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Pva based Nanocarrier for the Delivery of Acorus Calammus Based Nanoemulsion in the Management of Trigeminal Neuralgia

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KEYWORDS

Acorus calamus, nanoemulsion, PVA nanocarrier, zeta potential, particle size, Trigeminal neuralgia.

ABSTRACT:

Background:

Trigeminal neuralgia is a chronic neuropathic pain disorder characterized by severe, episodic facial pain. Conventional systemic therapies such as carbamazepine are associated with significant adverse effects, necessitating the development of alternative targeted delivery systems. Nano-based topical formulations offer improved drug localization and reduced systemic toxicity. To develop and evaluate a polyvinyl alcohol (PVA)-based nanocarrier for the delivery of Acorus calamus-loaded nanoemulsion in the management of trigeminal neuralgia. An Acorus calamus-based nanoemulsion was formulated and incorporated into a PVA polymeric nanocarrier system. The formulation was characterized for particle size distribution, zeta potential, and stability parameters. The optimized formulation demonstrated a particle size predominantly in the range of 100–180 nm with a peak around 140–160 nm, indicating nanoscale distribution. Zeta potential analysis revealed a narrow distribution around neutral charge, suggesting steric stabilization. Clinical effectiveness was assessed using pain intensity scales, including the Visual Analogue Scale (VAS). The developed nanocarrier exhibited a uniform particle size distribution with a unimodal pattern and nanoscale range, indicating suitability for topical delivery. Zeta potential results suggested a stable dispersion likely maintained by steric mechanisms. Clinical evaluation showed a reduction in pain scores, indicating therapeutic potential with minimal adverse effects. The PVA-based nanocarrier incorporating Acorus calamus nanoemulsion demonstrated promising physicochemical characteristics and clinical efficacy in reducing trigeminal neuralgia pain. This delivery system may serve as a potential alternative to conventional systemic therapies by enhancing localized drug delivery and minimizing side effects.

INTRODUCTION:

The trigeminal nerve is the largest cranial nerve supplying the face. Arises as 2 roots in the trigeminal nerve, which is the largest among all cranial nerves. It emerges from the anterior aspect of the pons by two roots: a sensory root that carries sensory information to the brain from the facial region, and a motor root that provides motor innervation to the muscles of mastication. These are four central brain stem nuclei that are (1) the mesencephalic nucleus, which mediates proprioception, (2) the main sensory nucleus, which mediates tactile sensation, (3) the motor nucleus,s which provides motor innervation, and (4) the spinal nucleus, which mediates pain and temperature sensation. These nuclei lie in the tegmentum of the lateral pons, along the anterolateral aspect of the fourth ventricle, and at the level of the root entry zone of the trigeminal nerve.

Trigeminal neuralgia (TN) is a facial pain syndrome characterised by paroxysmal, shock-like pain attacks located in the somatosensory distribution of the trigeminal nerve. British physician John Fothergill was the first to be given a detailed description of trigeminal neuralgia in 1773. Nicolas Andre was the first to coin the term tic douloureux in 1756 and mentioned it in a book, “Observations pratiques sur les maladies de l’urethre et sur plusieurs faits convulsifs” (Traite, 1756). Furthermore, he elaborated on the features, causes, and management of TN along with John Fothergill, Samuel (Fothergill’s nephew), and Charles Bell (Booth 1967, Fox, 1919).

The International Association for the Study of Pain defines trigeminal neuralgia as a sudden, unilateral, severe, brief, stabbing, and recurrent pain along the distribution of the trigeminal nerves. Neuropathic pain in trigeminal neuralgia is evoked by stimuli known as

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trigger factors, which include routine daily activities like washing, shaving, smoking, talking, and toothbrushing, or can occur spontaneously without a known trigger factor (Zarkrzewska, 2006).

