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Original Article

# A Novel Transethosomal Gel Formulation for Sustained Capsaicin Delivery in Post-Herpetic Neuralgia Treatment

**Vishal Mane, Kishori Prasanna Sutar*, Rashmita Kashinath Akkatangerhal**

Department of Pharmaceutics, KLE College of Pharmacy, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi, Karnataka, INDIA.

## ABSTRACT

**Objectives:** The study aims to develop a novel capsaicin loaded transethosomal gel for the treatment of Post-Herpetic Neuralgia (PHN) for sustained capsaicin delivery. **Materials and Methods:** Transethosomes were formulated by ethanol injection method and were optimized by $3^2$ factorial design. The concentration of soya lecithin and ethanol were selected as independent variables, Vesicle size (VS) and Entrapment Efficiency (EE) have been assessed in relation to the individual and combined effects of independent factors. Transethosomes were analyzed for particle size, encapsulation effectiveness, zeta potential, and cumulative percent drug release. Xanthum gum was used as a polymer for preparing Capsaicin-loaded transethosomal gel. **Results:** The optimized formulation (F1) exhibited a vesicle size of 61.57 nm and an entrapment efficiency of 73%. The homogeneous and spherical surfaces of Transethosomes were validated using Transmission Electron Microscopy (TEM) analysis. The *in vitro* drug release of transethosomal gel (84%) was more when compared with the capsaicin ointment (49%) and capsaicin plain gel (29%) and these studies were demonstrated a biphasic burst release profile, extending over 24 hr. The transformation of transethosomes into a gel using xanthan gum resulted in desired physical properties suitable for topical application. *In vitro* diffusion studies revealed sustained release of capsaicin from the transethosomal gel, indicating its potential for topical pain management. *Ex vivo* permeation studies shows that optimized transethosomal formulation is the highest drug permeation through porcine skin. The capsaicin-loaded transethosomal gel that has been developed presents a highly promising therapeutic strategy for the treatment of post-herpetic neuralgia. This gel combines the benefits of transethosomal administration with the analgesic properties of capsaicin. **Conclusion:** The results obtained demonstrated that this novel formulation presents a significant advancement in the management of post-herpetic neuralgia, addressing the need for effective and sustained pain relief, ultimately improving patient outcomes.

**Keywords:** Capsaicin, Transethosomes, Post-herpetic neuralgia, Factorial design.

**Correspondence:**
**Mrs. Kishori Prasanna Sutar M Pharm**
Assistant Professor, Department of Pharmaceutics, KLE College of Pharmacy, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi-590010, Karnataka, INDIA.
Email: kishorisutar@klepharm.edu

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## INTRODUCTION

Chronic and crippling nerve pain caused by the reactivation of the Varicella-Zoster Virus (VZV), which first causes chickenpox and then later develops as shingles, is an indication of PHN.[1,2] The prevalence and severity of PHN rise with age; around 80% of cases occur in those over 50. In seven Chinese cities in 2019, the prevalence of PHN was 2.3%.[3] The condition manifests when nerve fibers affected by the VZV become damaged or irritated during the shingles outbreak, leading to intense, persistent pain described as burning, throbbing, or shooting, lasting months or years post-rash healing. While the precise mechanisms of PHN are not entirely elucidated,[4,5] it's believed that VZV-induced nerve damage disrupts normal pain signal transmission.[6,7] Effective management of PHN necessitates a multifaceted approach addressing pain relief and overall well-being.

Capsaicin, derived from chili peppers, has been widely used for the management of herpetic neuralgia due to its ability to selectively desensitize nociceptive nerve fibers.[8,9] When applied topically, capsaicin acts as a potent analgesic by binding to and activating the Transient Receptor Potential Vanilloid-1 (TRPV1) receptors, initially causing a burning sensation but leading to desensitization and decreased pain perception over time.[10,11] However, the effective delivery of capsaicin through the skin remains a challenge.[12]

Transethosomes are a novel type of lipid-based nanocarriers designed to enhance the permeation of drugs through the skin and facilitate their delivery into deeper layers of tissue.[13,14] These nanovesicles are composed of soyalecithins, ethanol, and water, forming a flexible and highly deformable structure.[15]

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Transethosomes offer several advantages, including enhanced skin penetration, increased drug loading, improved stability, controlled and sustained drug release and potential for targeted delivery.[16,17]

Transdermal drug delivery, emerging in the late 1970s, offers controlled medication release through the skin, bypassing oral or injection routes. Leveraging skin permeability, it ensures steady drug levels in the bloodstream, reducing dosing frequency and bypassing first-pass metabolism.[18,19] This non-invasive method minimizes discomfort, making it appealing for various conditions like pain management and hormone therapy. Ongoing research aims to improve drug permeation and expand the range of deliverable drugs.[20,21] In summary, transdermal drug delivery enhances patient outcomes by providing efficient, patient-friendly medication administration, ensuring controlled release and minimal systemic side effects.[22]

