

Nanoemulgel Development for Topical Delivery: Formulation and Characterization

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ABSTRACT

Traditional treatments for inflammatory and microbial skin conditions, along with many potent bioactive compounds such as Curcumin, often fall short due to significant limitations in absorption and stability. Despite its well-documented therapeutic properties, Curcumin's clinical utility is severely hampered by its inherent drawbacks: poor water solubility, chemical instability, and rapid elimination from the body. These factors collectively reduce its bioavailability and ultimately its effectiveness when applied topically or administered systemically. To overcome these critical challenges and unlock Curcumin's full therapeutic potential, a sophisticated Curcumin-loaded nanoemulgel was developed. This innovative formulation was specifically engineered to significantly enhance Curcumin's solubility, improve its penetration into the skin, and ensure a sustained release at the target site. The development process involved creating an oil-in-water (O/W) nanoemulsion encapsulating Curcumin, which was then meticulously integrated into a Carbopol gel base to ensure optimal stability and topical applicability. Further enhancing the nanoemulgel's multi-functional profile, Eucalyptus oil was incorporated for its well-known antimicrobial properties and its ability to act as a penetration enhancer, facilitating deeper delivery of Curcumin into the skin layers. Additionally, Piperine was included in the formulation to synergistically boost Curcumin's absorption and bioavailability, leveraging its established role as a natural bioenhancer. Rigorous and comprehensive testing unequivocally demonstrated the success of this novel approach. The Curcumin nanoemulgel exhibited remarkable improvements in several key areas: significantly enhanced Curcumin solubilization, superior skin penetration, prolonged and sustained release of the active compound, and notable antimicrobial activity against relevant pathogens. This groundbreaking Curcumin nanoemulgel represents a highly promising, multi-functional platform. It effectively addresses and surmounts the inherent limitations of Curcumin, paving the way for more effective treatment of various skin disorders and ultimately leading to improved patient compliance and therapeutic outcomes.

Keywords: Nanoemulgel, Curcumin, Piperin A, Eucalyptus oil.

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INTRODUCTION

The evolution of modern drug discovery, driven by innovations in chemical synthesis and rapid screening methods, has increasingly prioritized lipophilic compounds. This focus is so pronounced that lipophilic molecules now constitute 90% of all drugs in the developmental pipeline and more than 40% of medications on the market. While beneficial for interacting with biological membranes, this lipophilic nature creates significant hurdles, primarily poor aqueous solubility. This, in turn, can lead to unpredictable absorption patterns and considerable variation in how the drug behaves both between different patients and for the same patient on different occasions. A variety of techniques are actively used to overcome these solubility limitations. These approaches range from fundamental physical and chemical modifications of the active drug ingredient to sophisticated formulation strategies, including micronization,

complexation, the creation of amorphous solids, and the engineering of nanoscale drug delivery vehicles^{1,2}. Functioning as a heterogeneous yet uniform system, a nanoemulsion is created by blending oil, water, and a surfactant. The result is a dispersion where either oil or water exists as minuscule droplets suspended in the other liquid. The key to their stability lies with the surfactant, which positions itself at the interface between the two liquids to form a film that prevents the droplets from merging³⁻⁶. Anti-inflammatory medications designed for topical use are administered directly onto the troubled area of the skin to reduce pain and manage local conditions like swelling and inflammation. Furthermore, delivering drugs through the skin, known as transdermal therapy, is considered a highly successful method because it allows for sufficient absorption of the medicine while causing fewer side effects. This approach utilizes various formulations, including patches, gels, emulgels, and nanoemulgels⁶⁻⁸.

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Curcumin is a water-insoluble polyphenol, specifically an o-methoxy phenol derivative, that is extracted from the rhizome of the *Curcuma longa* plant. This herb is a member of the ginger family, Zingiberaceae. Historically, curcumin has been utilized in traditional medicine to treat numerous conditions, a practice stemming from its extensive range of biological and medicinal properties⁹⁻¹². The principal active constituent of the turmeric rhizome (*Curcuma longa* L.) is curcumin. For a considerable time, it has been documented as a superior free radical scavenger, antimicrobial agent, and anti-inflammatory substance. These significant biological activities are linked to the diferuloyl-methane portion of its chemical makeup. Moreover, curcumin contributes significantly to the healing of different kinds of wounds¹³⁻¹⁵. Historically, cumin has been a staple in traditional medicine, valued for its effectiveness in addressing issues like flatulence, various digestive ailments, diarrhea, and wound healing. More recently, the focus has shifted

