# A Formulative Approach on *Premna latifolia* Loaded Niosomal Gel for Wound Healing

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**ABSTRACT:** *Premna latifolia* are straggling or and climbing trees, shrubs, undershrubs, rarely herbs in the family Lamiaceae. The aim of this research work was to develop a niosomal gel by incorporating a novel drug carrier such as a niosome containing herbal extract for treatment in eye diseases like wounds. The niosomal dispersion was prepared by varying concentrations of two surfactants while the drug and cholesterol concentration was kept constant. The optimization of the niosome was done based on the size and shape of the vesicle obtained from SEM analysis. The optimized niosomal dispersion was then converted to a niosomal gel and evaluations were carried out like pH, viscosity, gelling capacity, gel strength, isotonicity evaluation etc. The drug-loaded niosomes were stable in HPMC, HPMC K15M, and Carbopol 940 gel, and the optimum HLB value of the surfactant span 60 made this formulation more stable. The formulation provided good permeation through the cornea while the adhesion property of gel improved the contact time within the eye.

**Keywords:** Wound; Niosomes; Gel; *Premna latifolia;* Herbal

## 1. INTRODUCTION

The use of herbal remedies is important in the treatment of many disorders. The majority of individuals in the globe utilise herbal medicine to maintain their health. Many Indians regularly consume herbal medicines, including spices, natural cures, wholesome foods, etc. The primary component of ayurveda, naturopathic, homoeopathic, and other medical systems is herbal medicine [1]. Due to their fewer negative effects and higher efficacy, they are utilised to treat a variety of disorders. Its popularity and demand are currently rising daily. The use of whole plants or portions of plants to treat illnesses or wounds is known as herbal medicine. Better patient compliance and drug delivery at a specified rate are provided by an unique drug delivery system. By making medications more bioavailable, it also lessens the harmful effect [2]. Preparing the medication in the proper dosage form, such as an oral tablet or an IV solution, is the traditional method of administering medication. They have been discovered to have a few drawbacks. In order to overcome the shortcomings of traditional medication administration, new drug delivery systems are being developed. Niosomes, phytosomes, liposomes, nanoparticles, and ethosomes are just a few of the innovative

medication carriers that are currently on the market. Novel drug carriers provide for a more effective cure by making it simple to deliver the treatment to the patient's body's damaged areas. Additionally, herbal medications solubility and stability, toxicity protection, pharmacological action, tissue macrophage dispersion, prolonged delivery, and other properties can all be improved by combining them with innovative carriers.

The epidermis (surface, epithelial layer) and dermis (deeper, connective layer) of healthy skin function as a barrier against the outside world. A controlled series of biochemical reactions are launched when the barrier is breached to heal the harm. When a wound heals, a complicated series of cellular and molecular processes work together to restore it [3]. The process by which a living creature replaces lost or injured tissue with newly formed tissue is known as wound healing. The epidermis (surface, epithelial layer) and dermis (deeper, connective layer) of healthy skin function as a barrier against the outside world [4]. A controlled series of biochemical reactions are launched when the barrier is breached to heal the harm. In order for a wound to heal, a complex chain of normal wound healing progresses in predictable, timely phases; if not, healing may advance in an improper way, leading to either a chronic wound like a venous ulcer or pathological scarring like a keloid scar [5]. Continuous cell-cell and cell-matrix interactions enable the progression of the process through a variety of overlapping phases and processes, such as inflammation, wound contraction, reepithelialization, tissue remodelling, and the creation of granulation tissue with angiogenesis [6].

The management and treatment of wounds can greatly benefit from plants. Numerous plants are employed by tribal and folk medicine in numerous nations for the treatment of burns and wounds [7]. Through a variety of ways, these natural substances promote tissue regeneration and healing. These herbal remedies are not only inexpensive and accessible, but also secure. Scientists have examined plants to find potential wound healing qualities because they contain a variety of life-sustaining components [8]. Nowadays, a lot of phytopharmaceutical laboratories are focusing on figuring out the active components and mechanisms of action of numerous therapeutic plants. These plants medical significance comes from their bioactive phytochemical components, which have defined physiological effects on people.

