

FORMULATION AND EVALUATION OF CALOTROPIS-BASED EMULGEL FOR TOPICAL PAIN RELIEF

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Abstract

Musculoskeletal pain is a common health issue that adversely impacts daily activities and overall quality of life, which is commonly managed using oral non-steroidal anti-inflammatory drugs (NSAIDs), which are associated with gastrointestinal, renal and cardiovascular adverse effects upon prolonged use. Topical drug delivery systems provide localized action with improved patient compliance and reduced systemic toxicity. Emulgels, combining the advantages of emulsions and gels, enhance drug solubility, penetration, stability and sustained release. The present study focuses on the formulation and evaluation of a *Calotropis procera*-based emulgel for effective pain relief. *Calotropis procera* possesses well-documented anti-inflammatory and analgesic properties due to flavonoids, triterpenoids, alkaloids and latex enzymes. An emulsion containing clove oil was mixed with ethanolic leaf extract made by maceration. HPMC, Carbopol 934, sodium CMC, and xanthan gum were then used to create emulgels. Drug-excipient compatibility was verified by FTIR, and phytochemical screening. The formulations were compared with a plain extract gel and assessed for their physicochemical characteristics and *in-vitro* drug release. The improved effectiveness of the emulgel based on Carbopol 934 suggests that it may be a safe and efficient topical substitute for oral NSAIDs in the treatment of joint and muscle pain.

Key words: *Calotropis procera*, Pain relief, Emulsion, Gel, Emulgel.

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Introduction

Pain is a common, multifactorial ailment that negatively impacts quality of life. It is frequently linked to musculoskeletal conditions like migraines and arthritis, and it can develop into chronic conditions that have a substantial physiological and financial impact [1,2]. Long-term use of nonsteroidal anti-inflammatory medicines (NSAIDs) can result in negative gastrointestinal, renal, and cardiovascular effects, despite the fact that oral and topical analgesics are frequently used for this purpose [3]. Because they can include hydrophobic medicines, improve skin penetration, and enable regulated and prolonged drug release with improved patient compliance, topical drug delivery systems - especially emulgels have drawn interest in this setting [4–7]. Although there are certain drawbacks, such as the poor permeability of some medications and the possibility of skin responses, emulgels which combine the qualities of emulsions and gels, offer benefits like improved spreadability, stability and decreased irritation [8]. Recent developments highlight the use of emulgel-based systems in the treatment of pain and inflammatory disorders, where molecular weight, lipophilicity, formulation type, and skin state all affect drug release and skin penetration [9–11]. Emulgels offer a non-greasy, esthetically pleasing, and more stable substitute for traditional semisolid preparations like ointments and creams [12]. *Calotropis procera*, a medicinal plant rich in

bioactive chemicals, is one of the herbal options that shows promise for topical formulations due to its noteworthy anti-inflammatory, analgesic, antibacterial, and wound-healing characteristics [13,14]. Furthermore, clove oil, which contains eugenol, has strong antibacterial, analgesic, and anti-inflammatory properties that improve topical formulations' therapeutic efficacy [15]. By enhancing uniformity, stability, and drug release properties, the use of appropriate gelling agents as Carbopol 934, Na-CMC, and HPMC further enhances the formulation [16].

Thus, the creation of an emulgel based on *Calotropis procera* leaf extract—possibly in conjunction with clove oil—represents a logical and successful strategy for focused pain management, providing increased therapeutic advantages with few systemic side effects and better patient acceptability.

Materials and methods

Materials

The main ingredients used in the preparation of emulgel were Carbopol 934, Hydroxypropyl Methylcellulose (HPMC), Sodium Carboxymethyl Cellulose (Sodium CMC) and Xanthan gum which were procured from Central Drug House (New Delhi, India). Surfactants viz. Tween 80, Isopropyl Myristate and Propylene Glycol were obtained from Thomas Baker, Mumbai, India. Span 80 was purchased from Loba Chemie Pvt. Ltd. (Mumbai, India) and clove oil was procured from Nice Chemicals (Kochi, India). Fresh leaves of

Calotropis procera were collected from rural areas around Bengaluru, Karnataka, India and authenticated before use. All chemicals used in this study were of analytical grade and used without further purification.