Xinsheng Peng *et al*., has explored the development and evaluation of cubosome-based delivery systems, using phytantriol (F1) and glycerol monooleate (F2), for the transdermal administration of capsaicin. The cubosomes were produced via emulsification and homogenization, Structural analysis confirmed their Im3m crystallographic space group through small-angle X-ray scattering. *In vitro* release studies demonstrated that the cubosomes provided sustained release of capsaicin. Furthermore, Franz diffusion cell tests revealed significantly higher capsaicin retention in the stratum corneum (2.75±0.22 µg versus 4.32±0.13 µg, respectively) when delivered through cubosomes compared to conventional cream (0.72±0.13 µg). The formulations also showed good stability under stress conditions and minimal skin irritation in repeated application tests on mice. Overall, the findings suggest that phytantriol- and glycerol monooleate-based cubosomes offer a promising approach for targeted, sustained, and skin-friendly transdermal capsaicin delivery.[23]

Phunsuk Anantaworasakul *et al*., The purpose of this research was to formulate lipid-based nanoparticles that could encapsulate a significant amount of capsaicin (0.25%) from an extract of capsicum oleoresin. The purpose of the carefully designed Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) was to encapsulate capsaicin without the use of a hazardous solvent. To assess skin irritancy, the RHE model-based *in vitro* skin irritation test has been used, the percentage of cell viability from Gel NLC_C (91.85%±0.16%) was considerably ($p$<0.05) greater than that of chili extract gel (86.49%±4.34%), indicating that NLC caused less skin irritation than the free form alternative. The significantly faster transdermal penetration of the dermis and the extended release of capsaicin from the permeated NLC were key factors in the reduced cutaneous irritation of chili-encapsulated NLC.[24]

May Saab *et al*., the aim of the present research is to develop a capsaicin nanoemulgel that will enhance its ability to penetrate the skin and combat neuropathic pain. utilizing eucalyptus oil as the oily phase, Tween 80 as a surfactant, propylene glycol, ethanol, and isopropyl alcohol as co-surfactants, nano emulsions were created utilizing the low-energy emulsification method. The most effective formulation was developed as a nanoemulgel and tested on Franz Diffusion cells for skin penetration and alloxan-induced diabetic mice for the treatment of Diabetic Neuropathy (DN). Compared to the traditional gel, the nanoemulgel showed a roughly 4-fold increase in capsaicin cumulative penetration, and the treated diabetic mice showed an improvement in its antinociceptive qualities ($p$<0.05).[25]

In summary post-herpetic neuralgia is a chronic neuropathic pain condition requiring effective management. Capsaicin desensitizes nociceptive nerves but faces skin permeation challenges. Transethosomes, lipid-based nanocarriers, enhance skin penetration and controlled drug release. This study formulates, optimizes, and characterizes capsaicin-loaded transethosomes using a cold method for improved topical delivery in treating post-herpetic neuralgia. The future scope of advancing this delivery system to target other neuropathic pain conditions or skin-related disorders can significantly expand its clinical utility. Furthermore, the formulation's non-invasive nature and ease of patient compliance make it particularly suitable for elderly individuals, who are most commonly affected by PHN. Progress in nanocarrier technologies and polymer science holds the potential to enhance drug targeting precision, regulate release rates, and improve skin absorption efficiency. Future studies might also investigate incorporating biosensors or stimuli-responsive components into the transethosomal gel, enabling smart, on-demand drug delivery systems.

## MATERIALS AND METHODS

### Materials

Capsaicin was obtained from Herboil Chemicals, Mumbai, India. Xanthan gum was sourced from Lubrizol Advanced Materials India Private Limited, India, Soya lecithin was acquired from Lipidome Life Sciences, Gujarat, India, Acetonitrile was purchased from Fisher Scientific, India, Ethanol was also sourced from Fisher Scientific, India, Tween 80 was provided by Hi-Media Laboratories Pvt. Ltd., Mumbai, India, Potassium dihydrogen phosphate and Sodium dihydrogen phosphate were both obtained from Himedia Laboratories, India.