The first-line treatment for patients with classic TN and idiopathic TN is pharmacologic therapy. The most commonly used medication is the anticonvulsant drug carbamazepine (Gambeta E et al, 2020). Carbamazepine - the therapeutic range is normally between 800mg and 1200mg. Carbamazepine is an anticonvulsant as well as an antiepileptic drug, which is considered a gold standard drug in the treatment of trigeminal neuralgia. Along with carbamazepine, ox-carbamazepine and baclofen are also given in combination. Carbamazepine has a property of calcium channel inhibitory action, which is involved in the conduction of the pain pathway, thereby inhibiting the Pain activity. It can be given at a maximum dosage of 1200mg per day. Although it has a property of calcium channel inhibition, it has a common side effect of bone marrow suppression, causing agranulocytosis and drowsiness. Agranulocytosis is more dangerous when the total neutrophil count decreases to 100 cells/mm3. Dosage ranges from 100 mg to 1200 mg per day. Due to the most common side effect of carbamazepine, such as agranulocytosis, there is a need for an alternative to minimise the side effects of carbamazepine.

Due to enhanced drug penetration, targeted local action, reduced side effect and prolonged and controlled release, there is a need for topical formulations, especially in neuropathic pain (Chelladurai et al. 2026). *Acorus calamus*, a well-known medicinal plant used in traditional medicine for the management of liver and hepatobiliary carcinomas. It has a scientific name of vacha. A wide variety of metabolites are used in the management of cancers. Rhizome of *Acorus calamus* has properties such as anticancer properties, antioxidant properties, as well as neuroprotective properties by inhibiting the action of calcium channels, which are mainly responsible for the pain conduction pathway. Similar to carbamazepine, it has sodium channel blocking activity and neuroprotective properties.

MATERIALS AND METHODS:

2.1 PREPARATION OF EMULSION:

2.1.1. Materials

Tween 80 was obtained from LOBA Chemie Private Limited, Mumbai, India. Eucalyptus oil was collected from a natural products shop in Chennai, India. *Acorus calamus* rhizome was collected from a garden at ECR Chennai-Pondicherry Highway, India.

2.2. Pulverisation

A known number of rhizomes were dried in an oven for 24 h at 40° C. The final rhizomes were pulverised in a grinder, and the final weight was recorded. The Preparation was stored separately in a Scott bottle at room temperature for further usage.

2.3. Extraction and sample preparation

Dried rhizomes were dissolved separately in distilled water, methanol, and hexane with a ratio of 1:20 (g/mL). The extract was treated with a 40°C horizontal bath shaker at a medium shaking speed for 3 h. Afterwards, the content was filtered using No.1 Whatman filter paper. The solvent was evaporated from the filtrate through a rotary evaporator at 40 °C for 40 min. For preparing a 100 mg/mL extract stock solution, a known amount of dried extract was dissolved in DMSO. The mixture was treated with ultrasonication for 30 min to achieve full dissolution. The membrane residue was used to remove the undissolved residues.

2.4. Preparation of nanoemulsion

The extraction process was performed using a Soxhlet apparatus. Here, a 10 g dried sample was used for the aqueous extraction of bioactive compounds. The extract was evaporated, and the powder was collected by using rotary evaporation. In order to prepare a nanoemulsion, 10 g of Acorus calamus rhizome was added to 10 mL of water. To which 60 mL of palm oil and 30 mL of Tween 20 were added to prepare an oil-in-water emulsion. Then, the mixture was ultrasonicated for 60 min using an ultrasonics processor. The formation of a milky white coloured solution indicates the formation of an emulsion. The nanoemulsion formulation was further characterised by using various techniques. The size distribution of the droplet was identified by the dynamic light scattering method. The stability of the emulsion was determined by using a Zetasizer.

2.5. Methodology

Tween 20 was purchased from Loba Chemie Private Limited, located in Mumbai, India. Eucalyptus oil was purchased from a natural-based plant company in Chennai, India. Extract of *Acorus calamus* was collected from a naturally available herbal centre located at Madurai, India.

2.6. Addition of PVA to the prepared nanoemulsion

Total volume of preparation: 20ml

Preparation of PVA:

Total volume 20ml

10ml distilled water

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0.8 g sodium alginate

Procedure:

0.2ml PVA were added and heated for 2 hours at 70 °C, and then 10ml of Acorus calamus nanoemulsion was added and ultrasonicated for 30 minutes. Spread the preparations in a Petri dish, and keep in the hot air oven at 120 degrees overnight. After getting the samples dried, allow the samples to undergo characterisation.