Methods

Preformulation Studies

Before formulation, physicochemical properties of *Calotropis procera* leaf extract and drug-excipient compatibility studies were performed.

Analysis of Drug

Physical Appearance

The physical properties of *Calotropis procera* leaf extract like colour, texture and odor were visually observed.

FTIR Spectroscopic Analysis [17]

The pharmaceutical compound's functional groups were identified using Fourier Transform Infrared (FTIR) spectroscopy. The sample was combined with potassium bromide (KBr) to create pellets, and an FTIR spectrophotometer was used to record the spectra in the 4000-400 cm⁻¹ region. The acquired spectra were examined and contrasted with established reference data.

Determination of λ_{max}

A concentrated solution containing 1000 µg/ml of *Calotropis procera* leaf ethanolic extract was made. A proper dilution was conducted in phosphate buffer pH 7.4 to achieve the concentration of 10 µg/ml. The UV-visible spectrophotometer's absorption spectra in the 200–400 nm range was used to calculate the wavelength of maximum absorption (λ_{max}).

Solubility Assessment [18]

The solubility of extract was determined by adding small quantity of the drug to known volume of the solvent and mixed at room temperature. The solution was visually examined for clarity or the presence of undissolved particulates.

Preparation of Calibration Curve

Standard solutions in the concentration range of 2–20 µg/ml were created by diluting a stock solution of the extract (1000 µg/ml) with phosphate buffer pH 7.4. Using phosphate buffer pH 7.4 as a blank, the absorbance of each solution was measured at the predefined λ_{max} , and a calibration curve was constructed.

Drug–Excipient Compatibility Studies

Drug–excipient compatibility was evaluated using FTIR spectroscopy. A physical mixture of *Calotropis procera* leaf extract, Carbopol 934, HPMC, Sodium CMC and Xanthan gum was prepared and analysed using an ATR-FTIR spectrophotometer. The spectra were compared with that of the pure extract to identify any possible interactions.

Extraction of *Calotropis procera* leaf [19]

The ethanolic extract of *Calotropis procera* leaves was prepared by the maceration method. Fresh leaves were collected from a clean rural area, thoroughly washed with tap water to remove

adhering impurities, and shade-dried at room temperature for 7–10 days in a well-ventilated area. The dried leaves were powdered using a mechanical grinder and sieved. Accurately weighed powdered material (20 g) was transferred into a clean conical flask and macerated with 100 ml of ethanol at room temperature (25–30 °C) for 72 hours with occasional shaking. After maceration, the mixture was filtered through muslin cloth, and the filtrate was concentrated in a desiccator containing calcium chloride to obtain the crude extract. The dried extract was stored in an airtight container for further phytochemical and formulation studies.

Phytochemical Screening [20]

Several qualitative tests were performed in order to determine the phytochemical components that were present in the alcoholic leaf extract of *Calotropis procera*. Multiple tests were conducted to determine the content of alkaloids, flavonoids, tannins and terpenoids, which provide analgesic and anti-inflammatory activities.

Test for alkaloids

Mayer's test: Mayer's test: When Mayer's reagent is added to the extract, the presence of alkaloids is indicated by the production of a cream or pale-yellow precipitate.

Dragendorff's test: Add Dragendorff's reagent to the extract; if an orange or reddish-brown precipitate forms, alkaloids are present.

Test for Flavonoids

Shinoda test: Shinoda test: The presence of flavonoids is indicated by the development of a pink, red, or orange color when a tiny amount of magnesium turnings and a few drops of strong hydrochloric acid are added to the extract.

Ammonia test: Add a few drops of ammonia solution to the extract; the presence of flavonoids is indicated by the development of a yellow hue that goes away after standing.

Test for Terpenoids

Salkowski test: After combining the extract with chloroform, gently apply a coating of strong sulfuric acid. Terpenoids are indicated by a reddish-brown hue near the contact.

Test for Tannins

Ferric chloride test: Add a few drops of a 5% ferric chloride solution to the extract; if tannins are present, the extract will turn blue-black or greenish-black.