### Methods

#### *Formulation of Capsaicin-loaded Transethosomes*

Capsaicin-loaded Transethosomes were formulated using the ethanol injection method, which involves the use of two separate beakers.[26,27] In one beaker, a mixture of ethanol, capsaicin, soya lecithin, and surfactant was prepared, while Millipore water was used as the aqueous phase in the other beaker. The aqueous phase was then added dropwise into the organic phase using a 22-gauge

needle. During this addition, the stirring speed was maintained at 700 RPM and the temperature at 30°C. After the complete addition of the aqueous phase, the mixture was stirred for 20 min at 1200 RPM. The resulting dispersion was then allowed to stand undisturbed for 30 min to form a cloudy solution of Transethosomes. This dispersion was subsequently subjected to probe sonication for 10 min at 35% amplitude to reduce the particle size. Finally, the prepared Transethosomal dispersion was stored at 4°C until further analysis.

## Optimization of Transethosomes dispersion

The optimized Transethosome batch was selected from nine formulations based on its highest entrapment efficiency and smallest particle size. Among the evaluated batches, formulation F1 was chosen for further investigation, exhibiting a maximum entrapment efficiency of 70% and a particle size of 147.65 nm. Subsequent evaluation trials were conducted using this optimized batch.

## Experimental Design for formulation of Transethosomes Loaded with Capsaicin

Based on a review of the existing literature, the drug-to-lipid ratio was determined, while maintaining a constant drug concentration lipid-(Soya lecithin) ratio was varied from low (400), medium (500) and high (700). Ethanol ratio varied from low (6), medium (7), High (8). The formulation was optimized using DESIGN EXPERT® software [version 13] through a two-factor, three-level factorial design. Based on the screening, it was found that the concentration of lipid (X1) and ethanol (X2) were vital factors for the transethosomes since they directly influenced both particle size (Y1) and Entrapment Efficiency (EE) (Y2), this design yielded nine formulation batches, as illustrated in Table 1.

## Evaluation of Capsaicin–Loaded transethosomal formulation

### *Vesicle size analysis*

The size distribution and Polydispersity Index (PDI) of the vesicular delivery systems were assessed using Dynamic Light Scattering (DLS).[27,28] A computerized Malvern Zetamaster-nano, ZEN 3600 inspection system from Malvern Instruments was utilized for the measurements, with a scattering angle of 90°. The collected data were analyzed using the integrated Dispersion Technology Software, part of the Malvern Zetasizer computer program.

## Encapsulation Efficiency

The ultracentrifugation technique was used to assess the entrapment effectiveness of TELs.[29,30] At a temperature of 4°C, the TELs were centrifuged at 15,000 rpm for 60 min. The sediment and supernatant were separated after centrifugation the drug content within the sediment was assessed by disrupting the vesicles using methanol and subjecting supernatant for measuring the drug concentration using spectrophotometry. The entrapment efficiency was calculated using the formula below.

% Entrapment efficiency = (Amount of entrapped API)/ (Total amount of API)×100

## Structural morphology

Transmission Electron Microscopy (TEM) pictures were captured using the JEM-1400 microscope, which is made by JEOL in Japan.[28,31] The accelerating voltage used by the microscope was 120 kV. Distilled water was used to optimise and dilute the Transethosomal dispersions by a factor of 10. A copper grid covered with carbon was subsequently coated with these diluted dispersions. A minute later, filter paper was utilised to carefully remove any remaining dispersion. Negative staining has been carried out by directly adding a 2% phosphotungstic acid (w/w) solution to the deposited sample for 45 sec in order to improve the contrast of the samples. The samples were then allowed to air dry before being analysed further under a TEM.

## Formulation of capsaicin-loaded transethosomal gel

In the formulation of a topical gel for transethosomal dispersions, the incorporation of xanthan gum was pivotal.[32,33] Initially, transethosomal dispersions were blended with xanthan gum at a concentration of 1% (w/w). This step facilitated the creation of a gel base suitable for topical application. Triethanolamine was added dropwise during this phase to ensure proper neutralization of the gel base and methyl paraben and propyl paraben were added as preservatives. The prepared gel stored in refrigerator until further evaluation.

## Evaluation of Transethosomal gel

### *Physical Appearance*

The Physical Appearance of the Capsaicin loaded transethosomal gel was determined by eye perception.

## Determination of pH

The pH of both the Capsaicin-loaded transethosomal gel and the plain (drug-free) gel was evaluated using a calibrated digital pH meter.[34,35] For the analysis, 2 g of each gel formulation were accurately weighed and dispersed in 50 mL of distilled water in a beaker. The dispersion was stirred gently to ensure uniform mixing and allowed to stand for 1-2 min to attain equilibrium. The electrode of the pH meter was then immersed into the sample, and the pH was recorded once a stable reading was displayed. The measurements were performed at room temperature and in triplicate to ensure accuracy and reproducibility of the results.