3. Results

3.1. Particle size distribution

Particle size can be determined by measuring the random changes in the intensity of light scattered from a suspension or solution. This technique is commonly known as dynamic light scattering (DLS), but is also called photon correlation spectroscopy (PCS) and quasi-elastic light scattering (QELS). The particle size analysis by dynamic light scattering demonstrated a predominant, narrow intensity peak centred around ~100 nm, indicating that the majority of particles are within the nanoscale range. The distribution curve is unimodal with a sharp peak, suggesting a relatively homogeneous particle population.

A minor secondary peak was observed in the higher size range (in the micron region, ~5000–8000 nm), which may indicate the presence of trace aggregates or particle agglomeration. However, the intensity of this peak is negligible compared to the primary peak, confirming that the formulation is largely composed of nanosized particles.

The narrow distribution around 100 nm suggests low polydispersity and good uniformity, which is desirable for enhanced stability and efficient drug delivery. The nanoscale size range supports improved permeation and targeted delivery, particularly for topical applications. The particle size distribution (Fig. 2a) is used to depict the particle size at which the nanoemulsion is dimensionally stable.

3.2. Zeta potential:

Zeta potential is defined as the potential difference between the fluid layer adsorbed on a solid surface (such as a nanoparticle) and the bulk phase of the liquid, serving as an indicator of the mutual repulsion between nanoparticles and the stability of colloidal suspensions. The zeta potential analysis of the formulation showed a mean zeta potential of −26.98 mV, indicating that the particles possess a moderately negative surface charge. This value suggests fair electrostatic stability, as particles with zeta potential values close to ±30 mV are generally considered stable due to sufficient repulsive forces preventing aggregation.

The conductivity of the dispersion was 0.03449 mS/cm, reflecting a low ionic environment, which is suitable for accurate zeta potential measurement. The wall zeta potential and zeta deviation were recorded as 0 mV, indicating minimal interference from the measurement cell and high consistency in the obtained values.

The derived mean count rate (3941 kcps) and reference beam count rate (2199 kcps) confirm adequate signal intensity and proper alignment during analysis. Additionally, the quality factor of 2.099 indicates that the measurement is reliable and within acceptable quality limits for zeta potential determination.

The voltage and current versus time graph shows a consistent alternating electric field with a stable response, further validating the accuracy and reproducibility of the measurement. Fig. 2 demonstrates the zeta potential of the prepared nano gel.

The formulation exhibits a moderately stable colloidal system with a zeta potential of approximately −27 mV, supported by good measurement quality parameters. This suggests that the nanoemulsion system is sufficiently stable for topical drug delivery, with reduced likelihood of aggregation.

3.3. FTIR

Fourier Transform Infrared spectroscopy (FTIR) obtains an infrared spectrum of a substance, revealing information about its chemical composition and structure. FTIR spectroscopy is widely used in various fields for analysing organic and inorganic compounds. Figure 3 depicts that the FTIR spectrum of the formulation exhibited several characteristic peaks corresponding to functional groups present in the PVA-based nanocarrier system.

A broad absorption band at 3304.7 cm^{-1} is attributed to O–H stretching vibrations, indicating the presence of hydroxyl groups typical of polyvinyl alcohol and possible hydrogen bonding interactions. The peaks observed at 2925 cm^{-1} and 2873.2 cm^{-1} correspond to C–H stretching vibrations of aliphatic chains.

A distinct peak at 1714.2 cm^{-1} is indicative of C=O stretching, suggesting the presence of carbonyl groups, which may arise from residual acetate groups or incorporated components. The peaks at 1662.5 cm^{-1} and 1563.8 cm^{-1} can be assigned to C=C stretching or amide-related vibrations, indicating possible interactions between formulation components.

The band at 1406 cm^{-1} corresponds to C–H bending, while the peak at 1250.7 cm^{-1} is associated with C–O stretching vibrations. A strong and prominent peak at

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1110.1 cm^{-1} and 1033.7 cm^{-1} confirms the presence of C–O–C stretching, characteristic of the PVA backbone.

