide after removal. [11]

***Peel ability*:** Peel ability of the films was assessed by gently removing them from the skin and virtually evaluating their uniformity. The films peeled should be continuous and free of flakes.[11]

Tackiness: The tackiness of the film's outer surface was assessed by pressing cotton wool onto the dry film with light pressure. The degree of tackiness was classified based on the amount of cotton fibers left on the film, categorized as high, medium, or low. [11]

Physical Appearance: The appearance of the dried films was visually inspected and rated on a scale from 1 to 3. Films that were transparent, nearly invisible, and highly appealing were rated 1. Films that were opaque, slightly translucent with minor skin wrinkling, were rated 2. Films that were whitish, causing significant skin wrinkling and less attractive, were rated 3.[11]

RESULT & DISCUSSION

A. PHYSICO CHEMICAL PROPERTIES OF ROXITHROMYCIN:

Table 3: Physicochemical Properties of Drug

PHYSICO CHEMICAL TEST	*OBSERVATION*
Color	White
Odor	Odorless
Appearance	Crystalline Powder
Physical State	Solid

B. SOLUBILITY STUDIES:

Table 4: Solubility Studies of Drug

SOLVENTS	*SOLUBILITY (mg/ml)*
Water	0.5
Ethanol	40.1
Methanol	50.03

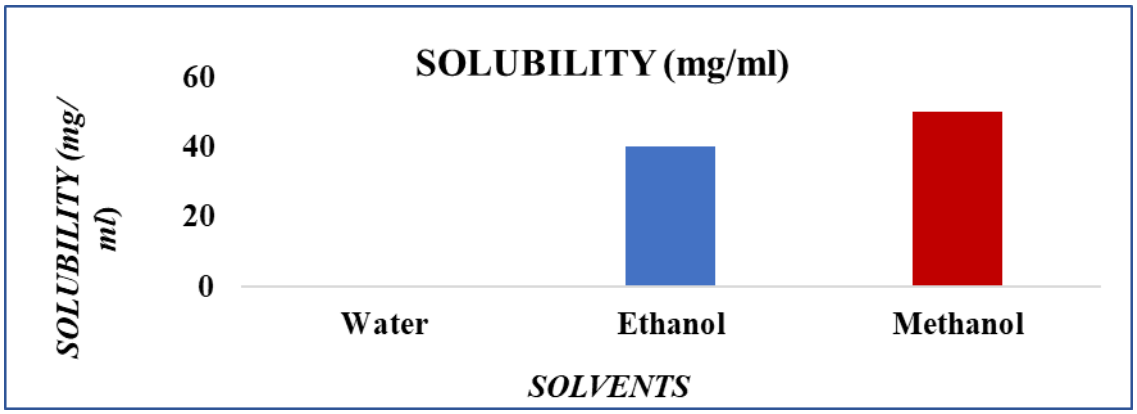


Figure 2: Solubility Profile of Roxithromycin in Solvents

OBSERVATION: Methanol exhibited the highest solubilizing potential for ROX followed by Methanol > Ethanol > Water.

C. MELTING POINT OF ROXITHROMYCIN:

Table 5: Melting Point of Drug

PURE DRUG	*STANDARD REFERENCE RANGE*	*OBSERVED RANGE*
Roxithromycin	115-120°C	118°C

OBSERVATION: The procedure for determination of melting point was conducted & ***the melting point was found to be 118°C*** i.e. within the standard reference range. Therefore, specifying the clarity of the obtained sample.

D. DETERMINATION OF ABSORPTION MAXIMA (λmax):

- ***UV- SPECTROSCOPIC ANALYSIS OF ROXITHROMYCIN***

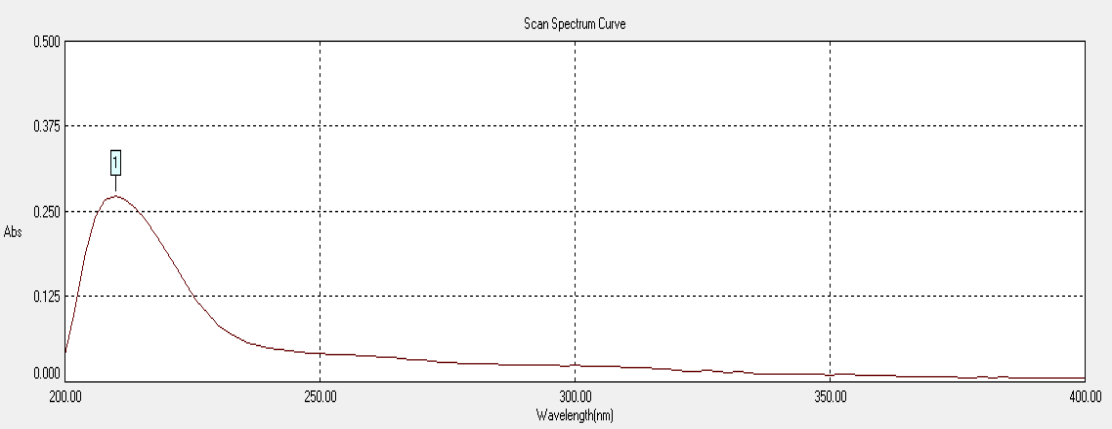


Figure 3: λmax for Roxithromycin

OBSERVATION*:** Roxithromycin drug solution with a concentration of 10 ug/ml underwent scanning within the wavelength range of 200-300 nm. ***The absorption spectrum exhibited sharpness, reaching its maximum intensity at 210 nm.

- **CALIBRATION CURVE OF ROXITHROMYCIN:**

Table 6: Calibration Curve Data

CONCENTRATION (µg/ml)	*ABSORBANCE nm*
0	0
5	0.119
10	0.211
15	0.319
20	0.436
25	0.534

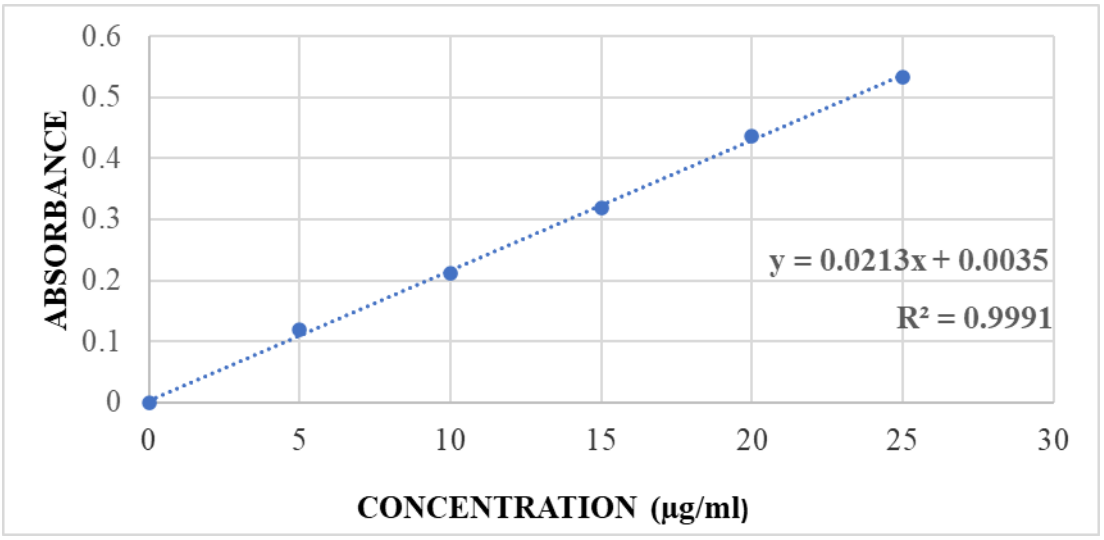


Figure 4: Calibration curve for Roxithromycin

OBSERVATION*:** The standard Roxithromycin graph demonstrated strong linearity, with an ***R^2 = 0.9991, signifying its adherence to the "Beer-Lambert" law.

E. SOLUBILITY PROFILE OF ROXITHROMYCIN IN OIL, SURFACTANTS & COSURFACTANTS:

Table 7: Screening Of Oils

OILS	*SOLUBILITY (mg/ml)*
Olive Oil	21.2
Tea Tree Oil	28.3
Black Seed Oil	43.2

Table 8: Screening Of Surfactants

SURFACTANTS	*SOLUBILITY (mg/ml)*
Span 80	42.0
Tween 20	33.2
Tween 80	47.0

Table 9: Screening Of Co Surfactants

CO SURFACTANTS	*SOLUBILITY (mg/ml)*
Glycerol	23.9
Ethanol	40
Propylene Glycol	21.7