## Determination of Viscosity

A Brookfield viscometer model DV-III with spindle number 40 (Brookfield Engineering Laboratories,[36,37] Inc., Middleboro, USA) has been employed to measure the viscosity of the gel considering

it is an essential parameter which determines its physiological performance. A beaker was filled with 20 g of transethosomal gel, followed by a viscometer spindle was added. After spinning the spindle at various rates, such as 0.5, 2.5, and 5 RPM, readings were shown on the viscometer dial. To obtain accurate findings, all viscosity measurements were performed in triplicate.

### Determination Spreadability

The therapeutic impact of Capsaicin-loaded transethosomal is determined on its spreading value.[38,39] To determine the gel's spreadability, 500 mg of the product was placed on a glass slide that had been marked with a 2 cm circle. After 5 min, the second glass slide was positioned on top of the first, and a 500 g weight was put on top of the higher slide. The gel's spread area was measured and calculated after 5 min. The outcomes were expressed as (mean±S.D., $n$=3) in triplicate. Table 3 shows the results of the Spreadability Determination of the optimized gel composition.

### *In vitro* Diffusion study

Using a Franz diffusion cell with a cellophane membrane that had been pre-soaked in PBS pH 7.4 for 24 hr prior to the experiment,[28,38] the transethosomal gel was examined for *in vitro* release investigations. Carefully cut clips were used to attach the cellophane membrane between the donor and receptor chambers. The cellophane membrane had a homogeneous distribution of the gel (1 g). 12 mL of PBS pH 7.4 was used as the dissolving liquid in the receptor compartment. The entire assembly was kept on a magnetic stirrer using a magnetic bead in the receptor compartment, and it was swirled continuously for 24 hr at 100 rpm with a temperature of 37±0.5°C. The sample was taken out of the sampling port and replaced with equal quantities of fresh dissolving medium at predetermined intervals of 0.5, 1, 2, 3, 5, 6, 7, 8 and 24 hr. The samples were spectrophotometrically analyzed at 253 nm, and the cumulative drug release percentage was calculated. The percent cumulative medication release over time was plotted on a graph to evaluate each gel composition.

### *Ex vivo* Permeation study

The skin was removed from the underlying cartilage and used after fresh goat belly skin had been collected from the slaughterhouse.[40,41] The skin hairs were removed and then skin was washed with regular saline. After being dried between two filter sheets, the skin was used straight away for the study without being stored. Capsaicin plain gel, Marketed Capsaicin gel and Capsaicin loaded transethosomal gel were compared for skin permeation study. A modified Franz diffusion cell was employed in the investigation with a receptor compartment volume of 50 mL of PBS at pH 7.4 which was magnetically agitated using magnetic stirrer at 100 rpm and the donor compartment was filled with the optimal formula. 1.74cm$^2$ skin membrane area was placed between the donar/compartment and receptor compartment. Samples (1.0 mL) were removed from the receptor compartment at predetermined intervals (1, 2, 3, 4, 5, 6, 12 and 24 hr) and an equivalent volume of new buffer solution was added to maintain the sink condition. After the sample withdrawal, samples were diluted and analysed spectrophotometrically obtaining the absorbance at 280 nm.

### Drug Retention Study in the Skin

The skin was repeatedly cleansed with pH 7.4 PBS to conduct the investigation on drug retention in the skin.[42] Any formulation that adhered to the skin's surface was then blotted away using tissue paper. To extract the drug deposited in the skin, the skin was sliced into small pieces and left in methanol for a whole day. The skin which is processed was sonicated for 15-20 min and then centrifuged, the supernatant obtained is collected in Eppendorf tube. Using a UV spectrophotometer, the extracted supernatant was filtered, examined, and the drug content was determined.

## RESULTS

### Experimental Design for formulation of Transethosomes Loaded with Capsaicin

A 3$^2$ factorial design was used to investigate capsaicin-loaded transethosomes, and Table 2 shows that lipid concentration (X1) and ethanol (X2) had a significant effect on dependent variables such as vesicle sizes (Y1) and percentage encapsulation efficiency (Y2).

### Determination of Particle size

The average particle size of the prepared capsaicin-loaded transethosomes was found to be in the range between 61.57 nm to 300.8 nm. As per the Design-Expert Software, X1=Soya lecithin[mg] and X2= Ethanol[mL] and responses Y1= Vesicle size[nm] and Y2=Entrapment Efficiency [%]. The polynomial quadratic equation obtained, demonstrates the effect of independent variables on particle size, which exhibit the precision of 7.4943. As the equation given below, both independent variables have the negative effect on the PS. That is as the concentration of soya lecithin increases the particle size decreases similarly as the concentration of ethanol decreases the particle size decreases.

The results are depicted below in Figure 1a.