Additional peaks at 927.67 cm^{-1} and 858.63 cm^{-1} are attributed to out-of-plane bending vibrations, supporting the structural integrity of the polymer matrix.

The FTIR spectrum confirms the presence of characteristic functional groups of PVA along with other formulation components, with no significant peak shifts or disappearance. This indicates compatibility between the polymer and the incorporated nanoemulsion, suggesting the absence of major chemical interactions and confirming the stability of the formulation.

3.4. TGA

Thermo-Gravimetric analysis (TGA) is a thermal analysis technique in which a sample's mass is tracked as its temperature varies over time. In addition to chemical events like chemisorptions, thermal breakdown, and solid-gas reactions (e.g., oxidation or reduction), this measurement offers information on physical phenomena like phase transitions, absorption, adsorption, and desorption [1]. Figure 4 depicts the thermogravimetric analysis of the formulation, which demonstrated a gradual and multi-stage weight loss pattern with increasing temperature, indicating the thermal behaviour of the PVA-based nanocarrier system. An initial minor weight loss was observed between 30°C and ~150°C, which can be attributed to the evaporation of physically adsorbed moisture and residual solvents. A major weight loss phase occurred between ~200°C and 300°C, where the weight decreased significantly, indicating the onset of polymer degradation. This stage corresponds to the decomposition of the PVA backbone, including the elimination of side groups and chain scission. Beyond 300°C up to 500°C, a gradual, continuous weight loss was observed, representing further degradation and breakdown of the polymer matrix, including carbonaceous residue formation. At temperatures above 500°C, the weight loss plateaued, leaving a residual mass of approximately 25–30%, which may be attributed to char formation and inorganic residues.

3.5. Antimicrobial property

Antimicrobial resistance (AMR or AR) occurs when microbes evolve mechanisms that protect them from antimicrobials, which are drugs used to treat infections. Antimicrobial activity is useful in seeing if the prepared sample is resistant to microbial organisms. Figure 5 depicts that the prepared sample shows a very good zone of inhibition of the microbes, which shows that the prepared gel has antimicrobial activity. The test was performed in Staphylococcus aureus (S.aureus) and Escherichia coli (E.coli). Figure 6 shows the antimicrobial activity of the PVA-based nanocarrier and the control (i.e., PVA). The antibacterial activity of the formulated system was evaluated against Staphylococcus aureus and Escherichia coli using the agar well diffusion method.

Against Staphylococcus aureus: The formulation PVA–Alginate + TET exhibited a prominent zone of inhibition, indicating strong antibacterial activity. In contrast, PVA–Alginate (without TET) showed minimal to no zone of inhibition, suggesting a negligible inherent antibacterial effect of the polymer matrix alone.

Against Escherichia coli: A clear zone of inhibition was observed for PVA–Alginate + TET, confirming its effectiveness against Gram-negative bacteria. The PVA–Alginate alone demonstrated very small or negligible inhibition, similar to the findings in S. aureus.

Overall Cytotoxic activity:

The cytotoxic effect of Acorus calamus, along with eucalyptus oil extract, was evaluated using the 3-[4,5-dimethylthiazol-2-yl] -2,5-diphenyl tetrazolium bromide (MTT) test to determine their effect on the proliferation of human epithelial cells. The cells with a passage number of 8 were subsequently grown in a humidified chamber at 37 °C and 5% CO2. The resulting cells were then transferred at a concentration of 5 × 10^4 cells/well onto 96-well culture plates. These preparations were added to the cells at different doses (10mg/l). Following a 24-hour incubation phase with the aqueous extract, each well received 100 µL of MTT solution after the media was drained. To promote the creation of formazan crystals, the cells were then cultured for a further four hours. Figure 6 shows the overall cytotoxicity of the prepared nanocarrier. The cytocompatibility of the formulation was evaluated using periodontal ligament (PDL) cells. The results demonstrated that the negative control (PDL only) exhibited nearly 100% cell viability, confirming the normal growth and viability of untreated cells. The membrane extract (24-hour incubation) also showed cell viability close to 100%, with no significant reduction compared to the control group. This indicates that the formulation does not exert any cytotoxic effects on PDL cells. The comparable cell viability between the control and treated groups suggests that the developed formulation is biocompatible and non-toxic. The absence of significant cytotoxicity supports its suitability for biomedical and topical applications, particularly in sensitive tissues.