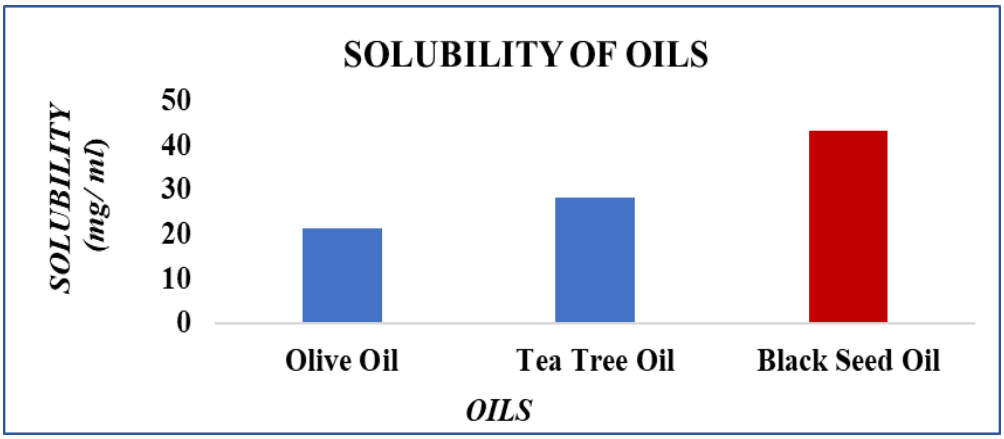


Figure 5: Solubility Profile of Roxithromycin in Oil

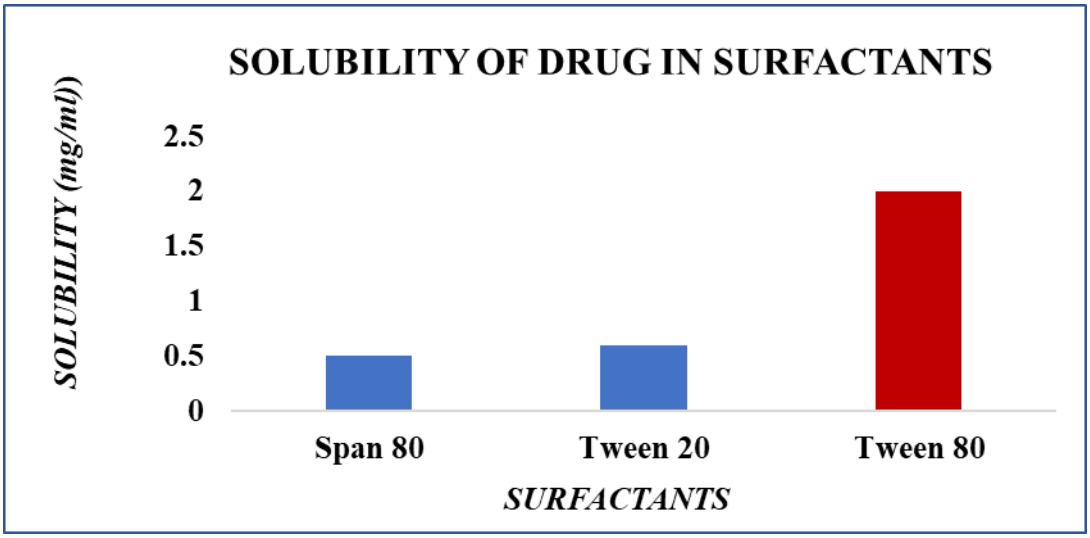


Figure 6: Solubility Profile of Roxithromycin in Surfactants

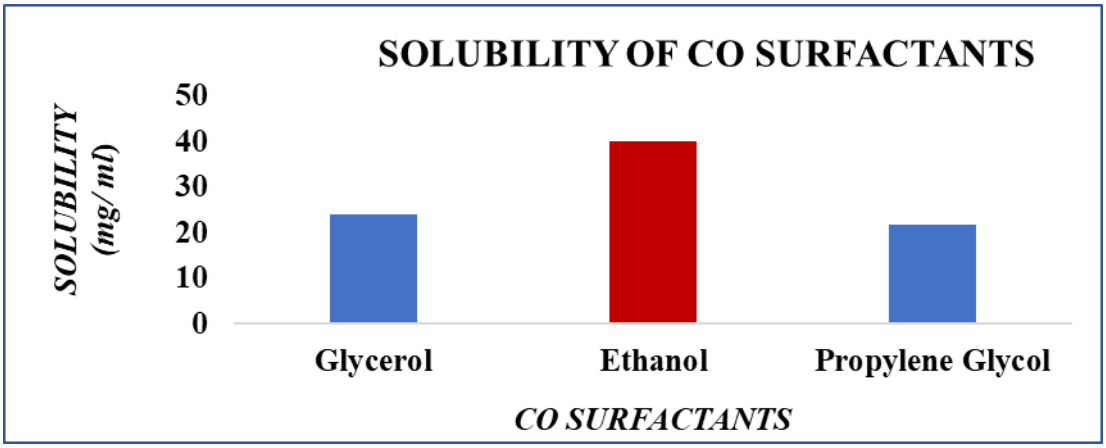


Figure 7: Solubility Profile of Roxithromycin in Co Surfactants

Among all the evaluated oils, the maximum solubility of ROX in oil was observed in Black Seed Oil (43.2 mg/ml).

Among all the evaluated surfactants, the maximum solubility of ROX in surfactant was observed in Tween 80 (47.0 mg/ml).

Among all the evaluated co surfactants, the maximum solubility of ROX in co surfactant was observed in Ethanol (40 mg/ml).

OBSERVATION*:** Therefore, ***Black Seed Oil as oil phase, Tween 80 as surfactant & Ethanol as co surfactant were chosen as they are best suitable for formulation of roxithromycin emulgel based on their solubility profile.

F. EMULSIFICATION STUDY OF OIL BY SURFACTANTS:

Table 10: Emulsification of Oil by Surfactants

SURFACTANTS	*AMOUNT OF OIL INCORPORATED (WITHOUT TURBIDITY) (ml)*
Span 80	0.5
Tween 20	0.6
Tween 80	2

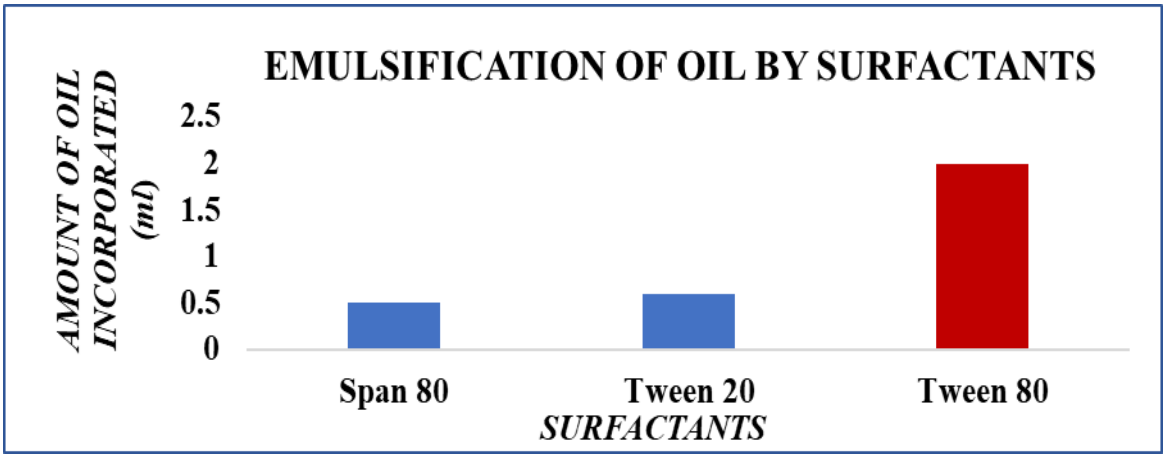


Figure 8: Emulsification of Oil by Surfactants

OBSERVATION*:** The surfactant which incorporated maximum amount of oil was selected as the best emulsifying agent. ***Therefore, as Tween 80 incorporated maximum amount of oil it was selected as the best emulsifying agent.

