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DEVELOPMENT AND *IN-VITRO* CHARACTERIZATION OF LIPOSOMAL GEL FORMULATION CONTAINING DRIED LEAF EXTRACT OF PLANTS *ACACIA LUCOPHLOLEA* AND *EUPHORBIA CYTHOPHORA* AND ITS COMPARATIVE ANTIBACTERIAL STUDY

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Keywords:

Acacia leucophloea, *Euphorbia cyathophora*, Liposomal gel, Phytochemical screening, Antibacterial activity, Liposome characterization, Topical formulation

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ABSTRACT: Background: Plant-derived bioactive offer promising alternatives for antimicrobial therapy, but their poor solubility and stability often limit topical application. Liposomal encapsulation can enhance their therapeutic potential. **Objective:** This study aimed to develop and characterize liposomal gel formulations containing ethanolic extracts of *Acacia leucophloea* and *Euphorbia cyathophora* leaves, and to evaluate their antibacterial efficacy. **Methods:** Leaves of both plants were extracted using ethanol and petroleum ether. Phytochemical screening identified alkaloids, glycosides, flavonoids, tannins, carbohydrates, and saponins predominantly in ethanolic extracts. Liposomes were prepared and characterized for particle size, zeta potential, and morphology. The optimized liposomal formulation (F5) was incorporated into a topical gel and evaluated for physicochemical properties, spreadability, and antibacterial activity using the agar well diffusion method. **Results:** The ethanolic extract yields were 2.31% for *A. leucophloea* and 2.16% for *E. cyathophora*. Formulation F5 showed the smallest particle size (42.53 nm), suitable zeta potential (-13.8 mV), and spherical morphology. The liposomal gel exhibited a pH of 6.8, viscosity of 1549 ± 0.26 cps, and good spreadability (34.26 g·cm/sec) without skin irritation. Antibacterial activity was significantly enhanced, with inhibition zones of 12 mm (against E. coli) and 8 mm (against S. aureus), compared to 5 mm and 3 mm for crude extracts. **Conclusion:** The developed liposomal gel demonstrated superior antibacterial efficacy and favorable physicochemical properties, supporting its potential as a plant-based topical therapeutic formulation.

INTRODUCTION: Liposomes have been extensively studied as drug carrier systems for parenteral delivery and, more recently, for topical applications such as dermal and ophthalmic treatments. When incorporated into topical dosage forms, liposomes can enhance localized drug delivery, improve solubility of poorly soluble drugs, and provide sustained release with minimal systemic absorption [1].

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Their ability to act as penetration enhancers and micro-reservoirs makes them promising vehicles for various therapeutic agents, including antibiotics, antifungals, and anticancer drugs [2]. *Euphorbia cyathophora* is a medicinal plant known for its diverse pharmacological activities, attributed to its rich content of bioactive compounds such as flavonoids, terpenoids, alkaloids, and phenolic acids.

Extracts from *Euphorbia* species have demonstrated significant anti-inflammatory, antioxidant, antimicrobial, and antitumor properties, highlighting their therapeutic relevance and potential for drug development [3, 4]. Similarly, *Acacia leucophloea* (Roxb.) Willd., belonging to

the family Mimosaceae, has been widely used in traditional and Ayurvedic medicine. Various parts of this plant possess antimicrobial, anti-inflammatory, and wound-healing properties. The bark and leaves are particularly valued for treating skin infections, ulcers, and respiratory ailments due to their astringent and antibacterial effects [5, 6]. Considering the therapeutic potential of these plants, liposomal encapsulation may enhance the stability, solubility, and skin penetration of their bioactive constituents. Therefore, the objective of this study was to develop and characterize liposomal gel formulations containing ethanolic extracts of *Acacia leucophloea* and *Euphorbia cyathophora* leaves and to evaluate their physicochemical properties and antibacterial activity for potential topical application.

MATERIALS AND METHODS:

Chemicals: Nitroprusside, ammonia, and sodium hydroxide were procured from Merck (India). Ethanol (analytical grade) was obtained from Molychem. Concentrated sulfuric acid (H_2SO_4) was purchased from Fizmerck. All other solvents, reagents, and chemicals used were of analytical reagent (AR) grade and procured from Rankem, Clorofiltind, and HiMedia Laboratories.