Particle size (PS) = 156.55-5.59A+101.03B

### Determination of Entrapment Efficacy

The average Entrapment efficiency of the prepared capsaicin-loaded transethosomes was found to be in the range between 53% to 79%. As per the Design-Expert Software, X1=Soya lecithin[mg] and X2= Ethanol[mL] and responses Y1= Vesicle size[nm] and Y2=Entrapment Efficiency [%]. The polynomial quadratic equation obtained, demonstrates the effect of independent variables on Entrapment efficiency, which exhibit the precision of

46.5403. As the equation given below, both independent variables have the negative effect on the entrapment efficiency. That is, as the concentration of soya lecithin decreases the Entrapment Efficiency increases; similarly, as the concentration of ethanol decreases the Entrapment Efficiency increases.

The results are depicted below in Figure 1b.

Particle size (PS) = 62.00-2.67A-10.00B+0.00AB+0.00A2 +4.00B2

## Structural morphology

**Transmission electron microscopy analysis** the spherical shape of the particles is confirmed by the Transmission Electron Microscopy (TEM) image shown in Figure 1, which depicts surfaces that are smooth, curved, and uniform. Furthermore, as Figure 2 illustrates, the size range is smaller than 200 nm.

## Evaluation of Capsaicin-loaded transethosomal gel

### *Physical Appearance*

The prepared formulations appeared white in colour, had a smooth texture, and showed good homogeneity and consistency, with no lumps or grittiness. Table 3 shows the results of the physical evaluation of the optimized gel composition.

## Determination of pH

The pH of Capsaicin-loaded transethosomal formulations turned out to be 6.83, while pure gel was found to be 6.6, indicating that skin irritation may be avoided. Table 3 shows the pH results of the formulations.

## Determination of Viscosity

The viscosity of gels was measured using a Brookfield viscometer. Capsaicin-loaded transethosomal gel had a viscosity of 1540 cps, while pure gel without the drug had a viscosity of 1358 cps.

## Determination of Spreadability

The therapeutic impact of Capsaicin-loaded transethosomal is determined on its spreading value. The spreadability of Capsaicin-loaded transethosomal gel ranged from 6.9 gm.cm/sec to 6.2 gm.cm/sec for pure gel. Table 3 depicts the results.

## *In vitro* diffusion study

Three formulations were evaluated for release characteristics in 24-hr *in vitro* research conducted at 37±0.5°C using a Franz diffusion cell: capsaicin ointment, Plain Capsaicin gel, and an improved capsaicin-transethosomal gel. Utilizing a cellophane membrane for evaluation, the results showed significant differences in drug release profiles. The optimized capsaicin-transethosomal gel demonstrated a remarkable increase in drug release, achieving over 84% cumulative release after 24 hr. In contrast, the capsaicin ointment and plain capsaicin gel exhibited lower cumulative release percentages, reaching approximately 49% and 29%, respectively, by the end of the 24-hr

**Table 1: Independent and Dependent Variables for Transethosomal Formulation Optimization.**

| Independent variables | | | |
|---|---|---|---|
| X1: Soya lecithin [mg] | 400 | 500 | 700 |
| X2: Ethanol [mL] | 6 | 7 | 8 |
| Dependent variables | | | |
| Y1: Vesicle size [nm] | Minimum | | |
| Y2: Entrapment efficiency | Maximum | | |

**Table 2: Shows that lipid concentration (X1) and ethanol (X2) had a significant effect on dependent variables such as vesicle sizes (Y1) and percentage encapsulation efficiency (Y2).**

| Formulation Batch | Independent variables | | Dependent variables | |
|---|---|---|---|---|
| | X1 [mg] | X2 [mL] | Y1 [nm] | Y2 [%] |
| F1 | 400 | 6 | 61.57 | 73 |
| F2 | 400 | 7 | 92.15 | 60 |
| F3 | 400 | 8 | 180.9 | 64 |
| F4 | 500 | 6 | 78.47 | 79 |
| F5 | 500 | 7 | 88.9 | 62 |
| F6 | 500 | 8 | 228.7 | 59 |
| F7 | 600 | 6 | 80.37 | 76 |
| F8 | 600 | 7 | 300.8 | 53 |
| F9 | 600 | 8 | 297.1 | 56 |

X1: Soya lecithin [mg]; X2: Ethanol [mL]; Y1: Vesicle size [nm]; Y2: Entrapment Efficiency [%].