to the essential oils found in cumin seeds. Researchers are increasingly interested in these oils, primarily due to their unique chemical makeup, specifically the abundance of oxygenated monoterpenes and monoterpene hydrocarbons. This rich composition is what makes cumin essential oils a subject of significant scientific exploration^{16,17}. Curcumin stands out as a successful example of a therapeutic compound derived from plants. Another significant naturally occurring compound, piperine, found predominantly in black pepper (*Piper nigrum*) and long pepper (*Piper longum*), boasts a range of biological activities, including notable anti-inflammatory and antioxidant properties. Research indicates that piperine can elevate TGF- β levels, aid collagen repair, and inhibit NF- κ B activation in the periodontal tissues of rodents¹⁸⁻²⁰. Eucalyptus oil, extracted from *Eucalyptus globulus*, is an essential oil where approximately 45.4% of its composition is 1,8-cineole, also known as eucalyptol (Eu). Eucalyptol is recognized for its potent antimicrobial properties against both human and foodborne microbes. While eucalyptol is the primary and most significant component, making up 60-85% of the oil, it's crucial not to confuse it with eucalyptus oil itself. Eucalyptus oil is a complex blend of various compounds, whereas eucalyptol is a specific, naturally occurring compound. Eucalyptol is typically isolated through the distillation of eucalyptus tree leaves²¹⁻²³. As Curcumin, eucalyptol, and Piperine A are essential for the synergistic action in wound healing, and nanoemulgel is an effective tool for increasing the therapeutic actions so in this research, we are going to formulate the nanoemulgel of curcumin, eucalyptol, and Piperine A.

MATERIALS & METHODS

Materials:

Curcumin (Anti-inflammatory), Piperine A (Bioenhancer), Eucalyptol (Penetration enhancer, analgesic), Arachis oil (Oil phase), Tween 80 (Surfactant), Propylene glycol (Co-surfactant), Carbopol 940 (Gelling agent), Triethanolamine (PH Adjuster), Glycerin (Humectant) , Sodium benzoate

(Preservative) , Vitamin E (Antioxidant) , Distilled water (Solvent).

Methods:

Experimental Design and Optimization –

Optimization trials were systematically designed using Design-Expert¹¹ software, focusing on critical formulation parameters such as emulsification efficiency and viscosity. The concentrations of Tween 80 (emulsifying agent) and Carbopol (gelling agent) were selected as independent variables for optimization.

Table no 1: Formulation optimization Batches by using Design Expert¹¹

		Factor 1	Factor 2
Std	Run	A: Tween	B: Carbopol 940
		%	%
5	1	11.5	1.25
2	2	11.5	1
9	3	12	1.5
3	4	12	1
4	5	11	1.25
7	6	11	1.5
1	7	11	1
6	8	12	1.25
8	9	11.5	1.5

Chromatography (TLC) and subsequently held at room temperature for further analysis.

Table no 2: Optimized Batch of Nanoemulgel by Design Expert ¹¹

Ingredients	%w/w	Quantity Used	Role
Curcumin	1.5	1.5	Anti-inflammatory
Piperin	0.2	0.2	Bioenhancer
Eucalyptus	2	2	Analgesic
Arachis oil	10	10	Oil phase
Tween 80	11.5	11.5	Surfactant
Propylene Glycol	5	5	Co surfactant
Vitamin E	0.2	0.2	Antioxidant
Distilled Water	Q. S	Upto 100 ml	Continuous Phase
Carbapol940	1.25	1.25	Gelling Agent
Glycerine	10	10	Humectant
Sodium Benzoate	0.2	0.2	Preservative
Triethanolamine	Q. S	Few Drops	Neutralizer
Distilled Water	Q. S	Upto 100 ml	Continuous Phase

Extraction of Phytochemicals

Extraction of Curcumin –

The extraction of curcumin from a turmeric sample (obtained from a local grocery store) was performed using a Soxhlet apparatus. Initially, approximately 50 grams of turmeric powder were loaded into a thimble. A round-bottom flask was charged with 250 mL of ethanol, and the system was set up for extraction. The sample was heated to a temperature range of 60–70°C for 4–6 hours, with an extra 250 mL of ethanol being introduced at regular intervals to ensure comprehensive extraction. Following the extraction, the solution was allowed to cool. Solvent evaporation was then carried out on the obtained extract through simple steam distillation at 50–60°C for 30 minutes. The resulting curcumin extract was assessed by Thin Layer