Plant Collection and Authentication: Fresh leaves of *Acacia leucophloea* and *Euphorbia cyathophora* were collected, cleaned, and shade-dried at room temperature for three days. The dried leaves were stored in airtight glass containers under cool, dry conditions to prevent contamination and degradation. The plant materials were authenticated by a qualified taxonomist, and voucher specimens were deposited for future reference [7].

Extraction Process: *Acacia leucophloea* and *Euphorbia cythophora* plant leaves were extracted using a systematic approach that involved a continuous hot percolation process with ethanol and petroleum ether in a Soxhlet apparatus. The plant leaves were initially dried in shade before being powdered into a fine powder. A weighed amount of powdered material (300g) was placed in a porous thimble and loaded into the Soxhlet extractor. Petroleum ether was accustomed to extract non-polar compounds at 60°C, followed by ethanol for polar compounds. A round-bottom flask was filled with 300-500 mL of relevant solvent and heated in a water bath. As the solvent evaporated, it condensed in the reflux condenser and permeated the plant material, dissolving bioactive substances. The procedure of extraction was continued for 6-8 hours until the solvent in the siphon tube became colourless. After extraction, using a rotary evaporator, the solvent was removed, and the concentrated extract was dried at 40 °C in a rotating vacuum evaporator (Buchi type). The dried extract was weighed, and the percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \text{Weight of extract} / \text{Weight of plant material used} \times 100$$

The dried extract was then held at low temperatures for further phytochemical examination and organoleptic properties (percentage yield, color, and smell) [8].

The Organoleptic Studies: Organoleptic studies of *Acacia leucophloea* and *Euphorbia cythophora* both plant extract such as general appearance, color, odour, and condition, were conducted and observed.

Solubility Study: The qualitative solubility of *Acacia leucophloea* and *Euphorbia cythophora* both plant extract in various solvents was examined utilizing Indian pharmacopoeia. *Acacia leucophloea* and *Euphorbia cythophora* both plant extract were weighed and placed into separate 10 ml test tube, where it was dissolved in the appropriate solvents (1 ml each of methanol, DMSO, distilled water, chloroform, and acetone).

Preliminary Phytochemical Screening: Qualitative phytochemical tests were performed to detect alkaloids, flavonoids, tannins, saponins, glycosides, phenols, terpenoids, and steroids using standard procedures. Changes in color or precipitate formation confirmed the presence of specific phytoconstituents [9].

Preparation of Liposomes Formulation: Liposomes were prepared by the thin-film hydration technique using a rotary evaporator. Five formulations (LSF1–LSF5) were prepared by varying the concentrations of soya lecithin (200–600 mg) and cholesterol (50–250 mg), while maintaining a constant extract ratio (1:1, 500 mg each of *A. leucophloea* and *E. cyathophora*).

The lipid mixture (lecithin, cholesterol, and extracts) was dissolved in 8 mL chloroform and 2 mL ethanol and evaporated under reduced pressure at 40°C (900 mm Hg, 80 rpm) for 30 minutes to form a thin lipid film. The film was hydrated with 10 mL phosphate buffer (pH 6.8) for 2 hours to form a milky liposomal suspension, which was centrifuged at 3000 rpm for 30 minutes and stored in airtight containers [10].

Compositions:

TABLE 1: COMPOSITION OF LIPOSOME FORMULATION

Ingredients	Formulations				
	LSF1	LSF 2	LSF 3	LSF 4	LSF 5
A. L : E.C Extract (500:500mg)	1:1	1:1	1:1	1:1	1:1
Soya lecithin	200	300	400	500	600
Cholesterol	50	100	150	200	250
Phosphate buffer pH (6.8)	10	10	10	10	10
Chloroform	8	8	8	8	8
Ethanol	2	2	2	2	2
Methyl paraben	0.02%	0.02%	0.02%	0.02%	0.02%
Propyl paraben	0.02%	0.02%	0.02%	0.02%	0.02%

Characterization Parameters of Liposomes Formulation:

Physical Properties of Liposomes by Visual Observation: After preparation, the liposomal suspension was examined for color, homogeneity, and phase separation [11].