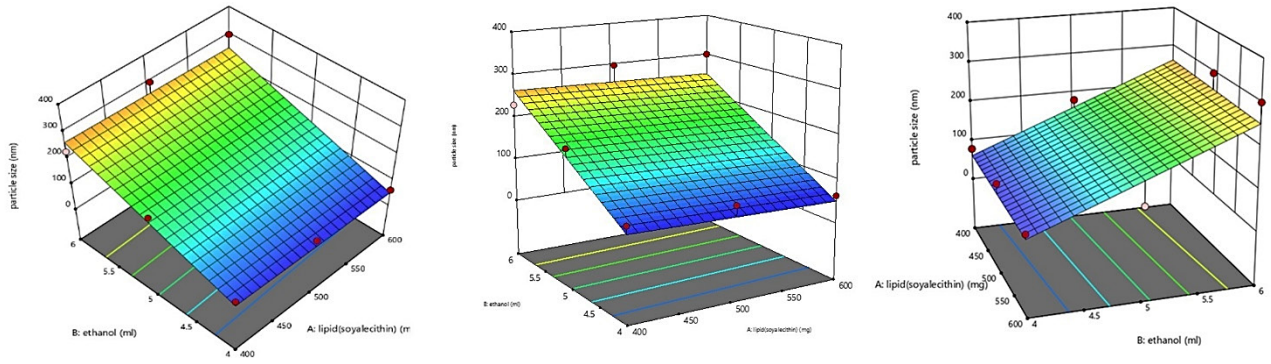


**Figure 1 (a):** 3D response surface chart exhibiting the influence of Lipid soya lecithin and Ethanol on particle size of Transethosomes.

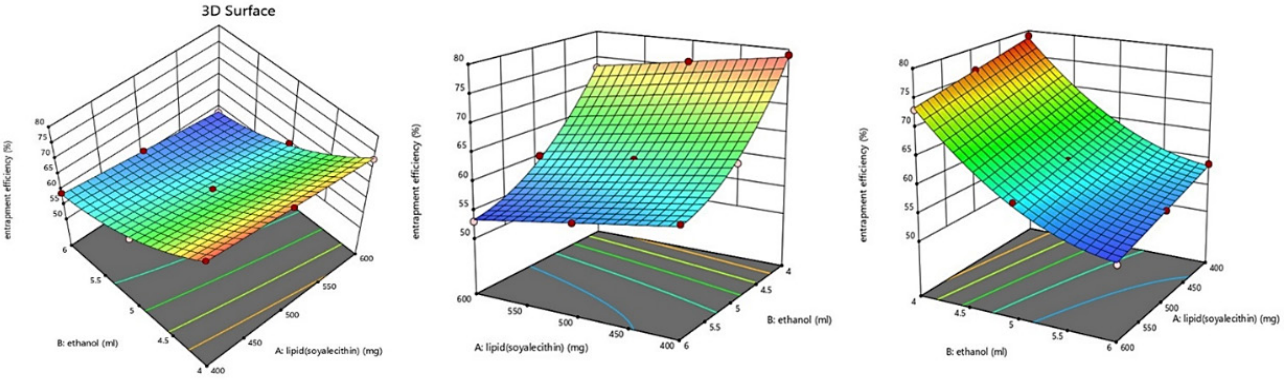


**Figure 1 (b):** 3D response surface chart exhibiting the influence of Lipid soya lecithin and Ethanol on Entrapment Efficiency of Transethosomes.

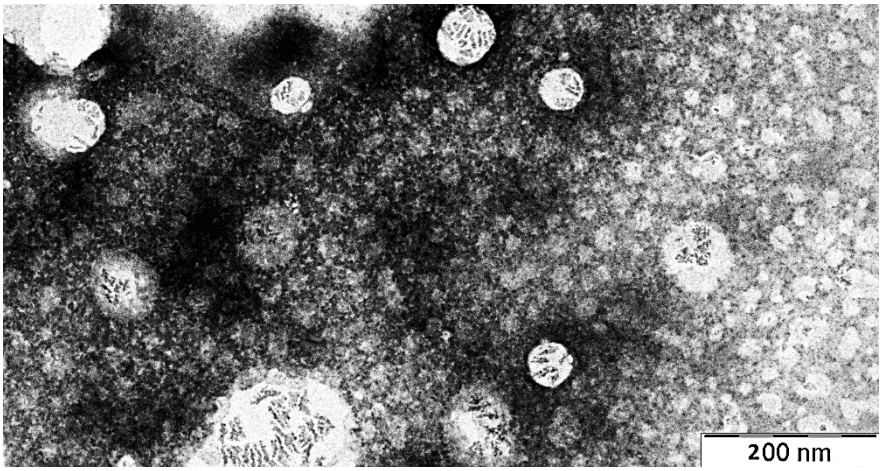


**Figure 2:** TEM image of Capsaicin loaded transethosomes – The Transmission Electron Microscopy (TEM) analysis of Capsaicin-loaded transethosomes.

period. Furthermore, drug release profiles of Capsaicin-loaded transethosomes in PBS with pH 7.4 indicated controlled release over 24 hr. These findings highlight the enhanced drug release capabilities of the optimized capsaicin-transethosomal gel, suggesting its potential for improved therapeutic efficacy in treating post-herpetic neuralgia. Figure 3, depicts the comparison diffusion study between capsaicin ointment, Plain Capsaicin gel, and an improved capsaicin-transethosomal gel.

