RESEARCH PAPER

FORMULATION OPTIMIZATION AND PRE-FORMULATION STUDIES OF p-CYMENE LOADED NANOEMULSION FOR ENHANCED INTRANASAL DELIVERY

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ABSTRACT

The present investigation aimed to develop and optimize a p-cymene-loaded nanoemulsion intended for enhanced intranasal drug delivery. p-Cymene is a naturally occurring aromatic monoterpene possessing anti-inflammatory, antioxidant, antimicrobial, and neuroprotective activities; however, poor aqueous solubility and volatility limit its pharmaceutical applicability. Nanoemulsion systems provide improved solubilization, permeability, and physicochemical stability of lipophilic compounds.

The nanoemulsion system was formulated using orange oil as oil phase, Tween 80 as surfactant, Carbitol as co-surfactant, and distilled water as aqueous phase. Pre-formulation studies including organoleptic evaluation, solubility analysis, UV spectrophotometric calibration, HPLC calibration, FTIR compatibility studies, and HPLC purity analysis were performed. Pseudo-ternary phase diagrams were constructed using aqueous titration method for optimization of surfactant systems.

Thermodynamic stability studies, dispersibility tests, and simulated nasal fluid evaluation were performed to identify optimized formulations. Dynamic Light Scattering analysis demonstrated nanosized globules with particle size of 118.8 nm. FTIR studies confirmed absence of significant drug–excipient interaction, while HPLC analysis confirmed purity of p-cymene with 98.33% area purity.

The developed nanoemulsion system demonstrated satisfactory physicochemical stability and promising characteristics suitable for intranasal delivery applications.

Keywords: p-Cymene, Nanoemulsion, Intranasal delivery, Pseudoternary phase diagram, FTIR, HPLC, Particle size analysis.

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1. Introduction

Intranasal drug delivery has emerged as a promising non-invasive route for administration of therapeutic agents because of rapid onset of action, avoidance of hepatic first-pass metabolism, improved patient compliance, and direct nose-to-brain transport pathways.[1, 2] Recent developments in intranasal nanocarrier systems have demonstrated significant potential for enhanced brain targeting and improved therapeutic efficacy.[3-5]

Nanoemulsion systems are isotropic colloidal dispersions composed of oil, surfactant, co-surfactant, and aqueous phase with globule sizes generally ranging between 20–200 nm. [6, 7] Due to their nanosized droplets and enhanced interfacial surface area, nanoemulsions improve solubilization and permeation of poorly water-soluble compounds.[8, 9]

p-Cymene is a naturally occurring aromatic monoterpene present in essential oils of several medicinal plants and exhibits anti-inflammatory, antioxidant, antimicrobial, analgesic and neuroprotective activities.[10] However, poor aqueous solubility and volatility restrict its pharmaceutical application.

Nanoemulsion-based systems may therefore represent an effective strategy to improve physicochemical properties and intranasal delivery characteristics of *p*-cymene.[11, 12] Several recent studies have demonstrated the applicability of intranasal nanoemulsions for brain targeting and improved therapeutic delivery.[5, 13]

Hence, the present investigation aimed to perform systematic preformulation investigations and optimization of *p*-cymene-loaded nanoemulsion using aqueous titration method.

2. Materials and Methods

2.1 Materials

p-Cymene was purchased from Sigma-Aldrich. Various oils including orange oil, olive oil, castor oil, and coconut oil were screened for selection of suitable oil phase. Different surfactants such as Tween 80 and Tween 20, and co-surfactants including Carbitol and PEG 400 were evaluated based on solubility and emulsification efficiency. Double distilled water was used as aqueous phase. Selection of optimized components was carried out

following preformulation and screening studies. All reagents and chemicals used during the investigation were of analytical grade procured from central chemical store R. V. Northland Institute, G. B. Nagar U.P. India.

2.2 Organoleptic and Physicochemical Evaluation

Table 1: Organoleptic and Physicochemical Properties of *p*-Cymene

Parameter	Observation
Nature	Liquid
Colour	Colourless liquid
Odour	Pleasant aromatic odour
Appearance	Clear
Boiling Point	177°C

The physicochemical properties confirmed characteristic features of *p*-cymene as a volatile aromatic monoterpene suitable for nanoemulsion formulation.