Size Distribution or Particle size: The resulting liposome formulations particle size was examined utilizing a Malvern Zetasizer based on Dynamic Light Scattering (DLS) [12].

Zeta Potential: A Malvern Zetasizer was used to analyze the manufactured liposome formulations zeta potential in order to evaluate surface charge and stability.

Scanning Electron Microscopic (SEM): The morphological properties of optimized liposome were determined using an electron beam from a scanning electron microscope. A vacuum sputter coater was then utilized to apply a thin (2-20 nm) layer of metal, such as platinum, palladium, or gold, to the liposome. The pretreatment specimen was then bombarded by an electron beam, which generated secondary electrons known as augers. Rutherford and Kramer's Law was accustomed to select and process just the electrons scattered at a 90° angle from this interaction between the electron beam and the specimens atoms to obtain surface topography images [13].

Formulation of Liposomal Gel: The optimized liposomal formulation (LSF5) was incorporated into a gel base using Carbopol-940 and Carboxymethyl cellulose. Carbopol-940 (1 g) was soaked in 50 mL warm water and stirred for 2 hours. A separate dispersion of CMC (1 g), methyl paraben (0.2 mL), and propylene glycol (0.5 mL) was prepared and mixed with the Carbopol dispersion. The pH was adjusted with triethanolamine (TEA) to form a smooth gel, and 10 mL of liposomal suspension was incorporated with continuous stirring until uniform.

TABLE 2: COMPOSITION OF LIPOSOMAL GEL FORMULATION

Name of Ingredient	Gel Formulation
Carbopol 940	1 gm
Carboxymethyl cellulose	1 gm
Propylene glycol	0.5 ml
Methyl paraben	0.2 ml
Extrct Loaded Liposome	10 ml
Triethanolamine	q.s
Water	100 ml

Characterization Parameters of Extract Loaded Liposomal Gel Formulation:

Physical Appearance: The formulation was inspected for color, clarity, uniformity, and the existence of any phase separation, grittiness, or particulate matter [14].

Measurement of pH: A calibrated digital pH meter was used to measure the extract-loaded liposomal gels pH.

Determination of Viscosity: A Brookfield viscometer was used to measure the liposomal gels viscosity [15].

Spreadability of Extract Loaded Liposomal Gel: A topical gel that is placed or rubbed over the skin surface should have a high spreading coefficient. About 1 g of formulation was put on a glass slide to evaluate this. The gel was sandwiched between the two glass slides and distributed at a predetermined distance by placing a 50 mg bulk on top of another glass slide that was the same length as the first one. It was noted how long it took the gel to move a specific distance from its starting point.

The spread ability was determined by the following formula.

$$S= M\times L/T$$

Where, S-Spread ability, g.cm/s M-Weight put on the glass slides upper L-length T-Time for spreading gel in sec [16].

Anti-microbial Activity of Liposomal Gel Formulation by well Diffusion Assay:

Preparation of Nutrient Agar Media: 2.8 g of Nutrient Media was dissolved in 100 mL of distilled water. The pH of the media was measured before sterilization.

To ensure disinfect the media, it was autoclaved for 15 min at 121 °C under 15 pounds of pressure. After pouring nutritional medium into plates, the plates were placed in laminar air flow until the agar became solid.

Well Diffusion Assay: *E. coli* and *S. aureus* bacterial suspensions were added to the shaker at concentration of 108 CFU/ml. After that, 100µl of the broth's inoculums (108 CFU/ml) were taken out using micropipette and inoculated onto a new, sterile, solidified Agar Media Plate. To inoculate the agar plate, the inoculums were applied to entire sterile agar surface using a sterilized spreader. A sterile cork-borer was used to bore four 6-mm wells into the solidified Agar Media Plate. Plant extract loaded gel (1 mg/ml) the solution was made and put into the wells.