G. DRUG EXCIPIENT COMPATIBILITY – FTIR

Table 11: FTIR Spectra of pure roxithromycin drug

FUNCTIONAL GROUP	*PEAKS OF ROXITHROMYCIN(CM^{-1})*
C=O	1744.4
C=N	1498.4
O-H	3026.6
N-H	1602.8
S=O	1185.3

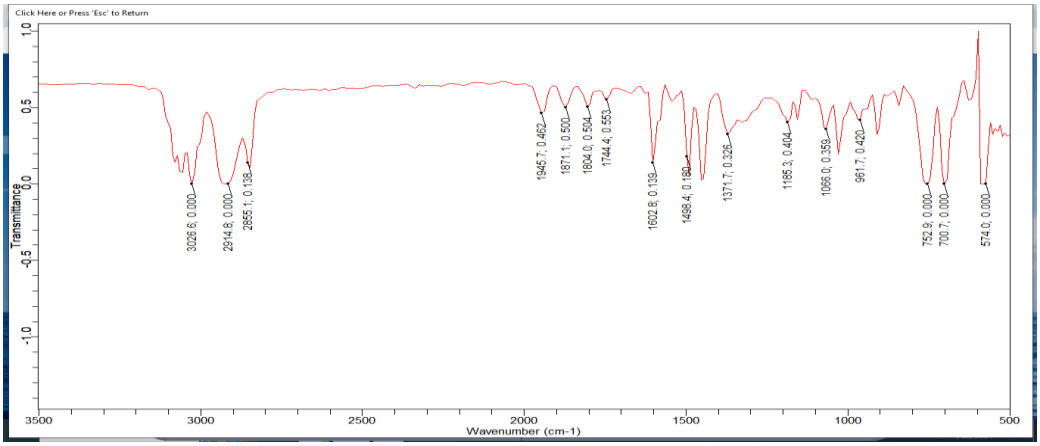
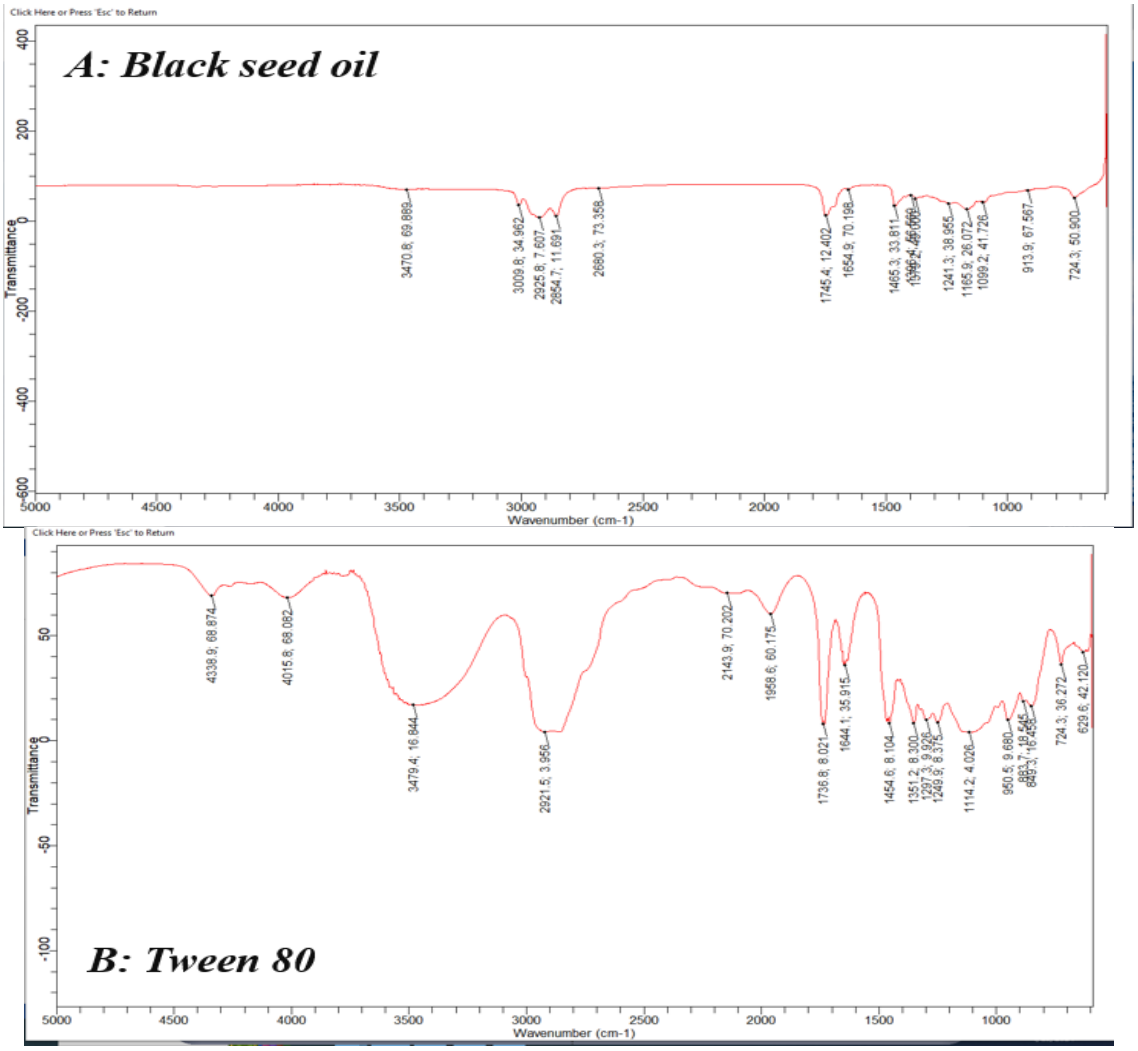


Figure 9: FTIR Spectra of pure roxithromycin drug



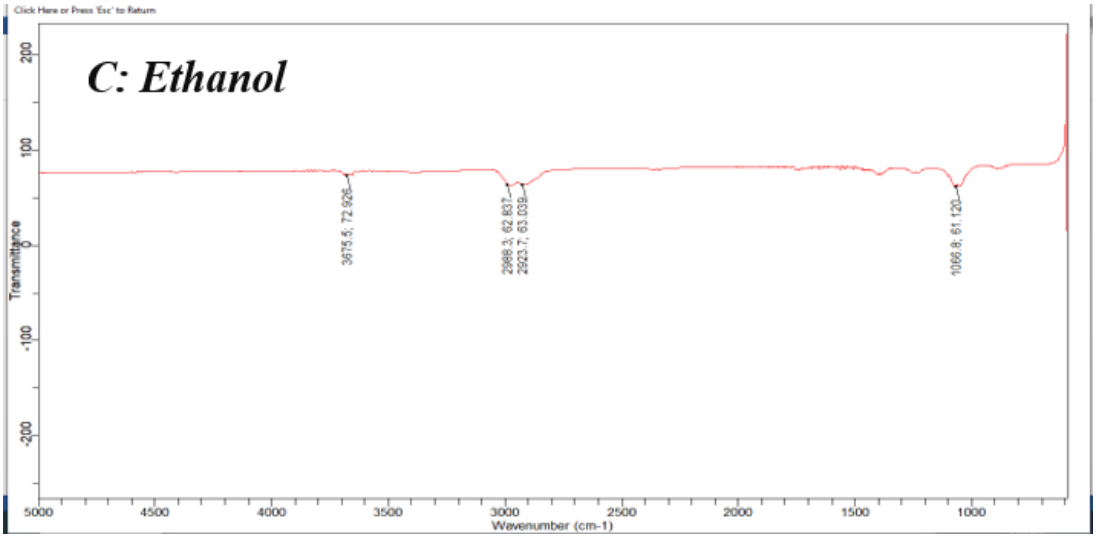


Figure 10: FTIR Spectra of Excipients – A: Black seed oil, B: Tween 80, C: Ethanol

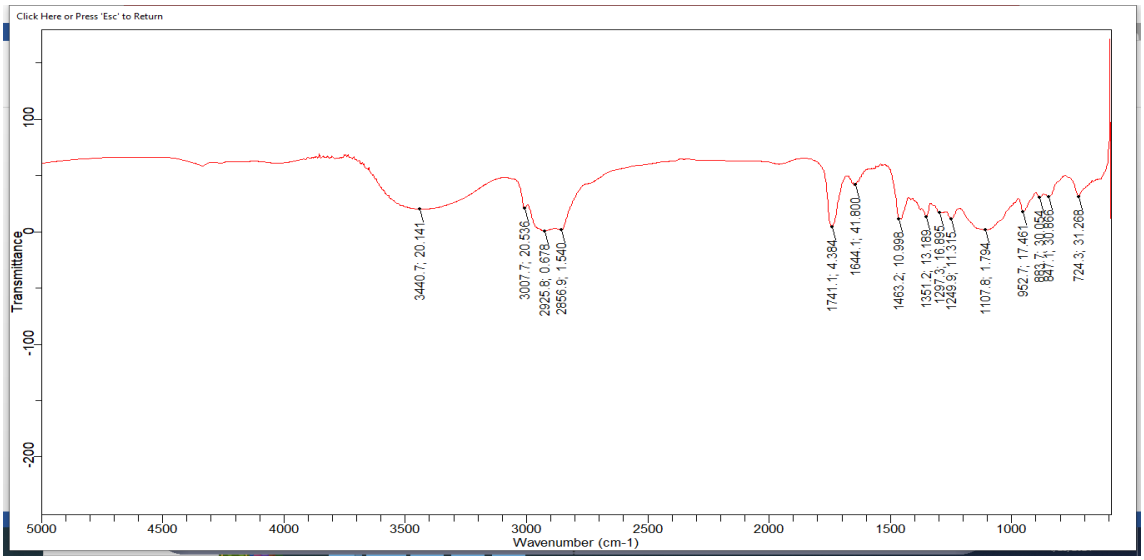


Figure 11: FTIR Spectra of pure drug along with Black seed oil, Tween 80 & Ethanol

Table 12: FTIR Spectra of pure roxithromycin drug with excipients

FUNCTIONAL GROUP	PEAKS OF ROXITHROMYCIN(CM^{-1})
C=O	1741.1
C=N	1463.2
O-H	3007.7
N-H	1644.1
S=O	1107.8

The analysis of the spectral data revealed that the main peaks of the drug closely matched across all physical mixtures with excipients, showing minimal variation. This indicates that the drug was uniformly dispersed within the excipients.

OBSERVATION*: *Therefore, confirming compatibility between the drug and excipients and stating the absence of any notable interactions.

H. PSEUDO TERNARY PHASE DIAGRAM:

The ternary phase diagrams constructed using surfactant and co-surfactant in 1:1 ratio exhibited large area of microemulsion. This ratio of surfactant and co surfactant was selected for microemulsion preparation. Concentration range of water, oil phase and

S mix was obtained from ternary phase diagram as given in Table 13.