Niosomes are non-ionic surfactant vesicles that are formed by non-ionic surfactants, with or without cholesterol and charge inducers. The size of niosomes ranges from 10 to 1000nm. They are amphiphilic, with a central core cavity acting as an aqueous phase, and a surfactant bi-layer acting as a non-polar phase. This enables the capture of hydrophilic drugs in the central cavity and hydrophobic drugs in the non-polar region present in the bilayer. As a result, hydrophilic and hydrophobic drugs may be incorporated into niosomes. Niosomes are the better drug delivery system due to their vehicle drug delivery potential, high chemical stability, and economy [9].

Gels are the solution or suspensions which undergo gelation after reaching a particular site to form a gel due to physicochemical changes. Gels provide convenience in administration as compared to eyed drops, suspension, or ointment [10]. The different administration routes for in

situ gel are oral, ocular, rectal, vaginal, injectable, and intraperitoneal. This is the most widely accepted new drug administration system that improves the viscosity of a formulation in the anterior region. This will lead to increased bio-availability, due to slower drainage of the cornea [11].

The role of *Premna latifolia* as an herbal medicine for the treatment of wound has not been widely reported. The aim of this research work was to gain an understanding of the role of *Premna latifolia* in wound treatment by developing a niosomal gel which improves its efficiency in treatment of wounds.

## 2. MATERIALS AND METHODS

### *2.1. Collection of plants*

The fresh stems of *Premna latifolia* were collected from an authorized vendor in Kannur district, Kerala, India in October 2019. The plant material was identified and authenticated by Dr. Ratheesh Narayanan MK, Assistant Professor, Payyanur College, Payyanur, Kerala [Voucher number-PNRCLG/DOB/2020-21/087-012].

### *2.2. Soxhlet extraction of plant materials*

The collected stems of *Premna latifolia* were shade dried at room temperature and coarsely powdered. The 50gm quantity of stem powder was loaded in a thimble and wrapped with filter paper. Then the thimble was placed inside the extractor and the required solvent (300ml) was taken in a round bottom flask and placed in the heating element [12]. The drug was then extracted by continuous hot extraction using 95% ethanol in the Soxhlet apparatus for about 72 hours until the solvent present in the siphon tube becomes colorless [13]. Ethanol retained within the extract can be recovered by the distillation process and it was then air-dried and concentrated.

### 2.3. Formulation of drug-loaded niosomes

Niosomes namely F1 to F8 has been prepared using lipid film hydration technology with two different concentrations of surfactant (2:1, 3:1) while cholesterol and drug level keeping constant [14]. Surfactant (Span 20, 60, Tween 20, 80), Cholesterol, and drug extracts were accurately weighed and dissolved in a 15ml mixture of chloroform: methanol (2:1 v/v ratio) [15]. The above mixture was sonicated for 1 min. Then it was vortexed in the round bottom flask at a temperature of 58-64°C to remove the solvent for about 30 min [16]. The thin lipid layer formed inside the flask was then moistened with 10ml of 7.4 pH phosphate buffer at 60°C for 1 hr. The resultant dispersion was cooled in an ice bath and then left for 4 hr. at room temperature for complete hydration and stored at 4°C overnight before use . The composition of the niosome is shown in Table 1.

**Table 1: Composition of developed niosome.**

| Formulation code | Surfactant used | Weight taken (in mg) | | | Surfactant: Cholesterol ratio |
|---|---|---|---|---|---|
| | | Drug *(Premna latifolia)* | Surfactant | Cholesterol | |
| F1 | Span 20 | 300 | 200 | 100 | 2:1 |
| F2 | | 300 | 300 | 100 | 3:1 |

| | | | | | |
|---|---|---|---|---|---|
| F3 | Span 60 | 300 | 200 | 100 | 2:1 |
| F4 | | 300 | 300 | 100 | 3:1 |
| F5 | Tween 20 | 300 | 200 | 100 | 2:1 |
| F6 | | 300 | 300 | 100 | 3:1 |
| F7 | Tween 80 | 300 | 200 | 100 | 2:1 |
| F8 | | 300 | 300 | 100 | 3:1 |

***2.8. Evaluation of niosomes***

*2.8.1. Vesicle size of niosomes*

The vesicle size of each formulation was determined by an optical microscope. Each formulation was spread uniformly on a glass slide and observed under the 45X magnification optical lens [17].

*2.8.2. Vesicle shape of niosomes*

The shape and morphological characteristics have been achieved by SEM photographs of the optimized niosomes were placed in circular aluminum tips with dual adhesive carbon tape and coated with gold in HITACHI ION SPUTTER E-1010 vacuum evaporator, it has been observed in HITACHI SU6600 FE-SEM (Field Emission Scanning Electron Microscope) having an acceleration voltage of 10.0kv and magnification of 60.0k-100.0 k [18].