Incubation Period for Observe Zone of Inhibition on Agar Plates: The bacteria on the Agar Media Plate were allowed to disperse for about half an hour at room temperature prior to being cultured for 18 to 24 hours at 37°C. Plates were inspected after incubation to determine whether a clear zone had developed around the well, signifying the antibacterial properties of the studied composition.

Zone of inhibition (ZOI) millimeters were measured and examined. Using a ruler resting on the back of an inverted Petri plate, zones were measured to the closest millimeter. A dark, non-reflective background was positioned a few inches above the Petri plate. The well's diameters and the zone of total inhibition (as perceived by the naked eye) were measured [17].

RESULT AND DISCUSSION:

Plant Collection: Leaves of *Acacia leucophloea* and *Euphorbia cyathophora* were collected, shade-dried, and used for extraction. The details of plant materials are summarized in **Table 3.**

TABLE 3: PLANT COLLECTION

Plant name	Plant part used	Weight
Acacia leucophloea and Euphorbia cythophora	Leaves	300 gm

Percentage Yield: The extraction yields varied depending on the solvent used **Table 4** and **Table 5**. Ethanolic extracts showed higher yields than petroleum ether extracts, indicating a greater presence of polar phytoconstituents. Specifically, *A. leucophloea* yielded 2.31% (ethanol) and *E. cyathophora* 4.50% (ethanol).

TABLE 4: PERCENTAGE YIELD OF CRUDE LEAVES EXTRACTS OF *ACACIA LEUCOPHLOEA* EXTRACT

Plant name	Solvent	Color of extract	Theoretical weight	Yield(gm)	% yield
Acacia leucophloea	Pet ether	Greenish brown	300	3.87	1.29%
	Ethanol	Green	283	6.56	2.31%

TABLE 5: PERCENTAGE YIELD OF CRUDE LEAVES EXTRACTS OF *EUPHORBIA CYTHOPHORA*

Plant name	Solvent	Color of extract	Theoretical weight	Yield(gm)	% yield
Euphorbia cythophora	Pet ether	Greenish Yellow	300	8.31	2.77%
	Ethanol	Green	272	13.52	4.50%

Preliminary Phytochemical Study: The qualitative phytochemical analysis **Table 6** and **7** confirmed the presence of major secondary metabolites including alkaloids, glycosides, flavonoids, tannins, carbohydrates, and saponins in both plant extracts, particularly in the ethanolic fractions.

TABLE 6: PHYTOCHEMICAL TESTING OF *ACACIA LEUCOPHLOEA* LEAVES EXTRACT

S. no.	Experiment	Presence or absence of phytochemical test	
		Pet. Ether extract	**Ethanolic extract**
1.		**Alkaloids**	
	Dragendroff's test	Absent (-)	Present (+)
	Mayer's reagent test	Absent (-)	Present (+)
	Wagner's reagent test	Absent (-)	Present (+)
	Hager's reagent test	Absent (-)	Present (+)
2		**Glycoside**	
	Borntrager test	Present (+)	Present (+)
	Killer-Killiani test	Present (+)	Present (+)
3.		**Carbohydrates**	
	Molish's test	Present (+)	Present (+)
	Fehling's test	Present (+)	Present (+)
	Benedict's test	Present (+)	Present (+)
	Barfoed's test	Absent (+)	Present (+)
	Iodine Test	Absent (-)	Present (+)
4.		**Flavonoids**	
	Shinoda Test	Absent (-)	Present (+)
5.		**Tannin and Phenolic Compounds**	
	Ferric Chloride test	Present	Present (+)
	Lead Acetate Test	Absent (-)	Present (+)
	Gelatin Test	Absent (-)	Present (+)
6.		**Saponin**	
	Foam test	Present (+)	Present (+)
	Froth Test	Present (+)	Present (+)
7.		**Test for Triterpenoids and Steroids**	
	Salkowski's test	Present (+)	Absent (-)
	Libbermann-Burchard's test	Present (+)	Absent (-)