Formulation of *Calotropis Procera* emulgel

Table: 1 Formulation table of *Calotropis Procera* emulgel for 20g

Sl. No.	Ingredients	F1	F2	F3	F4	F5
						(Plain gel)

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1	Calotropis extract (mg)	10	10	10	10	10
2	HPMC (%)	2.5	-	-	-	-
3	Carbopol 934 (%)	-	2.5	-	-	2.5
5	Sod. CMC (%)	-	-	2.5	-	-
6	Xanthan gum (%)	-	-	-	2.5	-
6	Triethanolamine (TEA) (ml)	0.5	0.5	0.5	0.5	0.5
7	Tween 80 (ml)	1	1	1	1	-
8	Span 80 (ml)	1	1	1	1	-
9	Clove oil (ml)	2	2	2	2	-
10	Isopropyl myristate (ml)	1	1	1	1	-
11	Propylene glycol (ml)	2	2	2	2	-
12	Menthol crystal (mg)	20	20	20	20	-
13	Propyl paraben (g)	0.02	0.02	0.02	0.02	0.02
14	Distilled water	QS	QS	QS	QS	QS

Preparation of calotropis-based emulgel [17]

The *Calotropis procera*-based emulgel was prepared by first dispersing the required gelling agent in distilled water and allowing it to hydrate for 2–4 hours, followed by neutralization with triethanolamine to obtain a transparent gel with pH adjusted to 6.5–7. Clove oil, isopropyl myristate, span 80, and menthol made up the oil phase, while distilled water and additional components made up the watery phase. The second phase was made up of Tween 80, propylene glycol, and propyl paraben in distilled water. The extract of *Calotropis procera* was added to this. After heating each component independently to 70 °C, the oil phase was gradually

introduced to the aqueous phase while being stirred, creating a composite of the two.

A stable oil-in-water emulsion was formed followed by 10 minutes of probe sonication. The prepared emulsion was then gradually incorporated into the gel base with gentle stirring to obtain the final emulgel formulation.



Figure:1 Overall process of preparation of Calotropis-based emulgel

Evaluation of emulsion

Microscopic test to identify the type of emulsion

A general microscopic test for oil-in-water (O/W) emulsions using Sudan Red dye involves staining the emulsion with Sudan Red, which selectively dissolves in the oil phase. Under a microscope, the dyed oil droplets appear as red-coloured dispersed particles within the continuous aqueous phase, confirming the presence of oil droplets in the emulsion.

Particle size and Zeta Potential Analysis

The sample was analyzed by Zetasizer Nano ZS (Make: Microtrac, Model: Nanotrac - USA). After five minutes of ultrasonication using an ultrasonic bath, the stock solution of nanomaterial generated at a concentration of 10 mg/ml in double-distilled water was transferred into the liquid cell and its particle size and zeta potential were evaluated. Zeta potential analysis was also used to assess the stability of nanomaterials.

Evaluation of emulgel [17]

Organoleptic

The emulgel formulation was periodically evaluated to assess quality control parameters, including colour, odor, texture, consistency, stickiness, and phase separation.

pH

The pH of herbal emulgels was measured using a digital pH meter that had been calibrated. The pH was determined by putting the pH meter's electrode into a glass beaker containing a 1% solution of the emulgel formulation. The pH should be measured in triplicate to assure accuracy. These were recorded and the means and SD were computed.

Viscosity

Viscosity measurement is one of the important parameters to be checked while evaluating the formulations of emulgel as it effects the application and effectiveness of the formulations. The digital viscometer is the most common to be used for this purpose due to its accuracy and reliability. Viscosity

is measured using Spindle 6 at a rotation speed of 10 revolutions per minute in the standard manner. Additionally, a wide-opening container makes it easier to put the spindle correctly into the emulgel sample, increasing measurement accuracy.

Extrudability

Emulgels' extrudability refers to how easily the product may be removed from its packaging. The force needed to extrude a 0.5 cm emulgel ribbon from a plastic tube in ten seconds is used to measure it. The extrudability of emulgel is assessed by calculating the average force after the test is repeated multiple times for accuracy.

$$\text{Extrudability} = \frac{\text{Weight subjected for the extrusion of the gel (g)}}{\text{Area (cm)}}$$

Spreadability [21]

By measuring the diameter of one gram of gel between two smooth, horizontal glass plates, the spreadability of the gel formulations was assessed. After the gel was placed on the lower plate, the initial diameter in centimeters was noted. Then, a second glass plate of the same dimension was put on top and a 100 g weight was applied for the duration of one minute until no further spreading occurred. Finally, the spread gel's diameter was measured in cm.