## *Ex vivo* Permeation study

According to the data, the optimized transethosomal formulation demonstrated the highest drug permeation through porcine skin when compared to other gel formulations; the Capsaicin plain gel formulation and the Marketed formulation did not significantly differ from one another; the CPLG formulation showed the highest permeation. The prolonged drug release of CPLG could be attributed to the slow release of drugs from the vesicles. Figure

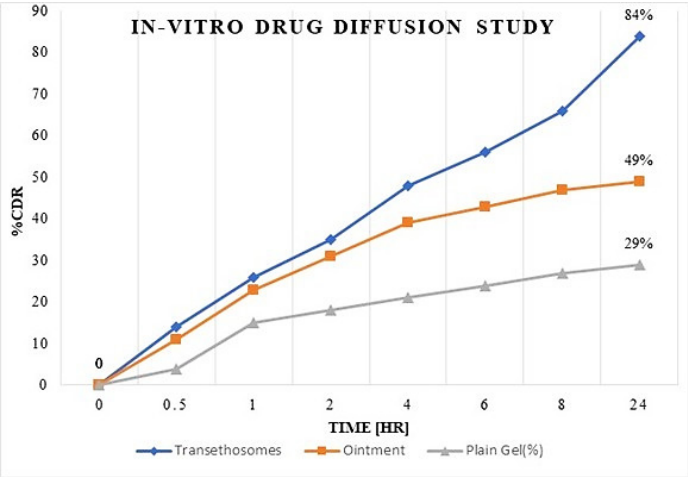


**Figure 3:** *In vitro* drug diffusion study suggests that after 24 hr, the capsaicin-loaded transethosomal gel exhibits superior performance compared to both capsaicin ointment and plain gel formulations.

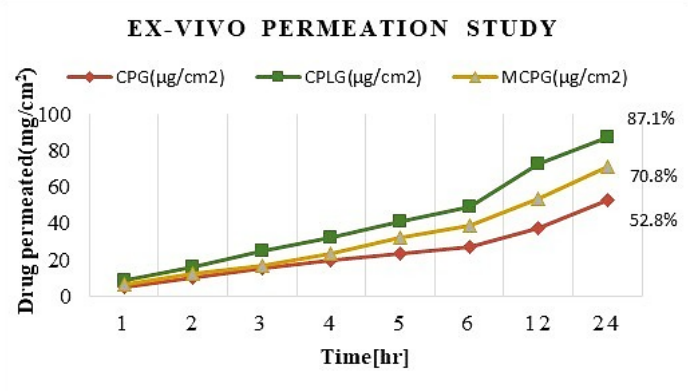


**Figure 4 (a):** The *ex vivo* permeation study suggests that after 24 hr, the capsaicin-loaded transethosomal gel exhibits the highest permeation compared to both capsaicin plain gel and Marketed gel.

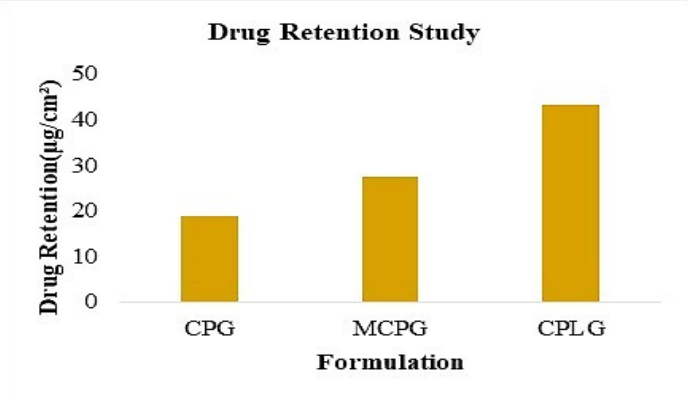


**Figure 4 (b):** Bar diagram showing drug retention (µg/cm²) of Capsaicin of various formulation.

4a depicts the findings of the drug permeation study of CPG and CPLG.