TABLE 7: PHYTOCHEMICAL TESTING OF *EUPHORBIA CYTHOPHORA* LEAVES EXTRACT

S. no.	Experiment	Presence or absence of phytochemical test	
		Pet. Ether extract	**Ethanolic extract**
1.		**Alkaloids**	
	Dragendroff's test	Absent (-)	Present (+)
	Mayer's reagent test	Absent (-)	Absent (-)
	Wagner's reagent test	Absent (-)	Present (+)
	Hager's reagent test	Absent (-)	Present (+)
2.		**Glycoside**	
	Borntrager test	Absent (-)	Present (+)
	Killer-Killiani test	Absent (-)	Present (+)
3.		**Carbohydrates**	
	Molish's test	Present (+)	Present (+)
	Fehling's test	Present (+)	Present (+)
	Benedict's test	Present (+)	Present (+)
	Barfoed's test	Absent (-)	Present (+)
	Iodine Test	Absent (-)	Present (+)
4.		**Flavonoids**	
	Shinoda Test	Absent (-)	Present (+)
5.		**Tannin and Phenolic Compounds**	
	Ferric Chloride test	Absent (-)	Present (+)
	Lead Acetate Test	Absent (-)	Absent (-)
	Gelatin Test	Absent (-)	Present (+)
6.		**Saponin**	

	Foam test	Present (+)	Present (+)
	Froth Test	Present (+)	Present (+)
7.	**Test for Triterpenoids and Steroids**		
	Salkowski's test	Absent (-)	Absent (-)
	Libbermann-Burchard's test	Absent (-)	Absent (-)

Organoleptic Properties: Organoleptic observations **Table 8** revealed characteristic color and odor for both extracts, confirming their identity.

TABLE 8: THE ORGANOLEPTIC STUDIES OF *ACACIA LEUCOPHLOEA* AND *EUPHORBIA CYTHOPHORA* LEAVES EXTRACT

Parameters	*Acacia leucophloea*	*Euphorbia cythophora*
Colour	Greenish brown	Green
Odour	Musky	Characteristic
Appearance	Greenish brown	Greenish yellow

Solubility Study: Solubility studies **Table 9** demonstrated good solubility in ethanol and petroleum ether, supporting their suitability for liposomal encapsulation.

TABLE 9: SOLUBILITY STUDY OF *ACACIA LEUCOPHLOEA* AND *EUPHORBIA CYTHOPHORA*

Solvents	*Acacia leucophloea*	*Euphorbia cythophora*
Ethanol	Freely soluble	Freely soluble
Distilled water	Soluble	Soluble
DMSO	Soluble	Slightly soluble
Chloroform	Sparingly soluble	Soluble
Acetone	Slightly soluble	Sparingly soluble
Petroleum ether	Freely soluble	Freely soluble

Evaluation Parameter of Liposomes Formulation: All five liposomal formulations (F1–F5) were milky and homogeneous **Table 10**.

TABLE 10: VISIBLE OBSERVATION OF PREPARED LIPOSOMES FORMULATION

Parameters	Liposome Formulation
Colour	Milky
Odour	Characteristics
appearance	Liquid

The particle size and zeta potential results are presented in **Table 11** and **12.**

Particle size: The particle size ranged between 42.53 and 118.36 nm **Table 11**. The smallest vesicle size was observed in formulation F5 (42.53 nm), which is desirable for enhanced skin penetration and stability.

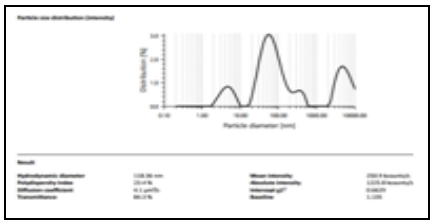

FIG. 1: PARTICLE SIZE (F1)

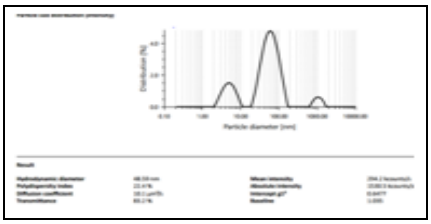

FIG 2: PARTICLE SIZE (F2)