*2.8.3. Zeta potential*

Zeta potential was determined using Malvern zeta sizer nano essential. The Zeta potential of niosomal formulation is related to the stability of the niosomal vesicle. The high value of zeta potential indicates the high degree of repulsion between the vesicle and excellent stability i.e., the dispersion will resist aggregation [19].

***2.9. Preparation of niosomal gel***

The required quantity of HPMC was dispersed in 50ml of purified water, HPMC K15M was added to the above solution and stirred slowly with a magnetic stirrer, care was taken that no lumps of HPMC were formed during stirring. Then Carbopol 940 was added to this solution and allowed hydration for one night [20]. After 24 hrs, the solution was again stirred with a magnetic stirrer and buffer salts (Citric acid, disodium hydrogen phosphate) were dissolved in the solution. Benzalkonium chloride was dissolved in niosomal dispersion (BKC). The above dispersion was added to the polymer solution under constant stirring until a uniform solution was obtained. Then the distilled water was added to make up the volume to 100 ml [21]. The prepared formulations have been autoclaved at 121°C for 20 min . The composition of niosomal gel is listed in Table 2.

**Table 2: Composition of niosomal gel.**

| Sr. No. | Ingredients | Quantity |
|---|---|---|
| 1 | Niosomal dispersion of *Premna latifolia* | 0.35% |
| 2 | HPMC | 0.5g |
| 3 | HPMC K15M | 0.4g |
| 4 | Carbopol 940 | 0.6g |
| 5 | Benzalkonium chloride | 0.03g |
| 6 | Citric acid | 0.400g |
| 7 | Disodium hydrogen phosphate | 1.150 g |
| 8 | Purified water | 100 ml |

### *2.10. Evaluation of niosomal gel*

*2.10.1. Physico-chemical evaluation*

The herbal niosomal gel was prepared and evaluated for color, odor, clarity, and appearance by visual observation .

*2.10.2. Homogeneity*

The developed niosomal gel has been set in a container and was tested for homogeneousness by visual inspection. The appearance and presence of aggregate material were also checked [22].

*2.10.3. pH*

The accurately weighed amount of gel (0.3g) was dissolved in 100ml distilled water. The pH was determined by using a digital pH meter at room temperature [23].

*2.10.4. Viscosity*

In ophthalmic formulations, viscosity is a useful factor in determining how long the drug remains in the eye. The viscosity of the gel was determined using a Brookfield viscometer (Model-RVT) with spindle number 3 and angular velocity run from 10-100rpm/min [24].

*2.10.5. Gelling capacity*

The in-vitro gelling capacity of the gel was determined by the visual method. It was determined by placing 1ml of gel formulation in a glass tube containing freshly prepared simulated tear fluid (7.4) and equilibrated at 37°C [34]. The composition to prepare artificial tear fluid is listed in Table 3. The gel formation was visually inspected [25]. The time needed for gelation and the time needed to dissolve the gel was also noted.

**Table 3: Composition of artificial tear fluid.**

| Sr.no. | Ingredients | Quantity |
|---|---|---|
| 1 | Sodium bicarbonate | 0.20 g |
| 2 | Sodium chloride | 0.67 g |
| 3 | Calcium chloride dehydrate | 0.08 g |
| 4 | Deionized water | 100 ml |
| Physiological pH (7.4 ± 0.2) adjusted by adding the required amount of 0.1 N HCL | | |

*2.10.6. Gel strength*

The measurement of gel strength was performed in a 50ml graduated cylinder. 25ml of the gel formulation was put in a graduated cylinder and on the surface of the gel, a weight of 14.3g was placed. The time in the second required to penetrate the weight 5cm into the gel was noted [26]. The measurements were carried out in triplicate (n=3).

*2.10.7. Isotonicity evaluation*

The formulations were mixed with a few drops of diluted blood on a slide. The grower's solution was used to make diluted blood and the slide was observed under a microscope at 45x magnification. Then it was compared with standard marketed ophthalmic formulation [27].

*2.10.8. Gel Erosion Time*

Briefly, niosomal gel solution (5 mL) was gently transferred into 200 mL of phosphate buffer solution (pH 6.5) tempered at 37 °C in a temperature-controlled water bath without shaking. Thereafter, the time needed for complete dissolution of gel was measured [27]. The measurements were conducted in triplicate.