2.3 Solubility Studies

Solubility studies were carried out to identify suitable excipients for nanoemulsion formulation. Excess quantity of *p*-cymene was added separately into selected oils, surfactants, and co-surfactants followed by continuous shaking and centrifugation.[14, 15]

Table 2: Solubility of *p*-Cymene in Oils

Oil Phase	Solubility (mg/mL)
Orange oil	96.8 ± 1.2
Olive oil	72.5 ± 1.0
Castor oil	61.4 ± 0.9
Coconut oil	58.7 ± 1.1

Table 3: Solubility in Surfactants and Co-surfactants

Excipient	Solubility (mg/mL)
Tween 80	112.4 ± 1.4
Tween 20	95.6 ± 1.3
Carbitol	105.2 ± 1.1
PEG 400	83.5 ± 1.0

Orange oil exhibited maximum solubilization capacity and was selected as oil phase for nanoemulsion preparation. Tween 80 was employed as surfactant and Carbitol as co-surfactant.

2.4 UV Spectrophotometric Calibration Curve

The λmax of *p*-cymene was determined by UV spectrophotometric scanning, and maximum absorbance was observed at 260 nm. Calibration curve was prepared using concentrations ranging from 1–18 µg/mL at 260 nm.

Table 4: UV Calibration Curve Data

Concentration (µg/mL)	Mean Absorbance	SD
1	0.045	0.001
2	0.108	0.001
4	0.232	0.001
6	0.282	0.0005
8	0.396	0.001
12	0.566	0.0005
18	0.865	0.00005

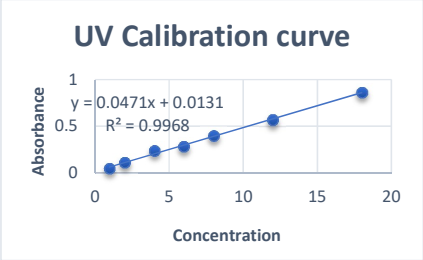


Figure 1. UV spectrophotometric calibration curve of p-cymene at 260 nm.

The calibration curve demonstrated satisfactory linearity and reproducibility suitable for quantitative estimation of *p*-cymene.

2.5 FTIR Compatibility Studies

FTIR analysis was performed to evaluate compatibility between *p*-cymene and selected formulation excipients.

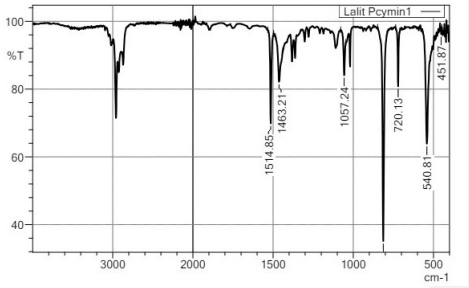


Figure 2. FTIR spectrum of p-cymene showing characteristic functional group peaks.

Table 5: FTIR Peak Interpretation of *p*-Cymene

Peak (cm^{-1})	Functional Group
3020–2960	Aromatic and aliphatic C–H stretching
1514.85	Aromatic C=C stretching
1463.21	CH_3 bending vibration
1057.24	C–H in-plane bending
813.37	Aromatic C–H out-of-plane bending
720.13	Aromatic ring deformation

The FTIR spectrum confirmed structural integrity of *p*-cymene and absence of significant drug–excipient interaction.

2.6 HPLC Analysis and Calibration Curve

HPLC analysis was performed to determine chromatographic behaviour and purity profile of *p*-cymene.

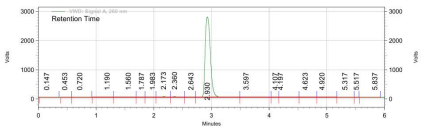


Figure 3. HPLC chromatogram of p-cymene showing major peak at retention time 2.930 min.

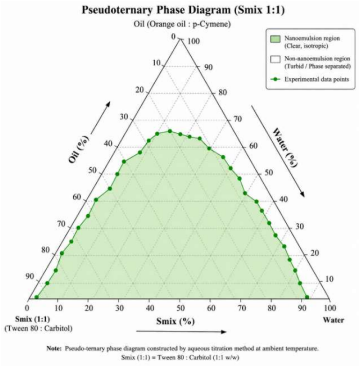
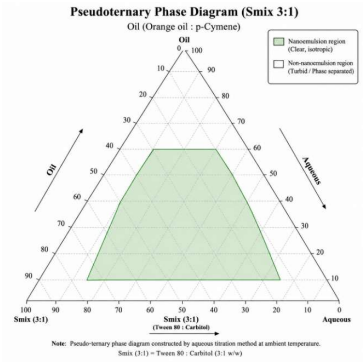


Table 6: HPLC Chromatographic Data

Retention Time (min)	Area %
2.930	98.33

Table 7: HPLC Calibration Curve Data



Concentration	Peak Area
1	38036552
5	59912822
25	155073081
50	268314669
75	388142127
100	521092644

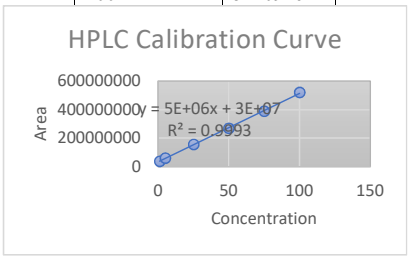


Figure 4. HPLC calibration curve of p-cymene showing relationship between concentration and peak area.