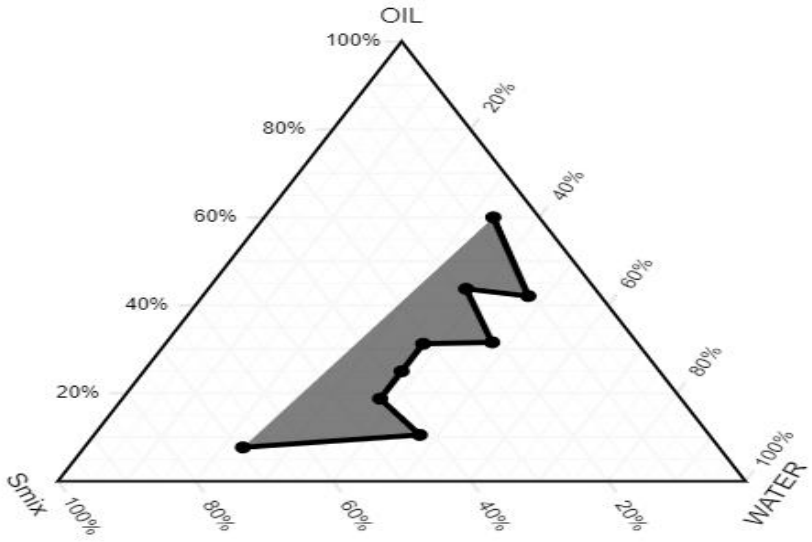


Figure 12: Pseudo Ternary Phase Diagram

Table 13: Formulation Of emulsion in %

S MIX	***OIL***	***WATER***
69.2	769	23.07
42.1	10.52	47.36
43.75	18.75	37.5
37.5	25	37.5
34.25	31.25	37.5
21.25	31.57	47.36

CHARCTERIZATION OF PREPARED ROXITHROMYCIN NAN0 EMULSION:

A. ***Particle Size:*** particle size of prepared Roxithromycin nano emulsions exhibited a size below 300 nm, rendering them suitable for topical administration. Notably, formulations F-II and F-V boasted the smallest particle sizes at 139.7 nm and 163.09 nm, respectively.

B. ***Zeta Potential:*** Stability was evidenced across the formulations, attributed to their zeta potentials, with formulation F-II displaying the highest stability (-20.2) and F-VI the least (-2.83).

C. ***Polydispersity Index:*** The polydispersity index of nearly all formulations fell within the acceptable range (<0.5), denoting formulation uniformity, barring F-IV, which exceeded the limit.

D. ***Drug Content Percentage:*** Formulations F-II and F-V showcased superior drug content percentages compared to others, at 97.6% and 95.3%, respectively.

Table 14: Characterization Of Nano emulsion Formulation

Parameters	***I***	***II***	***III***	***IV***	***V***	***VI***
Particle size (nm)	191.53	139.7	187.23	290.9	163.09	272.10
Zeta potential (mV)	-12.78	-20.2	-15.73	-4.18	-17.93	-2.83
PDI	0.415	0.372	0.434	0.810	0.402	0.20
Drug content (%)	92.2	97.6	73.6	72.1	95.3	86.1

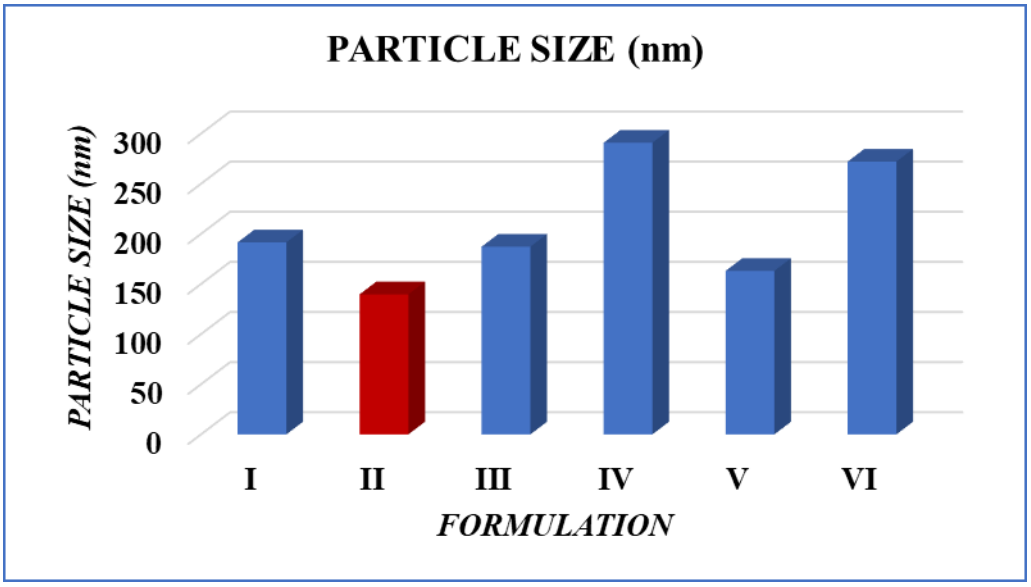


Figure 13: Particle Size of Prepared Roxithromycin Nano Emulsion (F I - F VI)

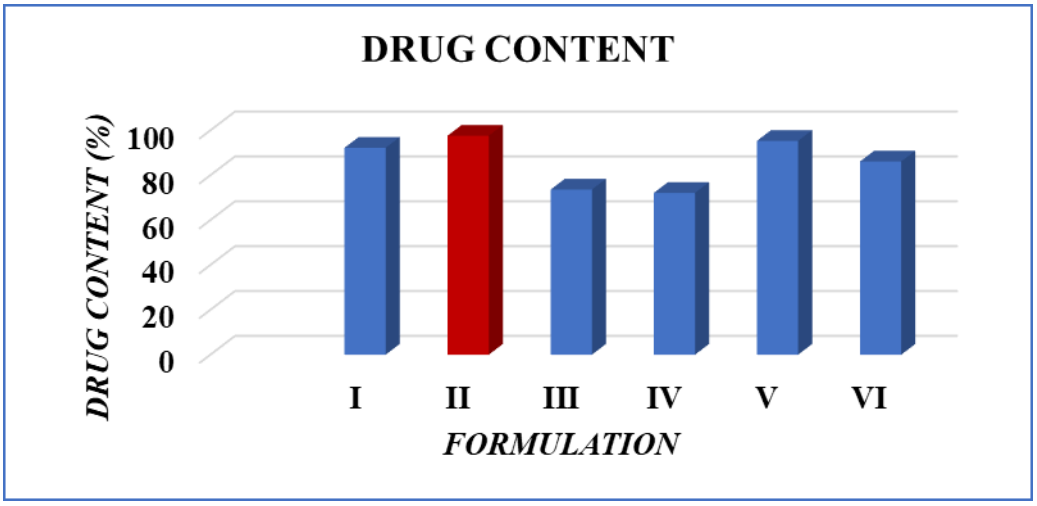


Figure 14: Drug Content of Prepared Roxithromycin Nano Emulsion (F I - F VI)

OBSERVATION: Of all the prepared formulation, owing to the particle size and percentage drug release, formulation ***F - II was found to be optimized formulation having particle size of 139.7 nm and drug release of 97.6%.***

E. IN VITRO DIFFUSION STUDIES:

Table 15: In vitro diffusion studies of FI - F VI Roxithromycin nano emulsion formulations in %

TIME (hr)	I	II	III	IV	V	VI
0	0	0	0	0	0	0
1	9.15	13.5	3.15	11.2	8.4	11.7
2	19.6	17.2	34.0	22.2	16.6	22.3
3	46.8	48.1	47.4	41.7	33.2	48.1
4	55.6	60.3	64.2	50.1	45	66
5	74.7	83.1	71.7	74.2	67.6	70.8
6	75	91.2	85.8	77.4	87.3	84.6

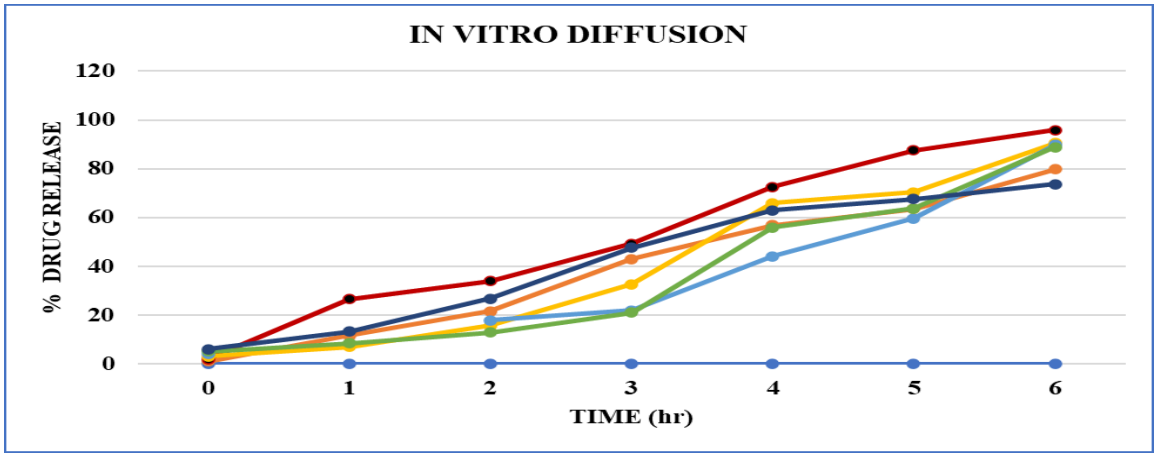


Figure 15: In Vitro Diffusion Studies of FI - FVI Roxithromycin Nano Emulsion formulations in percentage release

OBSERVATION: Maximum percentage drug release was found to be in formulation Roxithromycin F- II i.e. 91.2%