*2.10.9. Evaluation of Gelation Temperature*

The gelation temperature of the prepared gels was evaluated by the test tube inversion method where, 2 mL of tested formulations were placed in a vial (5 mL), which were then immersed in a thermostatically controlled water bath. The temperature was gradually increased by 0.5 °C/min, starting from 20 up to 40 °C, and at each set point the samples were tempered for one minute and then the test tube was inverted at 90°C [28]. The temperature at which no flow upon inversion was seen was set as a gelation temperature.

***2.11. Stability study***

The stability study was performed as per ICH guidelines. The formulated niosomal gel was placed in ambient colored vials and sealed with aluminium foil at different temperatures and humidity conditions like room temperature (25±2°C), and refrigerator temperature (5±3°C) for 3 months [29, 30]. The samples were evaluated every month for appearance, clarity, and pH.

***2.12. Statistical Methods***

The experimental data were processed using Graph Pad Prism® software program.

## 3. RESULTS AND DISCUSSION

*3.1. Plant collection and authentication*

The plant *Premna latifolia* were collected from Kannur district, Kerala (India) and was authenticated by Dr. Ratheesh Narayanan MK, Assistant Professor, Payyanur College, Payyanur, Kerala [Voucher number-PNRCLG/DOB/2020-21/087-012].

*3.4. Soxhlet extraction of plant material*

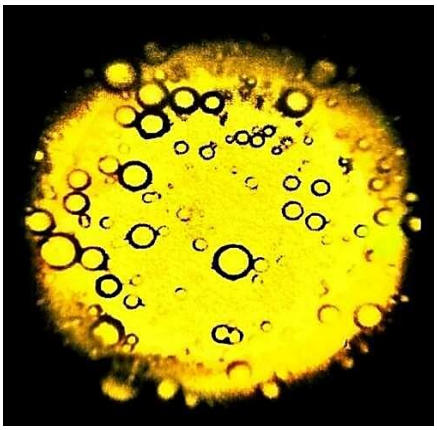
The extraction of dried stems of the plant *Premna latifolia* was carried out by the Soxhlet extraction process using ethanol as solvent. The extract obtained from the plant was then collected and concentrated which was then weighed and kept in a desiccator which was previously filled with fused calcium chloride until it was used for the preparation of niosomal gel. A total of 9.1gm of the extract was obtained from 50gm of crude drug powder. The percentage yield of *Premna latifolia* in the ethanolic extract was found to be 18.20%.

*3.6. Formulation of drug-loaded niosome*

Eight formulations containing *Premna latifolia* extract containing niosomes namely F1-F8 were prepared by different kinds of spans and tweens with varying ratios. The niosomal dispersion formed a pale brown color. Formulated niosomal dispersion and optical microscopic image are shown in Figure 6 and Figure 7 respectively.

**Fig 1. Formulated niosomal dispersion of drug-loaded niosome.**

**Fig 2. Optical microscopic image.**



*3.7. Evaluation of niosome*

*3.7.1. Vesicle size of niosome*

The vesicle size analysis of niosomes were carried out and listed in Table 6. The F4 showed least vesicle size of 1.75 µm when compared to other formulations.

**Table 4: Vesicle size of niosome.**

| Sr. No. | Formulation code | Mean particle size ± SD (µm) |
|---|---|---|
| 1 | F1 | 2.53 ± 0.01 |
| 2 | F2 | 3.10 ± 0.03 |
| 3 | F3 | 3.21 ± 0.08 |
| 4 | F4 | 1.75 ± 0.04 |
| 5 | F5 | 4.09 ± 0.06 |
| 6 | F6 | 4.65 ± 0.15 |
| 7 | F7 | 5.24 ± 0.01 |
| 8 | F8 | 6.75 ± 0.02 |

Values are expressed in mean ± SD (n=3)

*3.7.2. Vesicle shape of niosome*

The shape and surface characteristics of formulated niosome with least vesicle size (F4) was determined by scanning electron microscopy. SEM photographs are shown in Figure 8.