4. Discussion

The study aims to formulate a PVA-based nanocarrier for the delivery of A*corus calamus* in the management of trigeminal neuralgia. Acorus calamus, commonly known

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as sweet flag, has been used traditionally for various medicinal purposes. Its rhizome contains bioactive compounds, including asarone, which are responsible for its therapeutic properties. Nanoemulsion technology has emerged as a promising approach to enhance the efficacy and delivery of these compounds [2].

Alpha asarone is one of the major compounds found in A.*calamus*, 9.7% in the rhizome, and there is no Asarone content in the leaf part. [3]. The rhizome part of Acorus calamus was found to be less hydrophilic, so the extract preparation was done using water-in-oil type, followed by the reverse micelle principle. Rhizome of A.*calamus* naturally produces complex polyphenolic compounds, which might be the reason for the hydrophobic nature that exists with high affinity. Methanol was found to be the best solvent to extract the flavonoids of A.*calamus.*

Polyvinyl alcohol (PVOH, PVA, or PVAl) is a water-soluble synthetic polymer. It is commonly supplied as beads or as solutions in water. PVA is used in a variety of medical applications because of its biocompatibility, low tendency for protein adhesion, and low toxicity. Specific uses include cartilage replacements, contact lenses, laundry detergent pods and eye drops[4]. PVA-based polymers are used widely in additive manufacturing. For example, 3D printed oral dosage forms demonstrate great potential in the pharmaceutical industry. It is possible to create drug-loaded tablets with modified drug-release characteristics where PVA is used as a binder substance [5].

The current study examines FTIR, TGA, cytotoxic activity, zeta potential, particle size distribution, antimicrobial activity, and SEM image analysis. Neuroinflammation, peripheral sensitisation, and ectopic neuronal discharges are the main causes of TN pain. The potential mechanisms of action of A.calamus nanoemulgel include: direct modulation of nociceptor excitability through plant alkaloids/flavonoids; enhanced drug residence and penetration from the gel matrix to perineural tissues; antioxidant activity—limiting oxidative stress that sustains neuropathic signalling; and local anti-inflammatory effects by reducing cytokine/mediator-driven sensitisation.

Other bioactive chemicals found in the extracts were thought to have contributed to the antibacterial activity of A.calamus since the correlation data showed that the antibacterial activity of the plant was not concentration-dependent on TPC, TFC, or TAC. According to earlier research, extracts from A. calamus were found to have antibacterial activity. The abundance of flavonoids and phenolic compounds should theoretically be closely associated with A. calamus's antibacterial action [6]. Phenolic acids from other plants, such as gallic acid and caffeic acid, have been shown to have antibacterial properties. Another active ingredient thought to be in charge of the antibacterial activity in this investigation was beta-asarone. In addition, Joshi et al. (2012) found that beta-asarone had comparatively greater antibacterial action than alpha-asarone. This finding provided evidence that beta-asarone, rather than alpha-asarone, was the primary chemical responsible for the antibacterial action of A. calamus extracts.

In the present study, FTIR, TGA, antimicrobial activity, particle size distribution, zetapotential, SEM image analysis, and cytotoxic activity are studied. TN pain is driven by ectopic neural discharges, peripheral sensitisation, and neuroinflammation. The limitations of the current study reveal that, as there is a low number of studies on the nanoemulsion, there is a need for more studies in the future.

The future scope of the current study involves performing the cell line studies, followed by human trials to elaborate on the usage of the topical nanogel in the management of trigeminal neuralgia, along with carbamazepine in a fixed dosage of 200mg/day.