CHARCTERIZATION OF OPTIMIZED ROXITHROMYCIN NANO EMULSION

A. *PARTICLE SIZE OF OPTIMIZED ROXITHROMYCIN NANO EMULSION (F - II)*

Measurement Results

Date	:	10 July 2024 14:57:16
Measurement Type	:	Particle Size
Sample Name	:	ROX Nano Emulsion-1-SIZE
Scattering Angle	:	173
Temperature of the holder	:	25.0 deg. C
T% before meas.	:	17
Viscosity of the dispersion medium	:	0.894 mPa.s
Form Of Distribution	:	|Standard|
Representation of result	:	Scattering Light Intensity
Count rate	:	1697 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	148.4 nm	39.0 nm	142.1 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	148.4 nm	39.0 nm	142.1 nm

Histogram Operations

Size (Median)	:	142.5 nm
Mode	:	142.1 nm
% Cumulative (1)	:	5.0 (%) - 95.0 (nm)
% Cumulative (2)	:	10.0 (%) - 101.8 (nm)
% Cumulative (3)	:	20.0 (%) - 112.7 (nm)
% Cumulative (4)	:	30.0 (%) - 122.6 (nm)
% Cumulative (5)	:	40.0 (%) - 132.3 (nm)
% Cumulative (6)	:	50.0 (%) - 142.5 (nm)
% Cumulative (7)	:	60.0 (%) - 153.5 (nm)
% Cumulative (8)	:	70.0 (%) - 166.3 (nm)
% Cumulative (9)	:	80.0 (%) - 182.4 (nm)
% Cumulative (10)	:	90.0 (%) - 205.0 (nm)

Cumulant Operations

Z-Average	:	139.7 nm
PI	:	0.372

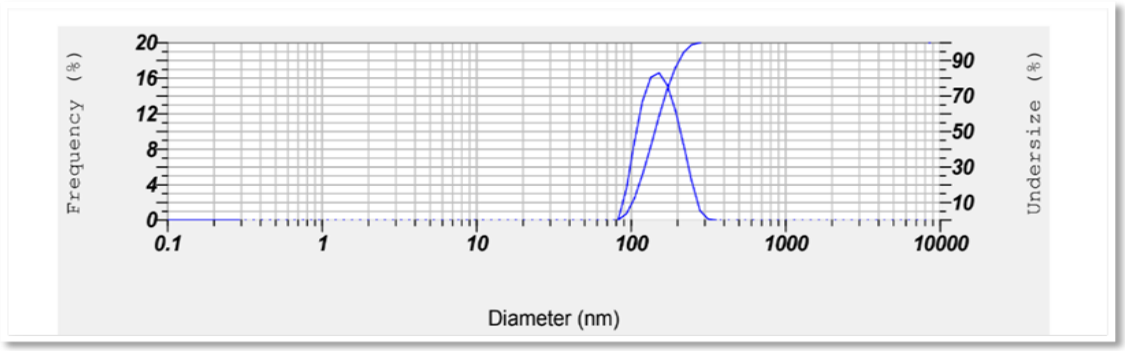


Figure 16: Particle Size of Optimized Roxithromycin Nano Emulsion (F - II)

B. ZETA POTENTIAL OF OPTIMIZED ROXITHROMYCIN NANO EMULSION (F - II)

Measurement Results

Measurement Results

Date	:	11 July 2024 12:06:08
Measurement Type	:	Zeta Potential
Sample Name	:	ROX Nano Emulsion-1-ZETA
Temperature of the holder	:	25.0 deg. C
Viscosity of the dispersion medium	:	0.894 mPa.s
Conductivity	:	0.376 mS/cm
Electrode Voltage	:	3.3 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-20.2 mV	-0.000157 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean)	:	-20.2 mV
Electrophoretic Mobility mean	:	-0.000157 cm^2/Vs

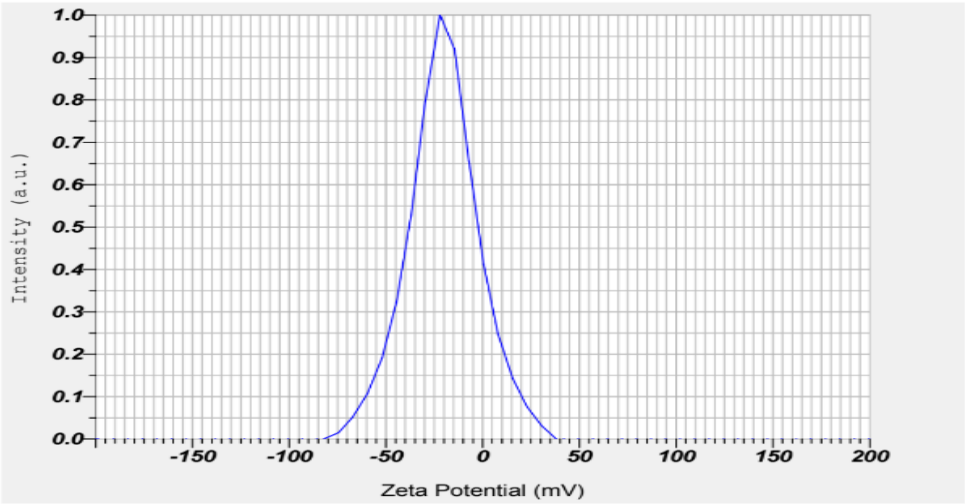


Figure 17: Zeta Potential of Optimized Roxithromycin Nano Emulsion (F - II)

C. SURFACE MORPHOLOGY OF OPTIMIZED ROXITHROMYCIN NANO EMULSION (F - II)

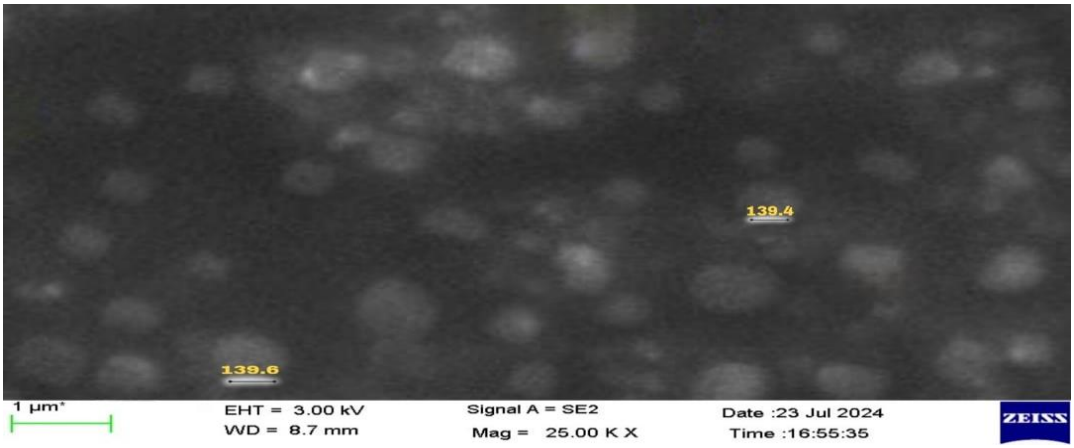


Figure 18: SEM of Optimized Roxithromycin Nano Emulsion (F - II)

EVALUATION OF OPTIMIZED ROXITHROMYCIN FILM FORMING EMULGEL

A. PHYSICO CHEMICAL PROPERTIES OF OPTIMIZED ROXITHROMYCIN EMULGEL

Table 16: Physicochemical properties of Roxithromycin Emulgel

PARAMETERS	*FFE - I*	*FFE - II*	*FFE - III*	*FFE - IV*	*FFE - V*
Appearance	White	White	White	White	White
pH	6.5	5.9	7.2	6.2	7.6
Viscosity (cps)	5400	4079	3735	4703	5523
Spread ability (cm)	2.5	5.5	3.2	4.6	5.1
Extrudability	2	1	2	3	2

OBSERVATION: The developed Roxithromycin emulgels exhibited a transparent appearance, demonstrating homogeneity and absence of aggregates across all formulations.

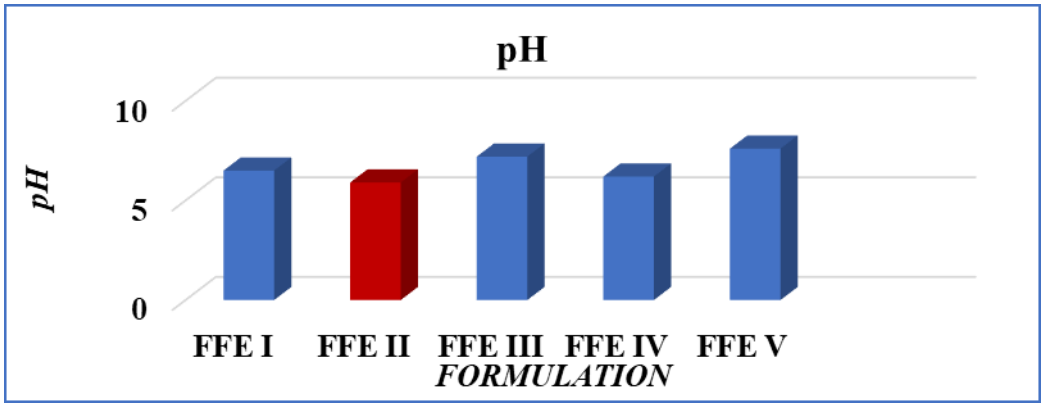


Figure 19: pH of Prepared Roxithromycin Emulgel

OBSERVATION: The pH levels of the prepared nanoemulgels ranged from 5.98 to 7.6, closely aligning with the skin's pH affirming the non-irritant nature of the emulgels.