Figure1. Soxhlet Extraction of Curcumin



Figure 2. Distillation

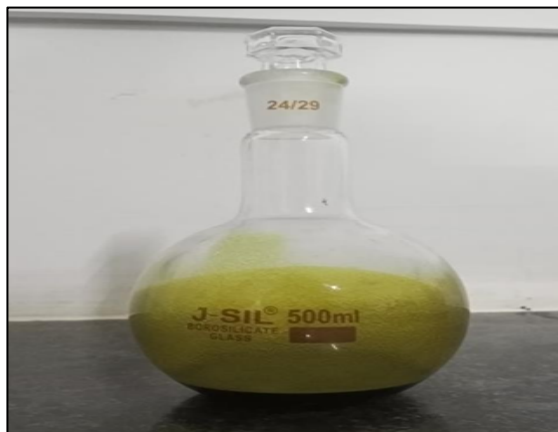
Figure 3. Curcumin Extract

Thin Layer Chromatography (TLC) of curcumin:

Analysis of the turmeric's ethanolic extract involved Thin Layer Chromatography (TLC), utilizing silica gel-G coated plates. We prepared the TLC plates by spotting the extract with a capillary tube and allowing it to dry. The mobile phase consisted of a 9:1 mixture of chloroform and methanol. These plates were then positioned in a developing chamber that was saturated with this solvent system, facilitating its upward movement via capillary action. After the development was complete, we air-dried the plates and sprayed them with ninhydrin reagent to make the spots visible. To quantify the migration, the retention factor (Rf) was computed by comparing the distance travelled by the curcumin spot against the distance of the solvent front.

Extraction of Piperine A:

To extract piperine, 10 grams of powdered black pepper were loaded into a thimble for Soxhlet extraction. A round-bottom flask containing 100 mL of ethanol was set up for the process, which ran for six hours at a temperature range of 60–80°C. After collection, the extract was subjected to simple distillation at 60°C for 30 minutes to concentrate it. The resulting piperine extract was then assessed using Thin Layer Chromatography (TLC) and subsequently kept at room temperature for any future analytical needs.

**Figure 5. Piperin Extract**

Thin Layer Chromatography of Piperine A:

The methanolic extract from black pepper underwent Thin Layer Chromatography (TLC) analysis. We used silica gel-G as the stationary phase and a mobile phase made of toluene and ethyl acetate in a 7:3 ratio. Once the extract was spotted and the plate developed, it was dried and treated with ninhydrin spray. The detection of colored spots on the plate provided evidence of piperine's presence. For characterization and comparative purposes, the Rf value was then determined.

Extraction of Eucalyptol:

The preparation for eucalyptol extraction involved collecting fresh eucalyptus leaves from campus. These leaves were dried in a hot air oven at 40–45°C for 4–5 hours, then cooled to room temperature and finely powdered. About 10 grams of the powdered leaves were

subjected to Soxhlet extraction, mirroring the methodology



employed for curcumin extraction and using ethanol as the solvent. Following extraction, the solvent was removed from the obtained extract via simple distillation, leading to a concentrated product. The resultant eucalyptol was then characterized by TLC and stored at room temperature.

Thin Layer Chromatography of Eucalyptol:

For the analysis of eucalyptus oil, we prepared a methanolic dilution and spotted it onto a silica gel-G TLC plate. The chromatographic separation was carried out using a mobile phase of hexane: ethyl acetate (8:2). After development in the TLC chamber, the plate was dried and sprayed with ninhydrin reagent. Subsequent gentle heating of the plate resulted in the visualization of spots, thereby confirming the presence of eucalyptol. To ensure accurate identification, the Rf value of the observed spot was then calculated.



Figure 6. Eucalyptus Extract



Figure 7. TLCs of All Extracts

Preparation of Nanoemulgel –
 The nanoemulgel was prepared by three main phases which are preparation of nanoemulsion, formation of the nanoemulsion, Preparation of the oil phase, Preparation of the Surfactant-Cosurfactant Mixture (Smix) , Preparation of the Gel Base, Incorporation of Nano emulsion into Gel Base (Nanoemulgel Formation).