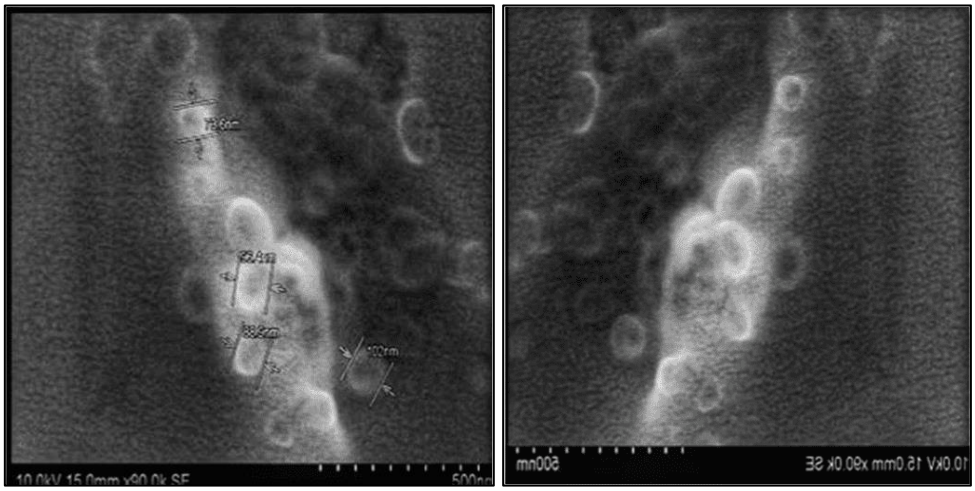


**Fig 3. SEM photograph of formulated niosomes (F4).**

*3.7.3. Zeta potential of niosome*

The zeta potential value of optimized niosomal formulation (F4) was calculated by Malvern zeta sizer nano essential and the zeta potential was found to be -39.9. It indicates that it possesses good stability. Higher zeta potential is indicative

of a stable colloidal system. Zeta potential photograph is shown in Figure 9.

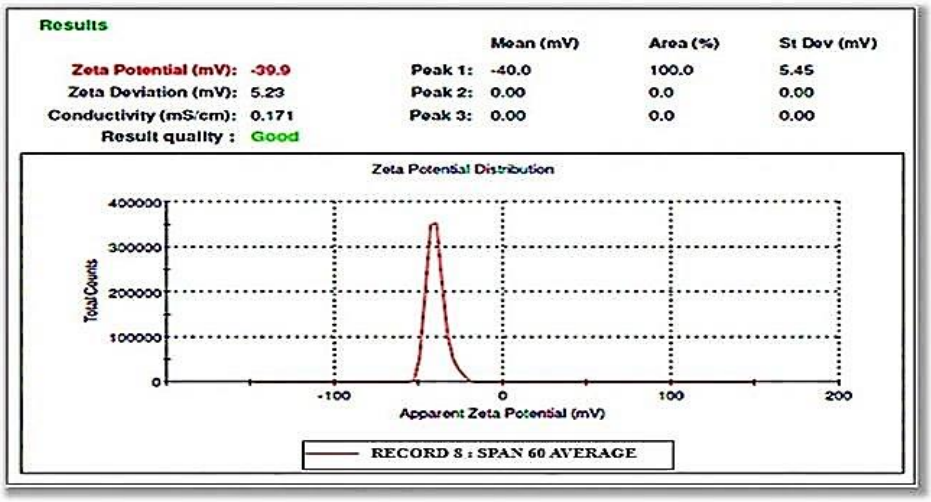
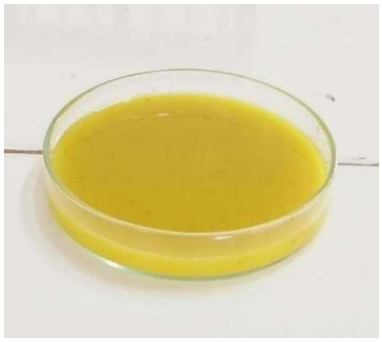



**Fig 4. Zeta potential of niosome (F4).**

*3.8. Formulation of niosomal gel*



Based on the above analysed parameter F4 was considered as the optimized formulation and was selected for further studies. The optimized niosomal dispersion F4 was used for the preparation of gel. The niosomal gel was prepared, which is shown in Figure 10.

**Fig 5. Formulated niosomal gel.**

*3.9. Evaluation of niosomal gel*

*3.9.1.Physicochemical evaluation*

The physical parameters such as color, odor, clarity, and appearance were checked and the results are given in Table 8 which were found to be acceptable.