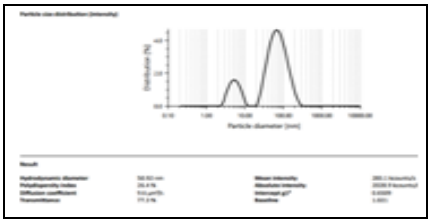

FIG 3: PARTICLE SIZE (F3)

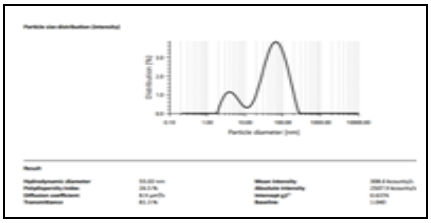

FIG 4: PARTICLE SIZE (F4)

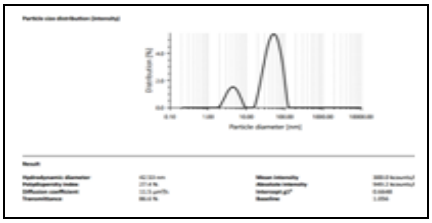

FIG 5: PARTICLE SIZE (F5)

TABLE 11: SIZE DISTRIBUTION OF LIPOSOME

Formulation	Particle size (nm)	PI value (%)
Liposome (F1)	118.36	23.4
Liposome (F2)	48.59	22.4
Liposome (F3)	50.92	26.4
Liposome (F4)	55.02	26.5
Liposome (F5)	42.53	27.4

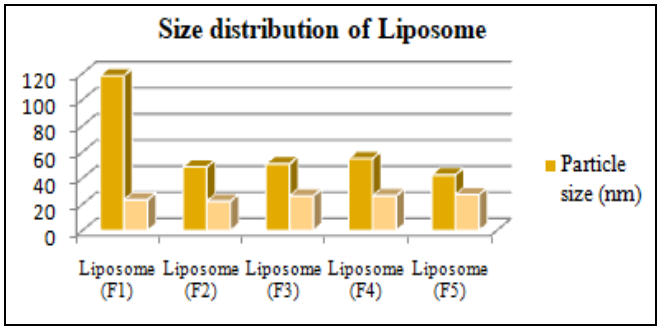

FIG. 6: GRAPHICAL REPRESENTATION OF SIZE DISTRIBUTION OF LIPOSOME

Zeta Potential: Zeta potential values ranged from –4.1 to –17.5 mV **Table 12**. F5 (–13.8 mV) exhibited moderate stability due to electrostatic repulsion between vesicles.

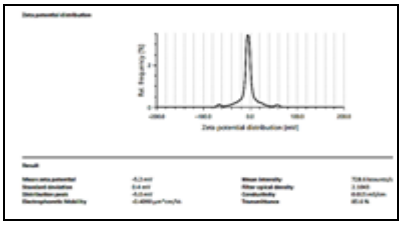

FIG. 7: ZETA POTENTIAL (F1)

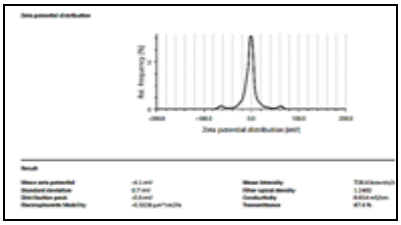

FIG. 8: ZETA POTENTIAL (F2)

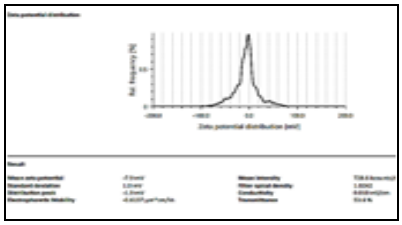

FIG. 9: ZETA POTENTIAL (F3)

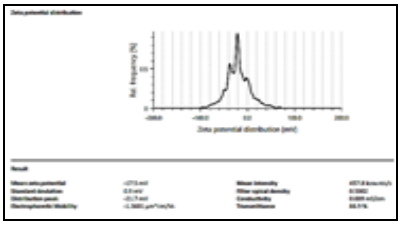

FIG. 10: ZETA POTENTIAL (F4)