Preparation of Nanoemulsion –
 To formulate the nanoemulsion, active ingredients (curcumin, piperine, eucalyptol) were dissolved in arachis oil. This oil mixture was then combined with a Smix (Tween 80 and propylene glycol). This prepared oil phase was



slowly introduced into distilled water while continuously homogenizing to yield a stable nanoemulsion.

Formation of the Nanoemulsion -

A stable, uniform nanoemulsion was achieved through a multi-step process. First, the Smix was slowly combined with the oil phase, stirring at 600–800 rpm for 10–15 minutes while keeping the temperature below 45°C. This was followed by low-energy emulsification, high-shear homogenization, and ultrasonication. (Figure 8)

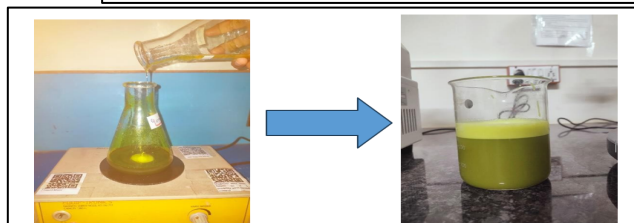
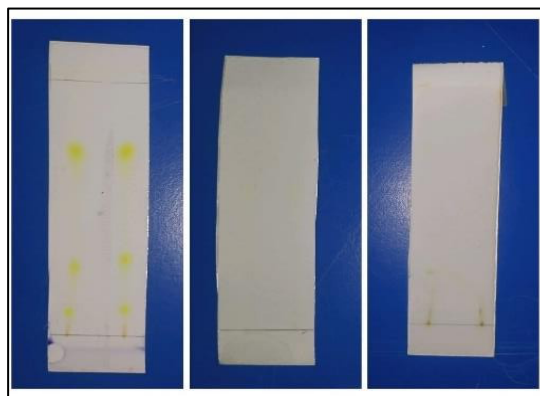


Figure 8. Preparation of Emulsion & Nanoemulsion

Preparation of the Oil Phase –

A homogeneous oil phase was formulated using 1.5 mL curcumin extract, 0.2 mL piperine extract, 2 mL eucalyptus oil (for enhanced permeation), and 10 mL arachis oil (as the main lipid). The mixture was gently heated to 40–45°C and stirred at 400–500 rpm until all components were fully solubilized. Figure 9.

Figure 9. Oil Phase

Preparation of the Surfactant-Cosurfactant Mixture (Smix)

A stable nanoemulsion was successfully prepared through a multi-step emulsification process. First, Tween 80 (12% w/w) was blended with propylene glycol to form a Smix, which was stirred until clear. This Smix was then gradually introduced into double-distilled water and intensely homogenized (5000–6000 rpm for 60 minutes) to yield a coarse emulsion. Subsequent 30-minute ultrasonication refined the droplet size, producing a translucent to slightly turbid nanoemulsion with excellent physical stability. The



final formulation was stored at room temperature ($25\pm 2^{\circ}\text{C}$) for further evaluation.

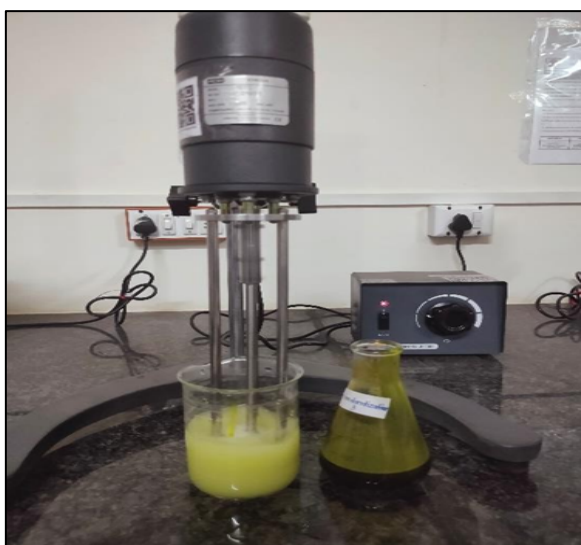


Figure 10. Homiginization

Preparation of the Gel Base: A Carbopol 940 hydrogel was formulated as a topical carrier. 1.5 g of Carbopol 940 was slowly added to 100 mL of distilled water ($40\text{--}45^{\circ}\text{C}$) and stirred for 30 minutes. Triethanolamine was then added to adjust the pH to ~ 6.69 , yielding a clear gel. Glycerin (10 mL) and sodium benzoate (0.2 g) were incorporated for humectant and preservative properties, respectively. The smooth, homogenous gel was rested for 30 minutes to ensure complete swelling and air removal before use.