Percentage Drug Content

A precisely weighed 1 g gel was put into a 100 ml volumetric flask and diluted with 100 ml of pH 7.4 phosphate buffer. To guaranty that the medication was completely dissolved, the liquid was thoroughly shaken. Whatman filter paper was used to filter the mixture. Using a UV spectrophotometer and pH 7.4 phosphate buffer as a blank, the absorbance of the mixture was measured at 275 nm.

$$\% \text{Drug Content} =$$

$$\frac{\text{Actual amount of Calotropis Procera extract in the gel}}{\text{Theoretical amount of Calotropis Procera extract in the gel}} \times 100$$

In-vitro Diffusion study

One end of a dialysis membrane was securely tied and filled with 1 g of emulgel containing 0.5 mg of calotropis procera extract. After that, the membrane was placed in contact with the receptor compartment's surface, which held 100 milliliters of pH 7.4 phosphate buffer that was kept at 37 ± 0.5 °C. A magnetic stirrer was used to continually agitate the receptor chamber at 100 rpm. For eight hours, five milliliter samples were taken out every hour and replaced with an equivalent volume of brand-new phosphate buffer (pH 7.4). A UV spectrophotometer was used to assess each sample's absorbance at 275 nm following the proper dilution.

Results and discussion

Preformulation studies

Analysis of drug

Physical appearance of the drug

The *Calotropis Procera* leaf extract was dark green in colour and exhibited a sticky consistency.

Identification of drug by FTIR spectroscopic analysis

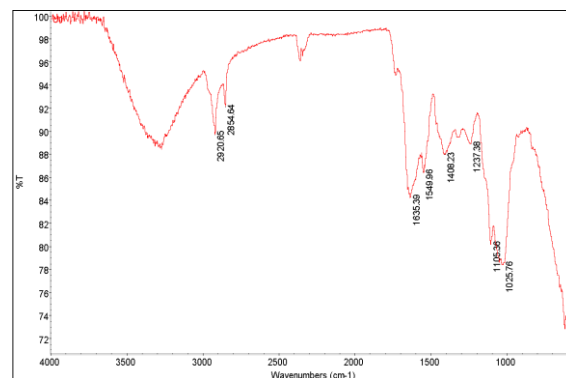


Figure:2 FTIR spectrum of Calotropis Procera leaf extract

The *Calotropis Procera* leaf extract's FTIR spectrum showed characteristic absorption peaks at 3300 cm^{-1} corresponding to N-H stretching vibrations, 2920.65 cm^{-1} indicating C-H stretching, 1635.39 cm^{-1} attributed to C=C stretching, and 1549.96 cm^{-1} also associated with C-C stretching. These peaks verify that the leaf extract contains functional groups typical of bioactive phytoconstituents.

Determination of λ_{max} of Calotropis Procera leaf extract

The leaf extract of *Calotropis procera*'s λ_{max} in phosphate buffer pH 7.4 was determined to be 275 nm (Figure. 8) and was utilized for additional spectrophotometric analyses.

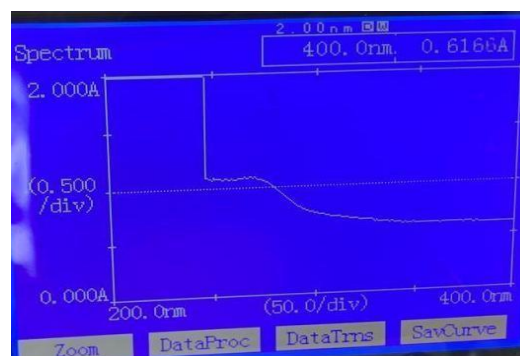


Figure:3 λ_{max} of Calotropis procera leaf extract

The *Calotropis procera* ethanolic extract showed a strong absorbance around 275 nm, indicating a high content of flavonoids such as quercetin and kaempferol. These bioactive substances show analgesic activity by inhibiting key enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing the production of prostaglandins and other inflammatory mediators. Additionally, they possess significant free radical scavenging and membrane-stabilizing properties, further contributing to their anti-inflammatory and analgesic effects.