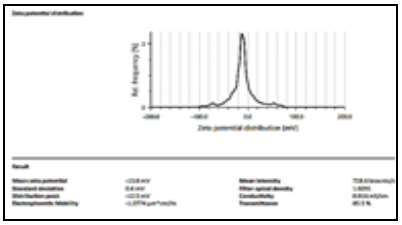

FIG. 11: ZETA POTENTIAL (F5

TABLE 12: ZETA POTENTIAL OF LIPOSOME

Formulation	Zeta potential
Liposome (F1)	-5.2 mV
Liposome (F2)	-4.1 mV
Liposome (F3)	-7.9 mV
Liposome (F4)	-17.5 mV
Liposome (F5)	-13.8 mV

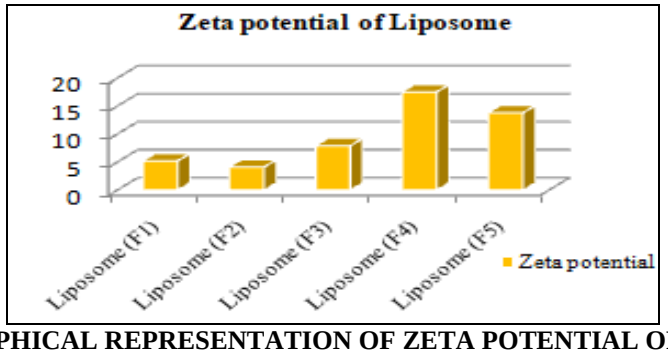

FIG. 12: GRAPHICAL REPRESENTATION OF ZETA POTENTIAL OF LIPOSOME

Scanning Electron Microscopic (SEM): SEM images of F5 **Fig. 3** revealed spherical vesicles with smooth surfaces, confirming uniform morphology typical of stable liposomal systems.

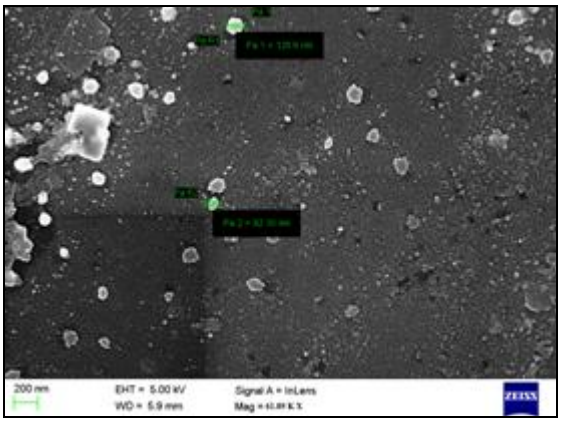

FIG. 13: SEM (F5)

Evaluation Parameter of Liposomal Gel Formulation:

Physical Properties: The optimized liposomal formulation (F5) was incorporated into a Carbopol-based gel. The gel was milky white, semisolid, and smooth **Table 13.**

TABLE 13: PHYSICAL PROPERTIES OF LIPOSOMAL GEL

Parameters	Results
Physical appearance	Semisolid gel
Colour	Milky white
Homogeneity	Absence of aggregates

Measurement of Liposomal Gel Formulation: Physicochemical analysis **Table 14** indicated pH 6.8, viscosity 1549 ± 0.26 cps, and excellent spreadability (13.26 g·cm/s). No skin irritation was observed, confirming topical safety.

TABLE 14: VISCOSITY, pH, SKIN IRRITATION STUDY AND SPREADABILITY TEST OF GEL FORMULATION

Formulation	Results (pH)	Skin irritation study	Viscosity Results (cps)	Spreadability test (gm.cm/sec)
Liposome (F5)	6.8	Not irritant observed	1549±0.26	13.26

Results of Antimicrobial Activity of Liposomal Gel F5 formulation:

Antimicrobial Activity of Liposomal Gel: Antibacterial testing against *Escherichia coli* and *Staphylococcus aureus* showed significantly enhanced activity of liposomal gel compared to crude extracts **Table 15, Fig. 4.**