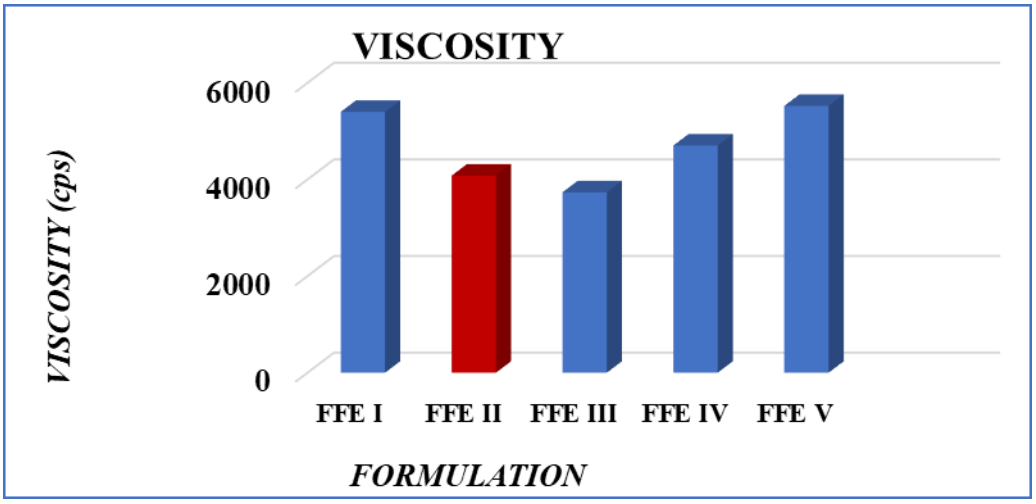


Figure 20: Viscosity of Prepared Roxithromycin Emulgel

OBSERVATION: Given the oil-in-water emulsion nature of the formulation, viscosity was notably low, facilitating rapid drug release. Notably, formulation FFE - II displayed medium viscosity compared to others.

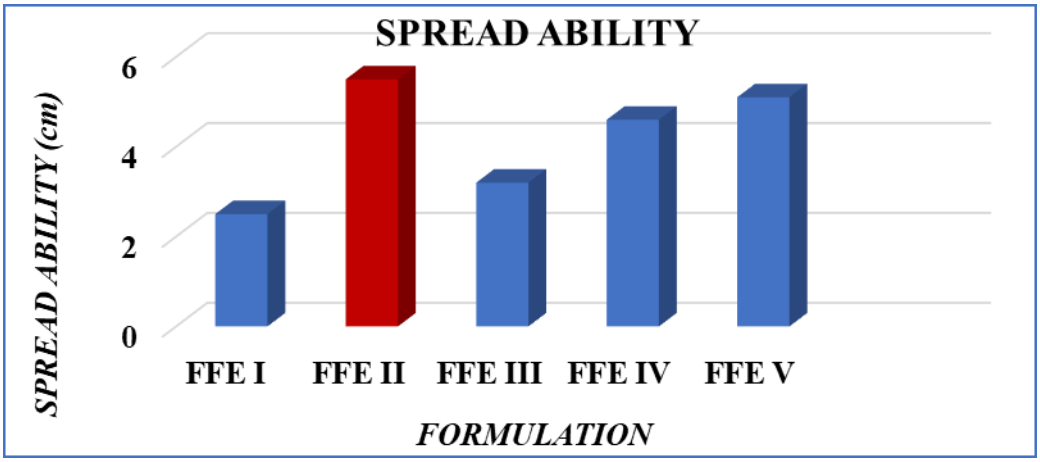


Figure 21: Spread ability of Prepared Roxithromycin Emulgel

OBSERVATION: The spread ability of different emulgel formulations was quantified, with diameters ranging from 3.2 g.cm/s to 5.5 g.cm/s, indicative of varying degrees of spread ability.

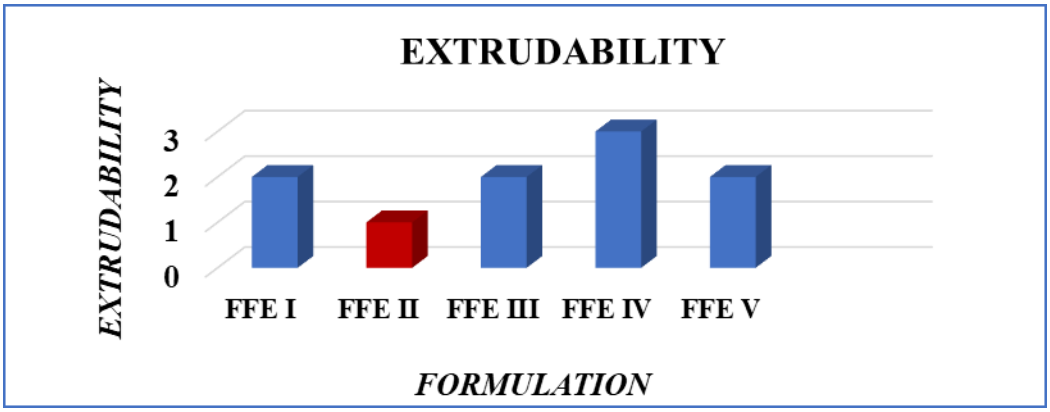


Figure 22: Extrudability of Prepared Roxithromycin Emulgel

OBSERVATION: With the exception of FFE – IV, remaining formulations demonstrated satisfactory extrudability.

B. DRUG CONTENT

TABLE 17: Drug Content of Roxithromycin formulations in %

Parameters	**I**	**II**	**III**	**IV**	**V**
Drug Content (%)	88.98	98.2	90.8	84.9	76.5

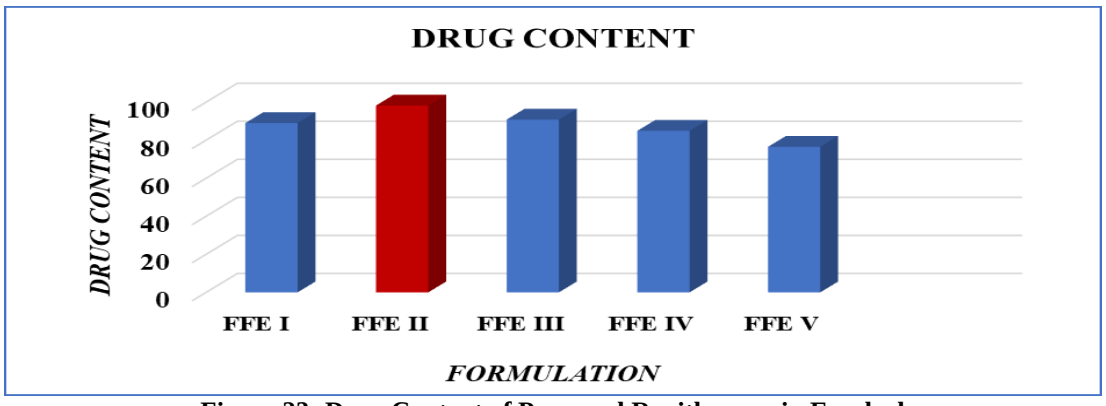


Figure 23: Drug Content of Prepared Roxithromycin Emulgel

OBSERVATION: The measured drug content of the Roxithromycin emulgel was assessed to be between 76.5 – 98.2%, indicating commendable uniformity in content.

C. IN-VITRO DIFFUSION STUDIES

Table 18: In vitro diffusion studies of Roxithromycin formulations in %

TIME (hr)	FFE - I	FFE - II	FFE - III	FFE - IV	FFE - V
0	0	0	0	0	0
1	5.9	4.9	6.7	8.5	13.2
2	11.7	12.7	15.6	12.92	26.8
3	19.8	26.5	22.5	21.6	47.6
4	21.6	33.9	29.9	49.8	50.33
5	42.9	49.2	32.6	55.9	62.98
6	56.9	72.65	65.9	63.7	67.5
7	63.5	87.4	70.3	77.9	70.5
8	79.87	95.5	90.5	88.8	73.6

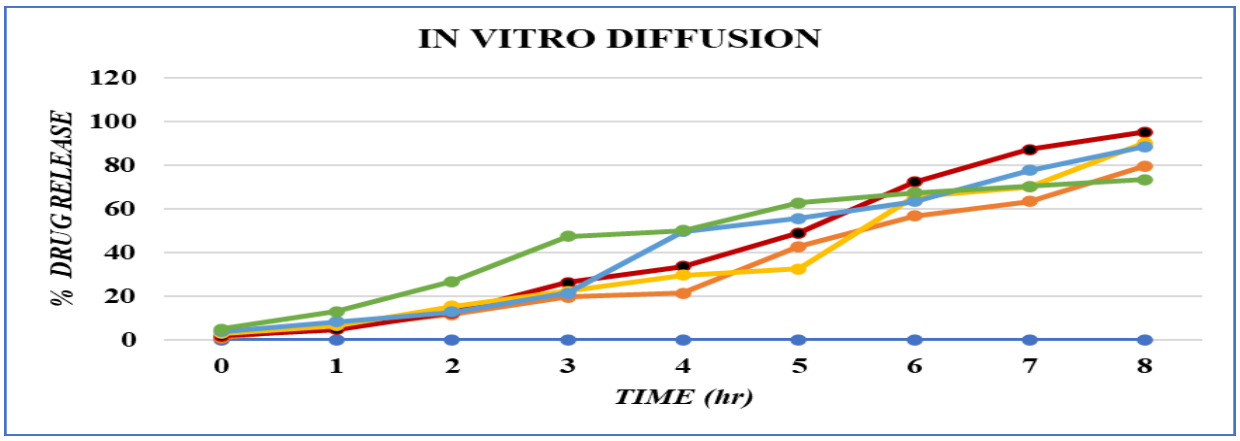


Figure 24: In Vitro Diffusion Studies of FI - F V Roxithromycin formulations in percentage release