Calibration curve of Calotropis Procera leaf extract in phosphate buffer pH 7.4

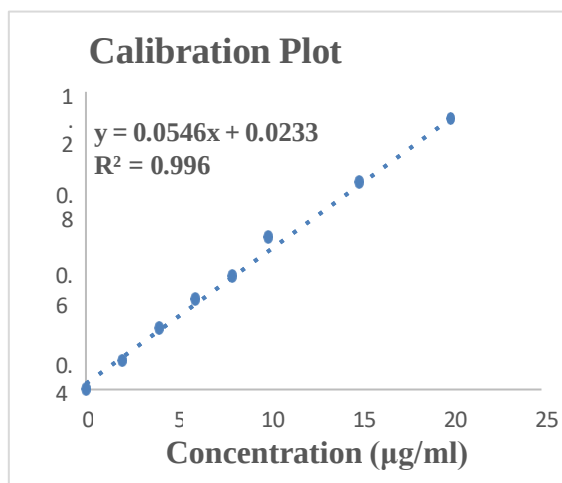


Figure:4 Calibration curve of Calotropis procera leaf extract in phosphate buffer pH 7.4

Drug-excipient compatibility study

FTIR spectrophotometric analysis of physical mixture

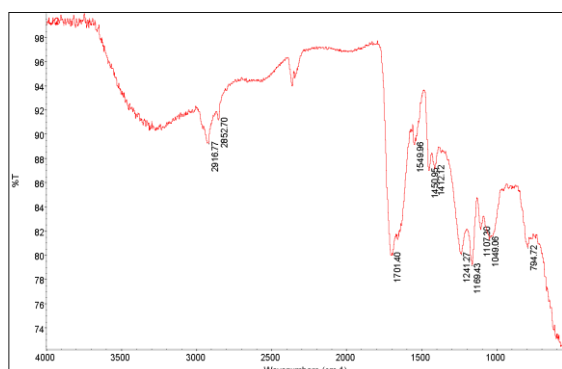


Figure: 5 FTIR spectrum of calotropis procera leaf extract and Carbopol 934, HPMC, Sod.CMC and xanthan gum

The pure Calotropis procera leaf extract's FTIR spectra showed distinctive peaks at 3300 cm⁻¹ (N-H stretching), 2916.77 cm⁻¹ (C-H stretching), 1701.40 cm⁻¹ (C=O stretching), and 1549.96 cm⁻¹ (C=C stretching). An analysis of the FTIR spectra of the pure extract with those of the physical mixtures containing Carbopol 934, HPMC, Sodium CMC, and Xanthan gum showed the presence of all major characteristic peaks with only negligible shifts in their positions. The absence of significant peak disappearance or formation of new peaks shows that there was no chemical interaction between the *Calotropis procera* leaf extract and the gelling agents, confirming the compatibility of the extract with the excipients used in the formulation of emulgel.

Phytochemical Screening Test

Table: 2 Phytochemical test results of ethanolic extract of calotropis procera

Chemical Test	Result
<u>Test for</u>	
<u>Alkaloids:</u>	
Mayer's test	+
Dragendorff's test	+
<u>Test for</u>	
<u>Flavonoids:</u>	
Shinoda test	+
Ammonia test	+
<u>Test for</u>	
<u>Terpenoids</u>	
Salkowski test	+
<u>Test for Tannins</u>	
Ferric chloride test	+

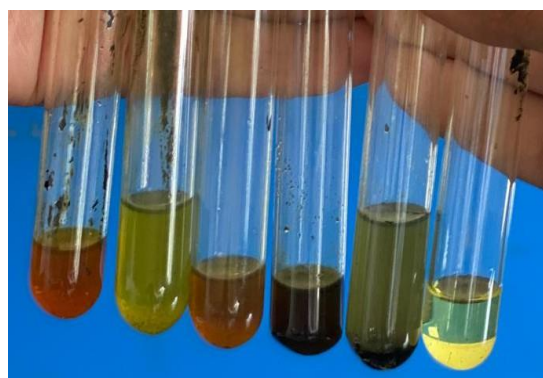


Figure: 6 Phytochemical test results of Calotropis Procera leaf extract

Initial phytochemical analysis of *Calotropis procera* leaf ethanolic extract revealed positive results for all the tested phytoconstituents. Alkaloids, flavonoids, terpenoids, and tannins were confirmed by their respective qualitative tests, indicating the presence of bioactive compounds accountable for the anti-inflammatory and analgesic properties of the extract.