Incorporation of Nanoemulsion into Gel Base (Nanoemulgel Formation)

An optimized nanoemulsion was incorporated into a Carbopol 940 gel base to create a topical nanoemulgel. Using a 1:2 ratio (33.3 mL nanoemulsion to 66.7 mL gel), the nanoemulsion was slowly added with stirring (300–400 rpm for 10–15 minutes) to ensure uniform blending and

stability. This yielded a smooth, homogeneous, semi-solid nanoemulgel, which was stored at $25\pm 2^{\circ}\text{C}$ in an airtight container for future evaluation. Figures 11 & 12

Figure 11. Gel Phase Preparation
12. Final Gel Prepared

Figure

Characterization of Nanoemulgel –

General Appearance –

Visually, the nanoemulgel was examined for its color, odor, consistency, and homogeneity. This involved checking under natural light against a white background for color and clarity, and noting any lumps, phase separation, or grittiness. The odor was assessed for pleasantness, and the consistency was evaluated by spreading it between fingers to determine smoothness and spreadability.

PH Determination –

To assess the nanoemulgels pH, a calibrated digital pH meter (Systronics model) was used. It was first standardized with pH 4.0 and 7.0 buffer solutions. A 1-



gram sample of the nanoemulgel was dispersed in 10 mL of distilled water, and the pH electrode was immersed in it, avoiding contact with the beaker's sides or bottom. The target pH range of 5.5–7.0 was considered, which is crucial for skin compatibility and formulation stability. (Figure 13)

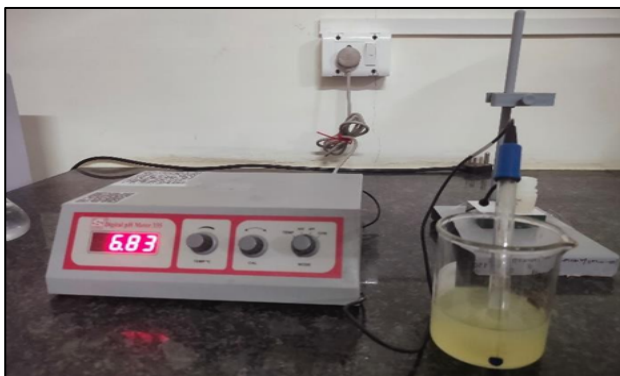


Figure 13. PH Determination

Viscosity –

The viscosity of the nanoemulgel was measured using an Ostwald viscometer. A 1% w/v solution was prepared by diluting 1 gram of the nanoemulgel with distilled water. Both the sample and distilled water (reference) were brought to room temperature before testing. The flow time of both was recorded using the viscometer, and the viscosity was calculated.

Spreadability –

To assess spreadability, 1 gram of the gel was centrally placed on an inverted Petri dish. Another Petri dish was then

Samples	Curcumin			Eucalyptus			Piperin		
	7.3	7.5	7.6	7.1	7.9	7.8	9.8	9.5	9.6
Solvent font									

positioned on top for one minute. Following this, a 50-gram weight was added before measuring the radius.

Particle Size and Zeta Potential –

The particle size and zeta potential were carried out by using the Nanoplus Instrument at H.R. Patel Institute of Pharmaceutical Education and Research, Shirpur.

Antimicrobial / Antifungal Test –

To evaluate sodium benzoate's effectiveness as a preservative for

Sample	Emulsifier (Tween 80) Concentration	Partical Size(nm)
Optimized Batch	12	973.2

curcumin, an antimicrobial study was conducted. The prepared samples were sent to the Department of Microbiology at Sant Gadge Baba Amravati University. The goal was to determine how well the formulation inhibited *Streptococcus aureus* growth, confirming sodium benzoate's preservative capabilities in the curcumin system.