OBSERVATION: The release profile of the different formulations assessed where FFE-II formulation showed the highest release profile i.e. 95.5%

D. EVALUATION OF OPTIMIZED ROXITHROMYCIN FILM FORMING EMULGEL

Table 19: Summary of Optimized Roxithromycin Nanoemulgel FFE- II

Evaluation	Results
Appearance	White
pH	5.92
Viscosity (cps)	4079
Spread ability (cm)	5.5
Extrudability	1
Drug content (%)	98.2
In vitro drug release (%)	95.5

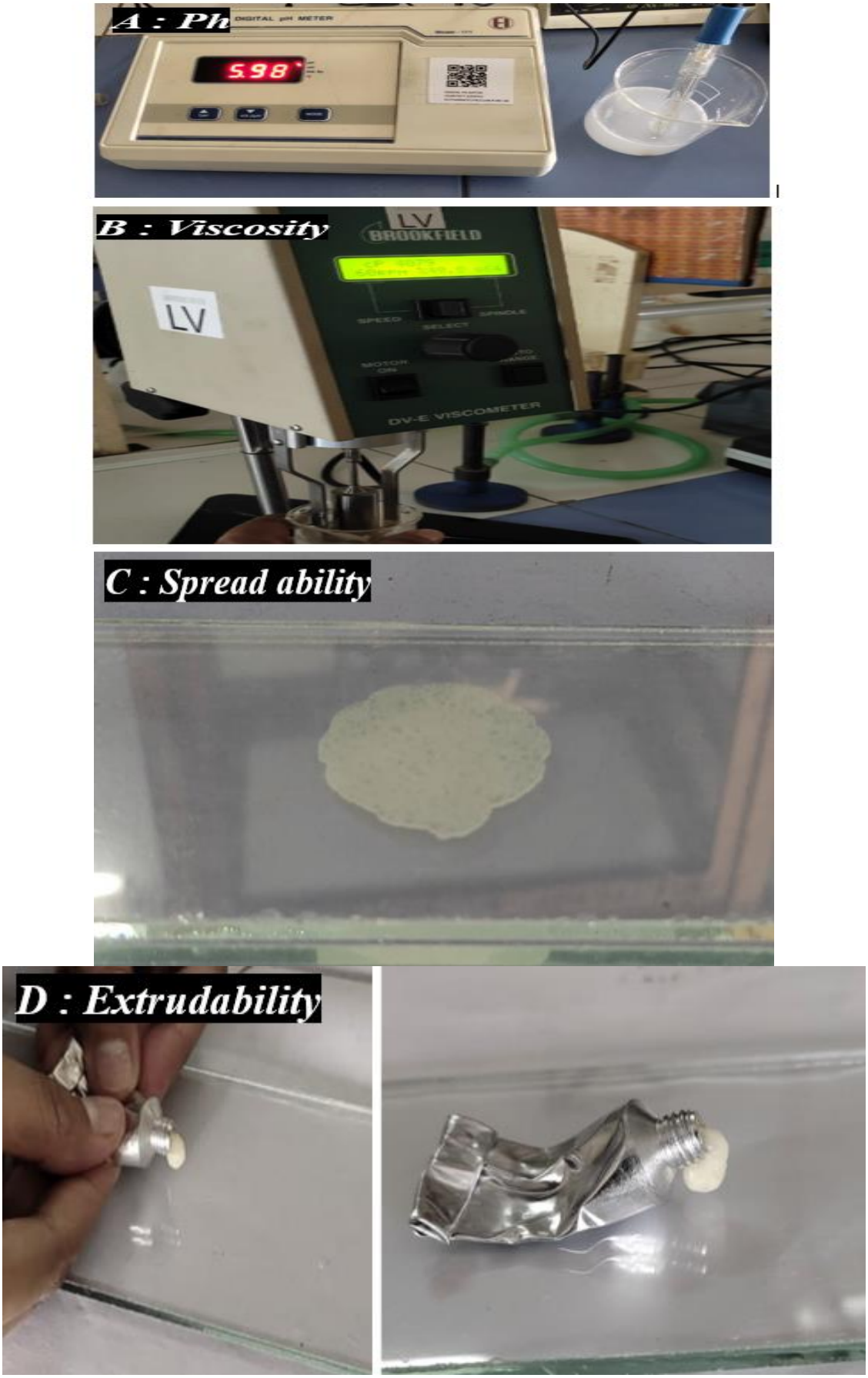


Figure 25: Optimized Roxithromycin Nanoemulgel Evaluations
A: Ph; B: Viscosity; C: Spread ability; D: Extrudability

OBSERVATION:

After evaluating various formulation parameters such as pH, viscosity, spread ability, extrudability, drug content, and in vitro diffusion, formulation FFE - II emerged as the optimized formulation. It maintained a skin-friendly pH of 5.9, exhibited a viscosity of 4079 cps, which signifies its rheological behavior. With a spread ability of 5.5cm, it ensures ease of application, crucial for patient compliance. Additionally, its extrudability scored 1, indicating the extrusion of continuous strands, the drug content was measured at 98.2% and showed highest release profile of 95.5%.

E. RELEASE KINETICS OF OPTIMIZED FORMULATION (FFE-II)

Table 20: Release kinetics of optimized formulation

Cumulative % Drug Release	Time (hrs)	Root (T)	Log Cumulative % Release	Log (T)	Log (%) Remaining	Release Rate	I / Cumulative % Release	Peppas Log Q / 100	% Drug Remaining	Q_0 1/3	Q_t 1/3	$Q_0^{1/3} - Q_t^{1/3}$
0	0	0	0	0	2.00	0	0	0	100	4.642	4.642	0
4.9	1	1	0.69	0	1.97	4.9	0.037	-1.31	95.1	4.642	1.698	2.943
12.7	2	1.41	1.10	0.301	1.94	7.8	0.079	-0.89	87.3	4.642	2.333	2.308
26.5	3	1.73	1.423	0.477	1.866	26.5	0.037	-0.57	73.5	4.642	2.978	1.664
33.9	4	2	1.530	0.602	1.820	16.95	0.029	-0.46	66.1	4.642	3.216	1.426
49.2	5	2.23	1.691	0.698	1.705	16.4	0.020	-0.30	50.8	4.642	3.652	0.99
72.6	6	2.44	1.861	0.778	1.436	18.16	0.013	-0.13	27.4	4.642	4.160	0.482
87.4	7	2.6	1.941	0.845	1.100	17.48	0.011	-0.05	12.9	4.642	4.448	0.194
95.5	8	2.8	1.980	0.903	0.653	15.9	0.010	-0.01	4.5	4.642	4.564	0.078