TABLE 15: ANTIMICROBIAL ACTIVITY OF LIPOSOMAL GEL *AGAINST E.COLI AND S. AUREUS*

Sample Name (mg/ml)	Zone of Inhibition (mm) of *E. coli*	Zone of Inhibition (mm) of *S. aureus*
Control	0 mm	0mm
Extract C1 (1mg/ml)	5 mm	3 mm
Liposomal gel (F5) C2 (1mg/ml)	12 mm	8 mm

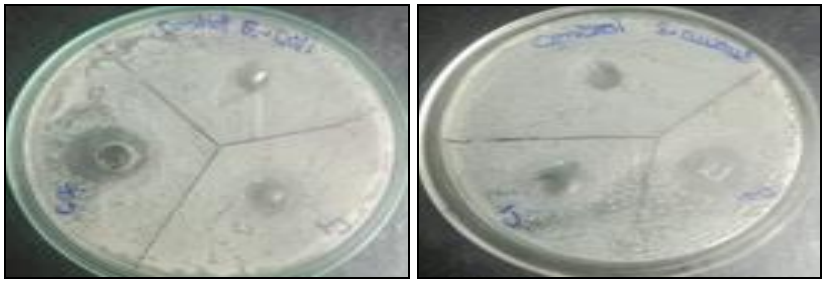

FIG. 14: PHOTOGRAPH SHOWING ZONE OF INHIBITION OF EXTRACT LOADED LIPOSOMAL GEL AGAINST A: *ESCHERICHIA COLI*, B: *STAPHYLOCOCCUS AUREUS*

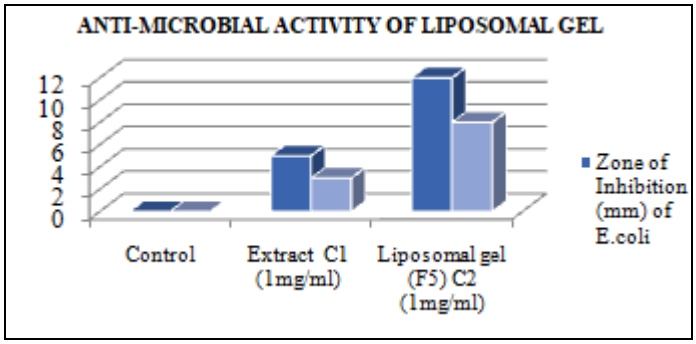

FIG. 15: ZONE OF INHIBITION OF LIPOSOMAL GEL USING PLANT EXTRACT AGAINST *E. COLI* AND *S. AUREUS* MICROORGANISMS

The improved antibacterial effect of the liposomal gel is attributed to enhanced solubility, sustained release, and improved penetration of phytoconstituents through bacterial membranes. These findings align with previous studies reporting superior antimicrobial action of liposomal formulations [1, 2].

Overall Discussion: The study confirmed that ethanol is an effective solvent for extracting polar phytochemicals from *A. leucophloea* and *E. cyathophora*. Phytochemical analysis verified the presence of bioactive components with known antimicrobial properties. The optimized liposomal formulation (F5) demonstrated ideal particle size, stability, and morphology. Incorporation into a topical gel resulted in a skin-compatible, stable, and effective antibacterial formulation. The synergistic action of both plant extracts in the liposomal gel offers a promising approach for herbal-based topical therapy.

CONCLUSION: The study successfully developed and characterized a liposomal gel formulation containing ethanolic extracts of *Acacia leucophloea* and *Euphorbia cyathophora*. The optimized formulation (F5) demonstrated desirable physicochemical properties, including small particle size, suitable zeta potential, and good stability, making it suitable for topical application.

Phytochemical screening confirmed the presence of bioactive compounds responsible for antibacterial activity. The liposomal gel showed significantly enhanced inhibition against *E. coli* and *S. aureus* compared to crude extracts, indicating improved drug delivery and efficacy. These findings suggest that liposomal gel systems are an effective approach for enhancing the therapeutic potential of plant-derived antimicrobials and can serve as promising candidates for future topical antibacterial formulations.

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