**Table 5: Physicochemical evaluation of gel.**

| Parameters | Observation |
|---|---|
| Color | Yellow |
| Odor | Characteristic |
| Clarity | Clear |
| Appearance | Transparent |

*3.9.2. Homogeneity*

The optimized niosomal (F4) was tested for homogeneity by visual inspection and checked for the presence of any aggregates. Results clearly indicated that gel possesses uniform distribution.

*3.9.3. pH*

The niosomal gel formulation prepared by using F4 showed favorable pH for successful ocular drug delivery. The average pH was found to be 6.62 ± 0.009.

*3.9.4. Viscosity*

The viscosity of gel formulation is an important factor in determining the residence time of the drug in the eye. Viscosity was determined by Brookfield viscometer in triplicate and was found to be 984.66 ± 1.52

*3.9.5. Gelling capacity*

Gelling capacity is an important gelling property to determine whether the formulation is suitable for use in gelling systems. The gelation time and the time is taken for it to dissolve were noted. Gelling capacity was determined by visual method, it was observed that the gel was formed immediately and remained for an extended period. F4 batch was observed and it was found to be 1.10 ± 0.01 min. required to form a gel.

*3.9.6. Gel strength*

The factors that affect gel strength were found to be the concentration of the gelling agent, bio-adhesive polymers, and also by pH. Optimal niosomal gel must have suitable gel strength to be administered easily and can be retained in the ocular region without leakage after administration. The gel strength time was measured in triplicate. The gel strength of the formulation was found to be 1.30 ± 0.006 sec.

*3.9.7. Isotonicity evaluation*

Isotonicity testing indicates that formulation F4 exhibited no change in the shape of blood cells. The size of blood cells was found in the 6-7µm range which reveals the isotonic nature of formulation as compared with standard ophthalmic marketed preparation. This indicates the maintenance of tonicity in prepared formulations.

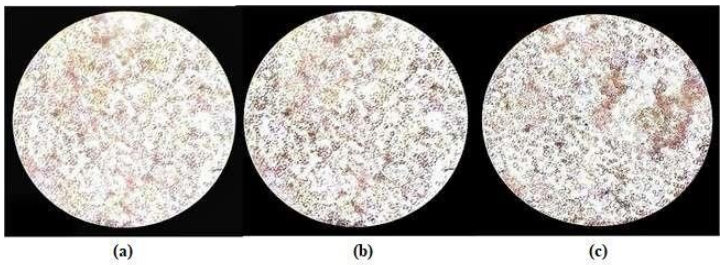



**Fig 6. shape of blood cells (a) Blood cells, (b) Blood cells with Marketed formulation, (c) Blood cells with *Premna latifolia*.**

*3.9.8. Gel erosion time*

The F4 formulated in situ gel was characterized with good gel erosion time of approx. 4 hours which was within acceptable limits.

*3.9.9. Gelation temperature*

The formulated in situ gel of *Premna latifolia* showed a gelation temperature of $34^0$C which was within acceptable limits.

*3.10. Stability studies of optimized formulation*

The stability studies of niosomal gel F4 were performed at room temperature (25±2°C) and refrigerator temperature (5±3°C) for 3 months. The result obtained is given in Table 11 and Table 12 respectively.

**Table 6: Stability studies of niosomal gel at 25±2°C.**

| Sr. No. | Evaluation parameter | After one-month observation | After two-month observation |
|---|---|---|---|
| 1 | Color | Yellow | Yellow |

| | | | |
|---|---|---|---|
| 2 | Appearance | Clear and transparent | Clear and transparent |
| 3 | Homogeneity | Homogeneous | Homogeneous |
| 4 | pH | 6.30 ± 0.03 | 6.40 ± 0.02 |
| 5 | Viscosity | 986.57 ± 0.025 | 986.23 ± 0.03 |
| 6 | Gelling capacity | +++ | +++ |
| 7 | Gel strength | 1.50 ± 0.06 | 1.30 ± 0.01 |

**Table 12. Stability studies of niosomal gel at 5±3°C.**

| **Sr. No.** | **Evaluation parameter** | **After one-month observation** | **After two-month observation** |
|---|---|---|---|
| 1 | Color | Yellow | Yellow |
| 2 | Appearance | Clear and transparent | Clear and transparent |
| 3 | Homogeneity | Homogeneous | Homogeneous |
| 4 | pH | 6.59 ± 0.001 | 6.62 ± 0.009 |
| 5 | Viscosity | 983.33 ± 0.01 | 984.45 ± 0.04 |
| 6 | Gelling capacity | +++ | +++ |
| 7 | Gel strength | 1.5 0± 0.03 | 1.50 ± 0.02 |