Accelerated Stability Study –

For checking the stability of the prepared nanoemulgel, the nanoemulgel was subjected to an accelerated stability study using Programmable environmental chamber 10 S (Remi Electrotechnics Ltd., India) for 3 months. The NPs were kept in a glass vial sealed with a rubber cap at 40 °C ± 2 °C and 75 % RH. The NPs were analyzed for particle size and viscosity²⁴.

Result And Discussion –

General description:

The results of the general description are mentioned in Table no 3;

Table no 3. General Evaluation

Parameter	Observation
Colour	Greenish Yellow
Odor	Pleasant
Consistency	Smooth, non-gritty
Homogeneity	Uniform, no phase separation

Thin Layer Chromatography-

The results of Thin Layer Chromatography are mentioned in table 4

Table no 4. TLC Results

Solute	5.3	6	6.1	6.1	7.5	5.5	5	5.1	4.5
Rf value	0.75	0.8	0.80	0.85	0.94	0.70	0.51	0.5	0.46
Avg	0.783			0.833			0.496		

PH Test –

The pH of the gel formulation was assessed to ensure skin compatibility. Although specific readings aren't available, the method of dispersing 1 gram of gel in 10 mL of water is suitable for topical products. Ideally, topical gels should have a pH between 4.5 and 6.5, closely mirroring the skin's natural pH. Maintaining this range helps reduce irritation risk and improves skin tolerance. Once the average pH is determined, it can be compared to this target to confirm dermal safety.

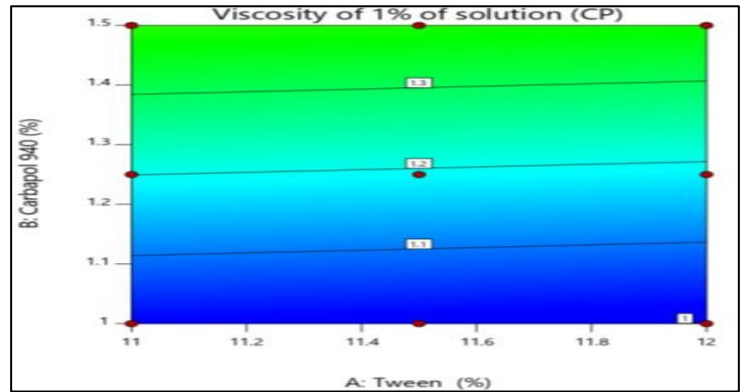
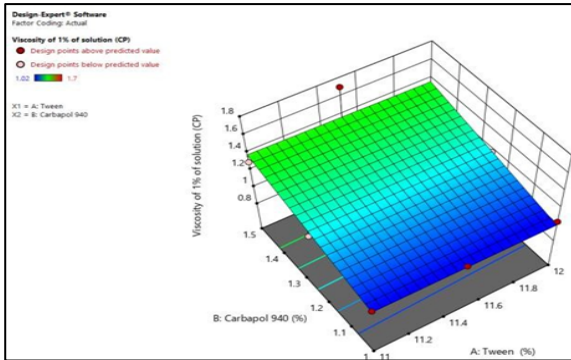
Table no 5 Observation of PH test

Viscosity (Ostwald Method)-

Viscosity is crucial for how well topical formulations perform and remain stable. Our gel, measured with an Ostwald viscometer, had a viscosity of 1.2 centipoise (cP), which is ideal for topical gels. This value is slightly higher than water's (0.01 cP), indicating the gel is appropriately thickened. This ensures it stays on the skin long enough without feeling sticky or being hard to spread. The similar densities of water (0.997 g/cm³) and our sample (0.999 g/cm³) also confirm that density differences didn't skew our viscosity calculations, making the result reliable.

Table no 7 Results of Particle Size Study

Table no 6 Observation of Viscosity Test



Sample	Viscosity of water	Flow time of water	Flow time of the sample	Density of water	Density of Sample	Calculated Viscosity
1 gm of Gel diluted in 100 ml of water	0.01	5	6	0.997	0.999	1.2 cp

Sample	Average PH	Target range
1 gm of Gel Diluted in 105.6 ml	5.6	to 7

Results of Optimization –

The ANOVA table for particle size indicates that Tween 80 concentration (Factor B) has a statistically significant effect ($p < 0.0001$) on particle size. The model's R^2 value of 0.9884 and Predicted R^2 of 0.9755 show a very good fit, confirming that the formulation variables reliably influence particle size. The smallest particle size observed was 686.5 nm, which falls in the nanometric range, making it suitable for enhanced dermal permeation