## Drug Retention in the skin

In contrast to other gel formulations, CPLG showed a relatively higher retention of the formulation inside the epidermal layers in this investigation. This is among the causes of the vesicular system's depot-forming function. The distinctive flexibility of the vesicular membranes, which aids in transporting the formulation through the strong horny layer of the skin while maintaining its trap in the dermal layers, may be the cause of the high drug retention observed with CPLG formulation. Figure 4b depicts the drug retention of Capsaicin plain gel formulation and the Marketed formulation and an improved Capsaicin-transethosomal gel

**Table 3: Evaluation of transethosomal gel loaded with capsaicin: This table offers thorough details on the assessment standards essential to identify the most effective possible formulation.**

| Parameters | Capsaicin gel | Capsaicin-loaded Transethosomal gel |
|---|---|---|
| Appearance | White | White |
| Spreadability (gm.cm/sec) | 10±0.816 gm.cm/sec | 13±1.63 gm.cm/sec |
| pH | 6.6±0.294 | 6.83±0.1203 |
| Viscosity (cps) | 1358±48.73 | 1540±30.41 |

## DISCUSSION

The study aimed to develop a transethosomal gel formulation for Post-Herpetic Neuralgia (PHN) treatment using capsaicin. Capsaicin was chosen for its ability to desensitize nociceptive nerve fibers, providing relief from PHN-associated pain. Ethanol injection method was employed, optimizing soy lecithin concentration and ethanol volume via a $3^2$ factorial design. Optimized Formulation (F1) Exhibited desirable characteristics with a vesicle size of 61.57 nm and an entrapment efficiency of 73%, as confirmed by Transmission Electron Microscopy (TEM). Drug Release Profile Demonstrated a biphasic burst release, ensuring sustained capsaicin release over 24 hr, crucial for prolonged pain relief and enhanced patient compliance. Xanthan gum was used as a gelling agent to formulate transethosomal gel, exhibiting favorable physical properties like smooth texture, good homogeneity, and appropriate pH and viscosity. *In vitro* Diffusion Studies confirmed sustained release of capsaicin from the transethosomal gel, indicating its potential efficacy in topical pain management. The developed capsaicin-loaded transethosomal gel offers a promising therapeutic approach for PHN treatment, combining the advantages of transethosomal delivery with capsaicin's analgesic properties.

## CONCLUSION

A Novel Capsaicin-loaded Transethosomal gel was successfully developed for the treatment of Post-Herpetic Neuralgia (PHN). Ethanol injection method and $3^2$ factorial design were used to optimize formulation parameters, achieving a vesicle size of 61.57 nm and entrapment efficiency of 73%. Transmission Electron Microscopy (TEM) confirmed the homogeneous and spherical morphology of Transethosomes. The gel formulation exhibited desirable physical properties, including appropriate viscosity,

pH, and Spreadability, ensuring ease of application. *In vitro* drug release studies demonstrated sustained release (84%) over 24 hr, outperforming capsaicin ointment (49%) and plain gel (29%). *Ex vivo* permeation studies indicated enhanced skin penetration and prolonged drug retention within the epidermal layers. The Capsaicin-loaded Transethosomal gel combines improved bioavailability, sustained release, and enhanced skin permeation, making it a promising alternative for PHN treatment. This innovative topical delivery system offers a non-invasive, effective, and patient-compliant approach for managing neuropathic pain.

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## ABBREVIATIONS

**API:** Active Pharmaceutical Ingredient; **cps:** Centipoise (unit of viscosity); **DLS:** Dynamic Light Scattering; **EE:** Entrapment Efficiency; **nm:** Nanometer; **PBS:** Phosphate Buffered Saline; **PHN:** Post-Herpetic Neuralgia; **PDI:** Polydispersity Index; **PS:** Particle Size; **RPM:** Revolutions per Minute; **TEM:** Transmission Electron Microscopy; **TRPV1:** Transient Receptor Potential Vanilloid-1; **UV:** Ultraviolet; **VZV:** Varicella-Zoster Virus.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## SUMMARY

The study presents the development of a novel capsaicin-loaded transethosomal gel aimed at providing sustained drug delivery for the treatment of Post-Herpetic Neuralgia (PHN). Using the ethanol injection method and a $3^2$ factorial design, transethosomes were formulated and optimized based on vesicle size and entrapment efficiency. The optimized formulation (F1) demonstrated a vesicle size of 61.57 nm and an entrapment efficiency of 73%. Xanthan gum was used to convert the transethosomal dispersion into a topical gel. The formulation was evaluated for physical properties such as pH, viscosity, and spreadability, along with *in vitro* drug diffusion, *ex vivo* skin permeation, and skin retention. Results indicated that the transethosomal gel provided a sustained drug release of 84% over 24 hr, outperforming both conventional capsaicin ointment and plain gel. *Ex vivo* studies confirmed superior skin permeation and higher drug retention within the epidermal layers, likely due to the deformable vesicular structure. Transmission Electron Microscopy (TEM) confirmed the uniform spherical morphology of the vesicles. Overall, the capsaicin-loaded transethosomal gel offers a promising, non-invasive, and patient-friendly alternative for the effective management of chronic pain associated with PHN.

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