Figure 26: Zero Order Release Kinetics

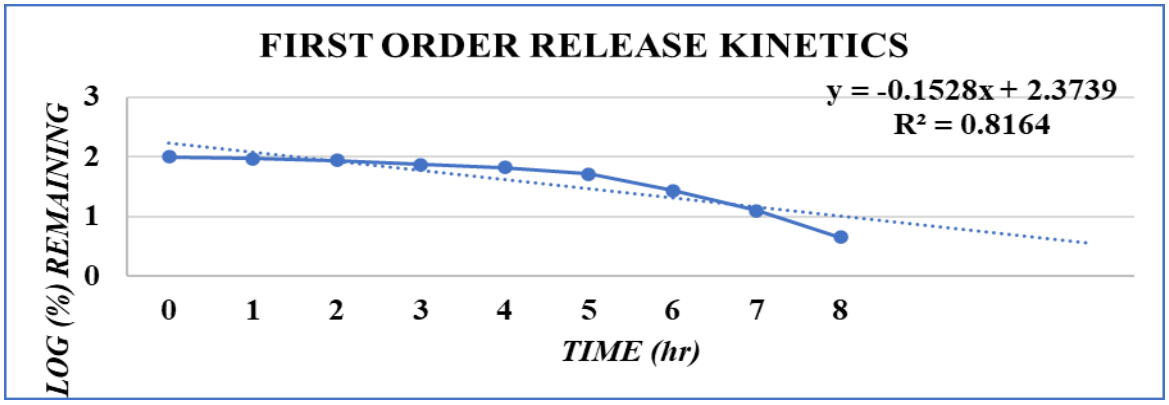


Figure 27: First Order Release Kinetics

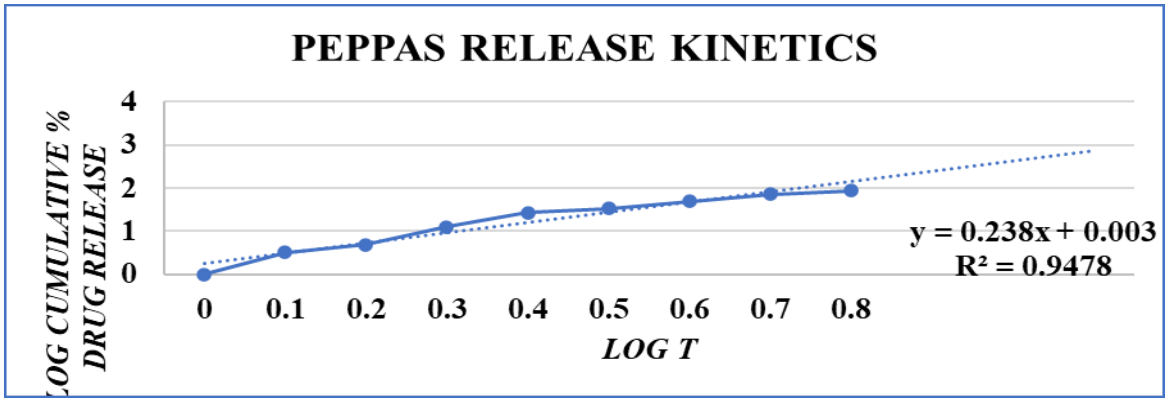


Figure 28: Peppas Release Kinetics

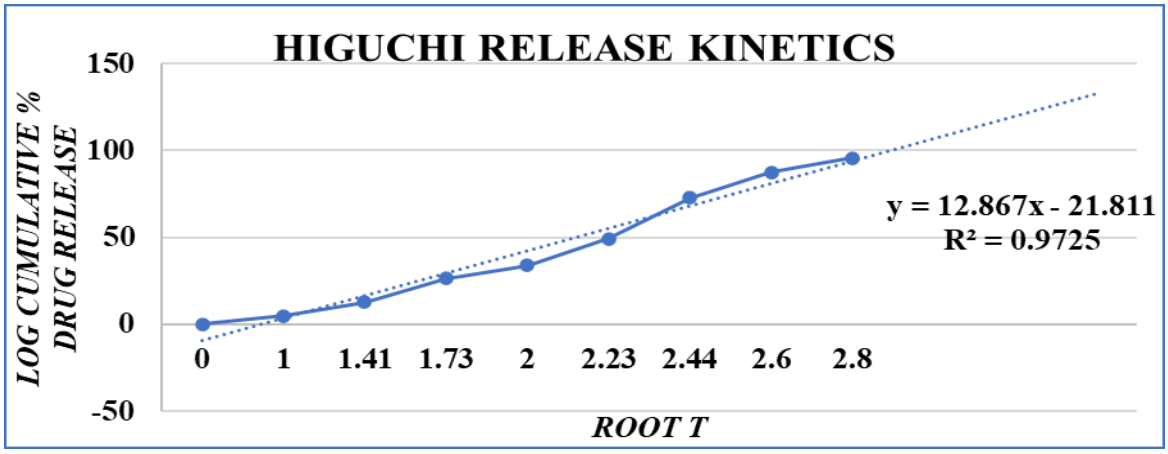


Figure 29: Higuchi Release Kinetics

Table 21: Release Kinetics summary

Parameter	Zero order (%CDR vs T)	First order (Log % vs T)	Peppas (Log C vs Log T)	Higuchi (%CDR vs √T)
Slope	-0.1125	-0.1528	0.238	12.867
Intercept	2.171	2.3739	0.003	-21.811
R^2	0.7486	0.8164	0.9478	0.9725

OBSERVATION: The first order & Higuchi release kinetics indicates the best release mechanism with R^2 0.8164 & 0.9725.

F. STABILITY STUDIES

Table 22: Stability study of Optimized Roxithromycin Emulgel FFE- II

Parameters	Initial	25±2°C,60±5%RH			40±2°C,75±5%RH		
		30	60	90	30	60	90
		Days					
Viscosity (Cps)	4079	4079	4079	4078	4077	4065	4068
Spread ability (cm)	5.5	5.5	5.5	5.4	5.3	5.3	5.2
pH	5.9	5.9	5.9	5.8	5.8	5.8	5.7
Drug Content (%)	98.2	98.2	98.2	98.2	97.9	97.8	97.8

OBSERVATION: The stability batches of samples demonstrated consistent physical properties and drug content. No significant variations were observed during storage, indicating that the emulgel remained highly stable.

EVALUATION OF FILM FORMED FROM ROXITHROMYCIN FEE

Table 22: Evaluation Of Film Formed from Roxithromycin

Parameters	**FFE - I**	**FFE - II**	**FFE - III**	**FFE - IV**	**FFE - V**
Film Forming Time (Min)	15	10	9	21	18
Adhesiveness & Peel Ability	Peelable, but with poor adhesiveness due to flakiness	Peelable, but with poor adhesiveness due to flakiness	Peelable uniform films, with good adhesivity & no flakiness	Peelable, but with poor adhesiveness due to flakiness	Non Peelable
Tackiness	Non tacky	Non tacky	Non tacky	Non tacky	Non tacky
Physical Appearance	2	2	1	2	3

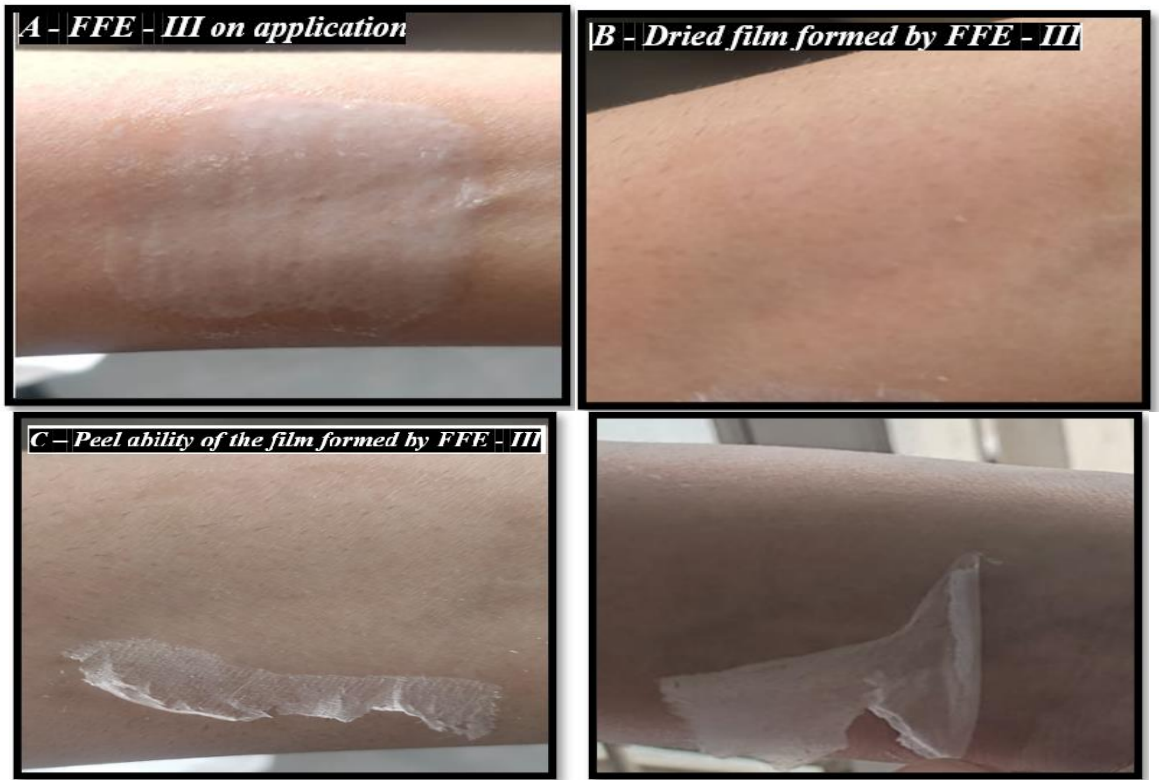


Figure 30: A - FFE - III on application; B - Dried film formed by FFE - III; C – Peel ability of the film formed by FFE – III

OBSERVATION: *Formulation FFE -III formed clear, adhesive, uniform film with good adhesivity with long retention time on the applied surface.*

CONCLUSION

The aim was to develop a topical film-forming nanoemulgel containing roxithromycin for effective treatment of Staphylococcus aureus-induced impetigo. Successful formulation of roxithromycin-loaded nano emulsions was achieved through sonication, with Formulation F-II demonstrating optimal characteristics such as a particle size of 139.7 nm, zeta potential of -20.2, and a high drug content & drug release of 97.6 & 91.2% respectively. The film-forming emulgels, particularly Formulation FFE-II showed favorable properties including a pH of 5.98, viscosity of 4079 cps, and high drug content and release of 98.2% and 95.5%, respectively. The drug release kinetics followed the first-order and Higuchi models with R^2 of 08164 & 0.9725 respectively indicating a controlled release. Stability studies showed minimal variation in the properties of the emulgel. Formulation FFE- III with its clear, adhesive, and uniform films, exhibited excellent properties suitable for prolonged adhesion and effectiveness, affirming the

success of the developed nanoemulgel for topical application.

SCOPE

- Further in vivo animal studies can be conducted in the current research.
- Long term stability testing can be performed.

Declaration by Authors

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Conflict of Interest: The authors declare no conflict of interest.

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