Figure 14 - 3D counter plots showing the effect of independent variables on the Particle size

Particle Size and Zeta Potential:

When crafting nanoformulations, particle size is a crucial factor influencing how the drug is released, absorbed, and its overall stability. Analysis using Scanning Electron Microscopy (SEM) and zeta potential measurements indicated that a higher concentration of the emulsifier, Tween 80, resulted in progressively smaller particle sizes. This observation highlights Tween 80's effectiveness in stabilizing the formulation and reducing droplet size. This is likely because increased Tween 80 leads to better coverage at the interface between the components, which in turn prevents droplets from combining. Sample 3, with a final particle size of 686.5 nm, falls within the acceptable range for nanoemulsions (10-1000 nm). This size suggests that the formulation is well-suited for improved penetration through the skin. While specific zeta potential values aren't given here, they're typically measured to confirm a nanoemulsion's electrostatic stability. Generally, a higher absolute zeta potential (meaning ± 30 mV or more) indicates better stability because it suggests stronger repulsion between droplets, preventing them from clumping together.

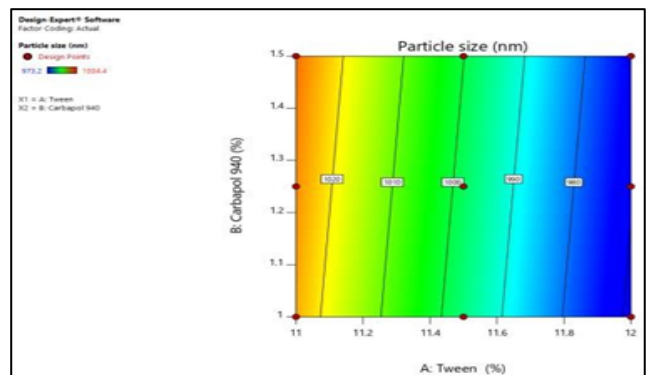


Figure 15 - 2D counter plots showing the effect of independent variables on the Particle size

Instead, the system's stability likely comes from steric hindrance, primarily due to the non-ionic surfactant Tween 80. This means Tween 80 physically prevents droplets from clumping together, rather than relying on electrical repulsion. Additionally, the presence of Carbopol and PEG might contribute to stability by creating a viscous environment that traps the droplets. Figure 19.

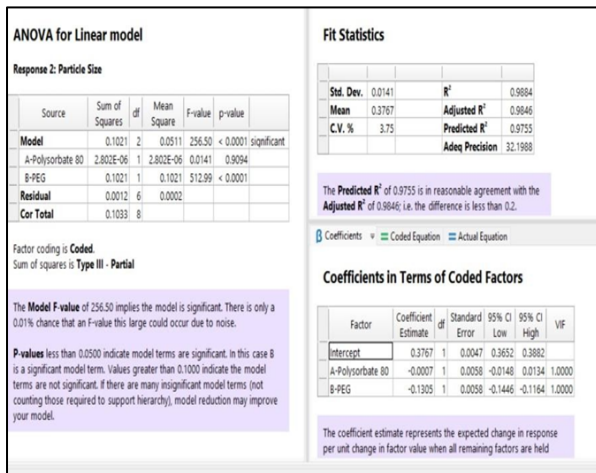


Figure no 16. ANOVA test results for Particle size

Figure 19. Zeta Potential Results

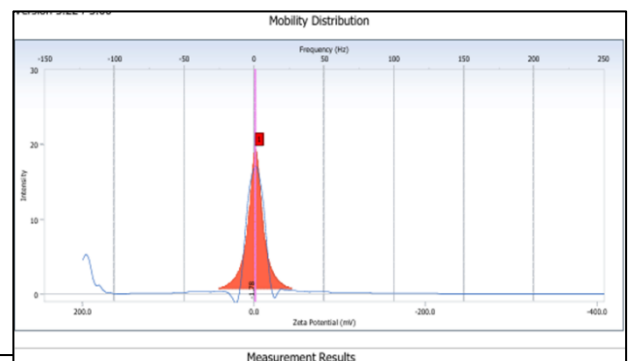


Figure No. 17 2D Counter plots showing the effect of independent variables on the viscosity