## 4. Discussion

In this work, an attempt was made to investigate the anti-wound potential of the extract of *Premna latifolia* when converted into niosomal gel. Herbal drugs are used globally to cure different diseases due to their higher safety margins and cost-effectiveness. Wound healing is a complex biological process that consists of hemostasis, inflammation, proliferation, and remodeling. Novel drug carriers can easily target the drug into the affected area inside the patient's body and can give a better cure. They can be used to deliver the herbal drug at a predetermined rate.

The collected stems of *Premna latifolia* were washed and dried. Then the extract of *Premna latifolia* was made by soxhalation process using ethanol as the solvent. The drug-loaded niosomes are prepared by varying concentrations of surfactants while the drug and cholesterol concentration remain unchanged. The cholesterol concentration was kept unchanged because above a certain amount will disrupt the bilayer formation and may increase the vesicle size. Eight different niosomal formulations were prepared by the lipid-film hydration method. The niosomal dispersions were then evaluated for various parameters like vesicle size, shape, zeta potential, and *in-vitro* antioxidant activity. The vesicle size was determined for 50 niosomes in each formulation where niosomes prepared by span 60 showed the lowest size.

Niosomal dispersion was also evaluated for its shape and surface morphology by using scanning electron microscopy. Niosomes were found to be spherical and formed as good surfactant bi-layered spheres. Surface morphology confirmed the formation of niosomes [49]. The zeta potential value of optimized niosomal formulation was determined by using Malvern zeta sizer nano essential and

the zeta potential was found to be -39.9 which indicates it possesses good stability. Higher zeta potential is indicative of a stable colloidal system.

The vesicle size, vesicle shape, and *in-vitro* anti-oxidant studies were taken as a criterion to optimize the formulation. Among the eight niosomal dispersions, the optimized formula (F4) showed comparatively smaller particle size (1.75 ± 0.04) . For plausible intravesical application an optimal insitu gel should be characterized with a gelling temperature in the range 30-35 °C and prolonged gel erosion time which was 4 hours and $34^0$C for the insitu gel containing niosomes of *Premna latifolia*.

From the physical examination, it was found that *the* gel was free from air entrapment and foreign matters. The color of the gel was found to be yellow. The formulation was clear and transparent. The pH value of the gel was found to be 6.62 ± 0.009 which lies in the normal pH of the eye and showed that the prepared gel was compatible with the pH of an eye. The viscosity was determined by Brookfield viscometer which is an important factor in determining the residence time of the drug in the eye. It possesses good viscosity of about 984.66 ± 1.52 cps. From a gelling capacity study conducted, it was found that the niosomal gel possesses immediate gelation and remains for an extended period. The gel strength of niosomal gel was found to be 1.30 ± 0.006 sec. The prepared gel was subjected to isotonicity testing and. the size of blood cells was found in the 6-7µm range.

The optimized niosomal gel possesses good anti-wound activity due to the plant *Premna latifolia.* The plant *Premna latifolia* has potent anti-wound activity which may due to the phytoconstituents such as flavonoids, alkaloids, steroids, and saponins.

Stability studies were conducted at two different temperatures where no color changes occurred and there was not much difference in parameters like pH, viscosity, gelling capacity, and gel strength.

**5. Conclusion**

To conclude, the findings of the present investigation showed that, the herbal niosomal gel was an excellent method to improve drug delivery in the case of wounds. The drug-loaded niosomes were stable in HPMC, HPMC K15M, and Carbopol 940 ocular gel, and the optimum HLB value of the surfactant span 60 made this formulation more stable. There were only a few numbers of investigations done on the herbal treatment of wounds. So that combining a novel drug delivery system with herbal drugs provides an excellent and efficient method to treat wound disease. The herbal drug-loaded niosomal gel can be introduced into the market for better wound healing activity. Finally, it can be concluded that the niosomal gel of *Premna latifolia* can be an alternative method to reduce the drawbacks of conventional topical dosage forms.

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**7. Authors contribution**

Gowtham Menon and Vishnu AS designed and performed the experiments, derived the models and analysed the data. Shendge R S and Ajith JS helped to supervise the project.

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Not applicable

**9. Conflict of interest**
The authors declare that they have no conflict of interest

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