Evaluations of emulsion

Microscopic analysis to determine the emulsion type

The emulsion was observed under a microscope, where the globules (dispersed phase) appeared red, while the continuous phase was colorless. The dye used here was Sudan Red, which is an oil-soluble dye. So, the observation confirmed that the emulsion was of the oil-in-water (O/W) type.

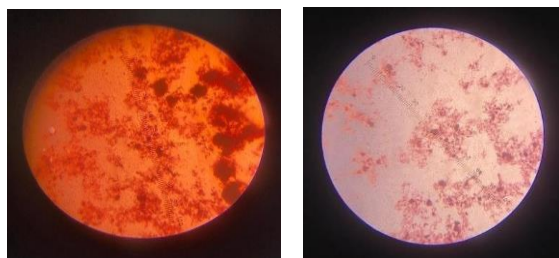


Figure:7 Microscopic view of emulsion

Particle size and Zeta Potential Analysis

The particle size distribution graph obtained revealed a bimodal distribution, with a significant portion of particles ranging from 200–600 nm and another peak between 2000–4000 nm, indicating the presence of larger droplets. This suggests that the emulsion did not fully reduce to the nanoscale range, and therefore cannot be classified as a true nano emulsion. While probe sonication improved dispersion to some extent, to the micro level.

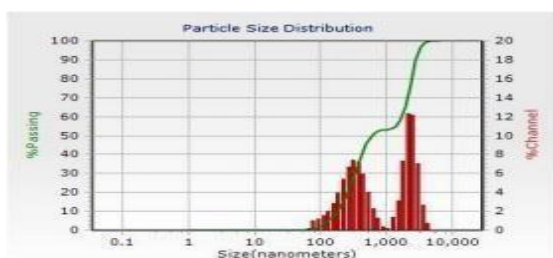


Figure:8 Particle size distribution of calotropis emulsion

Zeta Potential	
Mobility	0.01u/ s/ V/ cm
Zeta Potential	0.1 mv
Charge	0.00039 fC
Polarity	Positive
Conductivity	188 uS/ cm
Field Strength	5.0 kV/ m
Sample Information	
Fluid	
EMULSION	
Viscosity	0.834
Temperature	27.95 C
Dielectric Const	79
Dispersant	
pH	
Concentration	
Particle	
Concentration	0

Figure:9 Zeta potential data of emulsion

Zetapotential of the herbal emulsion was found to be 0.1mV. The electrical charge on the surface of particles or droplets in an emulsion is measured by zeta potential. It indicates the stability of the emulsion by reflecting the degree of repulsion between similarly charged particles. A high absolute zeta potential (positive or negative) usually means better stability, as it prevents droplet aggregation or coalescence. Zeta potential can be controlled to optimize the shelf life and performance of emulsions.

Physical appearance of the emulgel



Figure: 10 Various emulgel formulations

Table: 3 Physical appearance of the formulations

Formulation Code	Colour	Homogeneity	T r a	Consistency
F1	Green	Good	Excellent	Poor
F2	Green	Good	Good	Excellent
F3	Green	Good	Good	Good
F4	Green	Good	Good	Excellent
F5(Plain gel)	Light brown	Good	Good	Good

Other evaluations of the gel

Table: 4 Drug content, spreadability, pH, viscosity and extrudability of different formulations

Formulation Code	Drug content (%)	Spreading diameter of the gel (cm)	pH	Viscosity (cps)	Extrudability (g/cm ²)
F1	96±0.32	8.1±0.41	6.32±0.25	21063±0.46	33±0.34
F2	97±0.41	7.3±0.23	5.89±0.33	36456±0.52	28±0.25
F3	95±0.47	7.8±0.16	6.55±0.51	28591±0.28	30±0.51
F4	94±0.45	7.5±0.36	5.94±0.43	33830±0.44	29±0.24
F5	96±0.22	6.9±0.51	6.81±0.32	34192±0.35	28±0.33

(Mean±SD) n=3

Percentage Drug Content

All of the emulgel formulations' drug content was determined to be between 94 and 97%, showing that the active ingredient was distributed uniformly and that the incorporation was effective without causing any appreciable drug loss or degradation.

Spreadability

The spreading ability of the formulations was found to 6.9–8.1 cm indicating good spreading property. This facilitates application on the skin and enhances patient compliance.