5. Conclusion

When applied topically, a chitosan-based nanocarrier combined with an Acorus calamus nanoemulsion shows promise as an adjuvant treatment for trigeminal neuralgia. Because it targets the trigger zone specifically and helps to lessen the degree of pain, the topical application method is also recommended in therapy. More research is required to assess the pharmacological activities and mechanism of the created nanoemulsion, as there are fewer studies and pieces of evidence.

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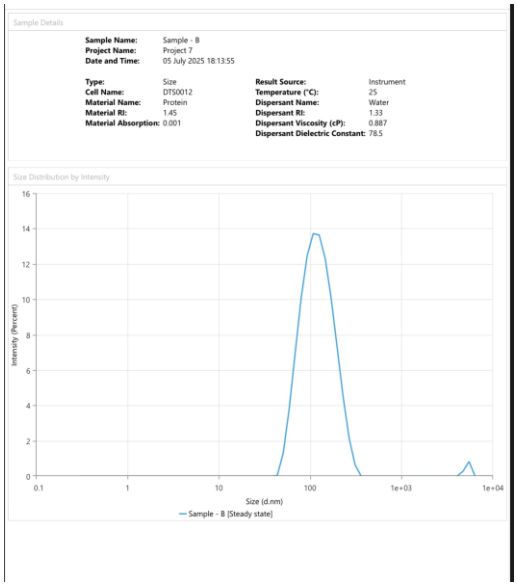
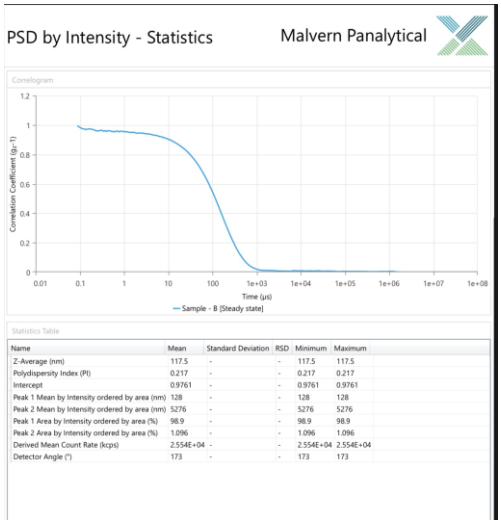
FIGURES

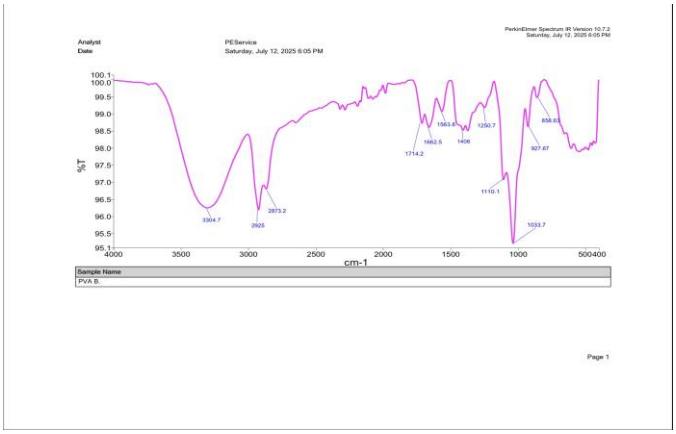
1) PARTICLE SIZE DISTRIBUTION



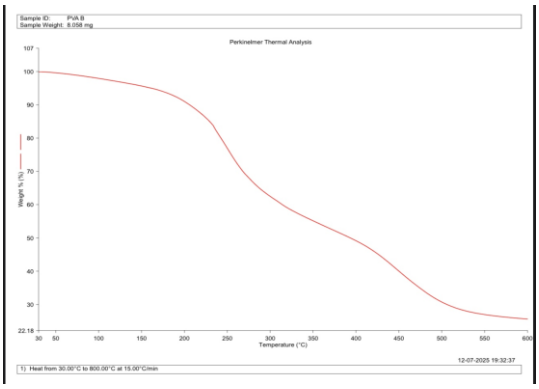


2) ZETAPOTENTIAL

3) FTIR



4) TGA



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5) ANTIMICROBIAL ACTIVITY

6) OVERALL CYTOTOXICITY