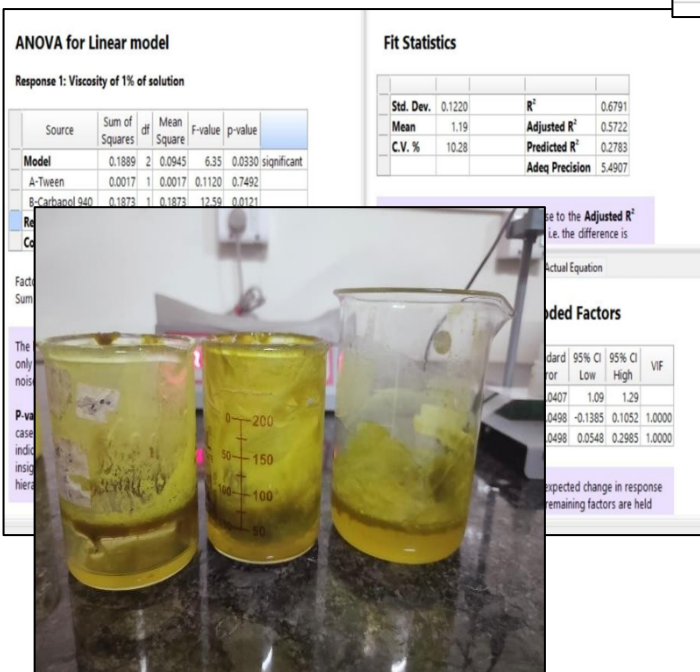


Figure 18. ANOVA test results for viscosity

Implications of Particle size + Zeta + ANOVA:

This nanoemulgel boasts consistent spherical particles within the nanometer range and demonstrates good physical stability, even with limited electrostatic stabilization. The inclusion of non-ionic surfactants (like Tween 80) and gelling agents (like Carbopol 940) provides steric and rheological stability. These combined attributes indicate a well-designed, stable formulation ideal for enhanced topical drug delivery.

Zeta Potential Analysis –

The nanoemulsion showed a zeta potential of -1.78 mV, which is quite low. While values greater than ±30 mV usually point to strong electrostatic stability, this low reading suggests that other factors are at play.

Figure 20. Spoiled Products, Final Gel

Stability Study –

We evaluated the stability of the optimized nanoparticle formulation by monitoring particle size. We observed only a minimal increase in particle size and viscosity. Table no 8.

Table no 8. Results of the Accelerated Stability study.

Evaluation Parameters	At zero day (Day 0)	At day 90
Particle Size (nm)	973.2 nm	982.1nm
Viscosity (%)	1.2 cP	1.45 cP

Antimicrobial Assay –

Figure No. 20 Antimicrobial test for Optimized Batch

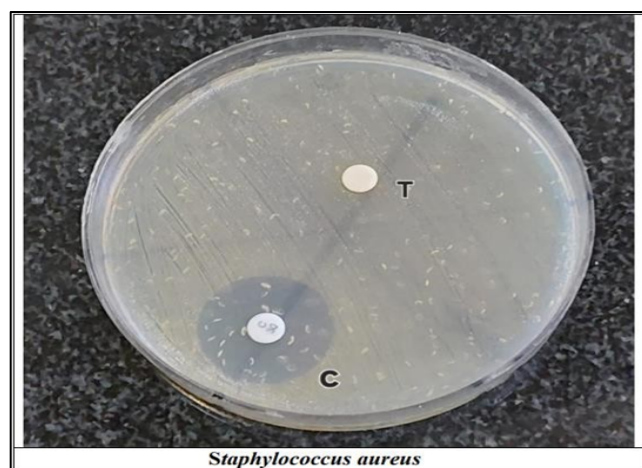


Table No. 9 Antibacterial activity Zone of inhibition in (mm)

CONCLUSION:

In the above research We synthesized environmentally friendly nanoemulgel. Utilizing the Nanoplus equipment we have analyzed the partical size and zeta potential along with that PH determination, antimicrobial assay, stability studies was also successfully carried out. The spreadability studies of prepared nanoemulgel was carried out and the optimization was carried out by using design expert 11 and we got all 2D, 3D plot of optimized formulation. Its future prospective is that to go for animal studies, so from the above we concluded that nanoemulgel was successfully formulated and characterized

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Sr. No.	Samples	Staphylococcus Aureus
1	Nanoemulgel	18mm
2	Chloramphenicol	23mm

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