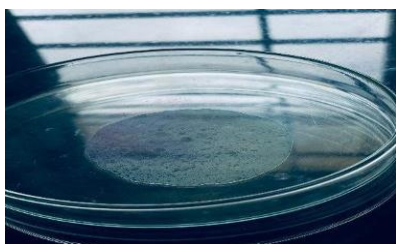


Figure: 11 Emulgel spreadability test

pH Assessment

The emulgels' pH values ranged from 5.89 to 6.81, which is near the physiological skin pH and suggests good dermal compatibility and a minimal chance of skin irritation.

Viscosity

The viscosity measurements, which varied from 21,063 to 36,456 cPs, verified that the formulations had the proper semisolid consistency, guaranteeing stability and permitting sufficient spreadability.

Extrudability

The extrudability values, which varied from 28 to 33 g/cm², showed that the emulgels could be readily extruded from collapsible tubes with little effort, improving user convenience.



Figure:12 Extrudability of emulgel

In-vitro diffusion of Calotropis-based emulgel

Table: 5 In-vitro diffusion of Acitretin SD from various gel formulations

Time (hr)	% CDR				
	F1	F2	F3	F4	Plain Gel
1	8.32	10.21	12.53	7.56	4.43
2	17.61	22.46	20.76	18.43	16.33
3	28.83	39.72	29.24	24.61	23.05
4	35.44	52.35	37.32	36.55	29.86
5	43.50	64.53	49.30	48.07	34.71
6	50.17	70.11	55.29	54.82	39.64
7	58.92	73.84	64.72	61.93	43.28
8	66.26	79.59	72.66	70.48	48.94

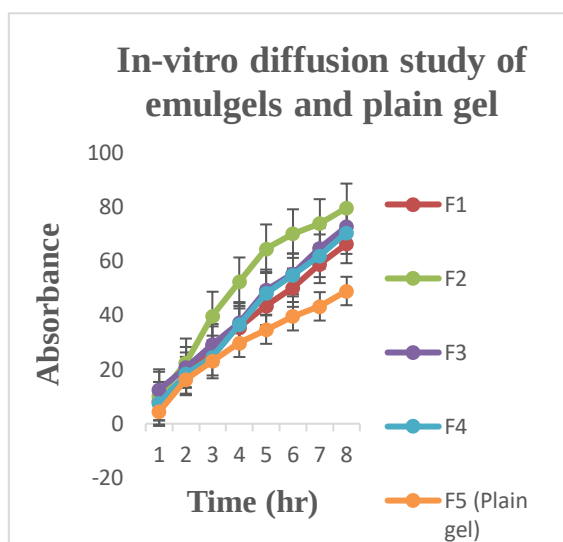


Figure: 13 *In-vitro* diffusion study of various emulgels and the plain gel

The basic gel containing Calotropis Procera extract released less than 50% of the drug during an 8-hour period, indicating restricted drug diffusion, according to the in-vitro drug release investigation. All emulgel formulations, on the other hand, showed noticeably more drug release. The emulgel based on Carbopol 934 (F2) exhibited the highest cumulative drug release of about 80% after eight hours. The emulsion-based gel system's better drug dispersion and penetration are responsible for the increased release from emulgel formulations. These findings show that emulgels can provide long-lasting therapeutic activity and are better than simple gels for topical drug administration.

Conclusion

The current study effectively developed and assessed an emulgel for topical pain alleviation based on Calotropis procera. FTIR analysis verified that the ethanolic leaf extract, which is high in alkaloids, flavonoids, tannins, and terpenoids, was compatible with the chosen gelling agents. After being made and described, oil-in-water emulsions containing clove oil were added to different gel bases. The Carbopol 934-based emulgel showed the best physicochemical characteristics of all the formulations, including pH 5.89, drug content of 97%, viscosity of 36,456 cPs, spreadability of 7.3 cm, extrudability of 28 g/cm², and the maximum in-vitro drug release of approximately 79.6% after eight hours. When compared to the plain gel, all emulgel formulations showed better drug release. These findings suggest that the Calotropis procera emulgel, especially when combined with Carbopol 934, is a safe, effective, and promising natural alternative for topical pain management that offers decreased systemic adverse effects, better patient compliance, and sustained drug release.

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