The HPLC calibration data demonstrated proportional increase in peak area with concentration, indicating acceptable analytical linearity.

2.7 Construction of Pseudo-ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed using aqueous titration method to identify nanoemulsion regions and optimize surfactant-to-co-surfactant ratios. S-mix ratios investigated included 1:1, 1:2, 3:1, and 4:1 systems. [16, 17]

Transparent and isotropic nanoemulsion regions were identified visually and optimized formulations

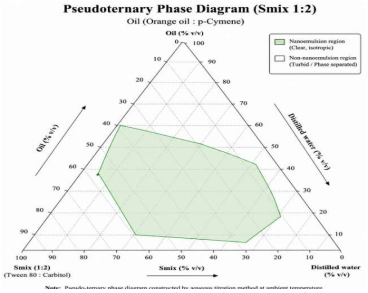


Figure 5. Pseudoternary phase diagram of Smix 1:1 system

were selected for further characterization.

2.8 Thermodynamic Stability Studies

Prepared nanoemulsion formulations were subjected to heating–cooling cycle, centrifugation cycle, and freeze–thaw cycle to identify physically stable systems. Formulations exhibiting phase separation, creaming, or aggregation were excluded from further investigations.[18]

2.9 Dispersibility Studies

Dispersibility studies were performed in distilled water and simulated nasal fluid (SNF) to evaluate physiological compatibility of nanoemulsion

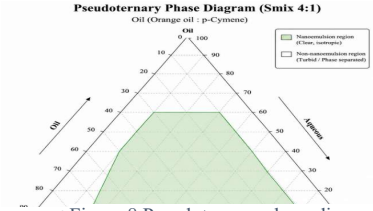


*Figure 7 Pseudo*Figure 8.Pseudoternary phase diagram of Smix 4:1 system

formulations.

Table 8: Grading Criteria for Dispersibility Test

Grade	Observation
A	Excellent dispersibility
B	Good dispersibility
C	Fair dispersibility
D	Poor dispersibility

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Formulations exhibiting satisfactory dispersibility behaviour in SNF were selected for further evaluation.

2.10 Optimized Formulations

Table 9: Composition of Optimized Formulations

Code	Oil	Smix	Aqueous
LP1	15	51.66	33.33
LP2	20	46.66	33.33
LP3	20	30	50
LP4	15.62	46.87	37.5
LP5	20.83	62.5	16.66

Based on thermodynamic stability and dispersibility studies, optimized formulations were selected for further physicochemical characterization.

3. Evaluation of Nanoemulsion

3.1 Particle Size Analysis

Particle size analysis was performed using Dynamic Light Scattering technique.

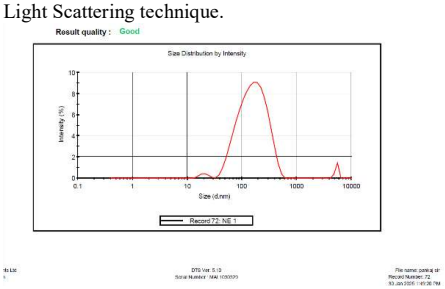

Figure 5 Particle size distribution graph of optimized p-cymene nanoemulsion.

Table 10: Particle Size Characteristics of Optimized Nanoemulsion

Parameter	Observation
Z-average size	118.8 nm
PDI	0.941
Major peak diameter	177.8 nm
Major peak intensity	96.7%
Result quality	Good

The optimized nanoemulsion exhibited nanosized globules suitable for intranasal delivery applications.

3.2 Zeta Potential

Table 11: Zeta Potential Values

Formulation	Zeta Potential (mV)
LP1	-18.5 ± 0.5
LP2	-22.4 ± 0.8
LP3	-28.6 ± 1.2
LP4	-24.7 ± 1.0
LP5	-23.6 ± 1.0

The optimized formulation demonstrated acceptable colloidal stability.

4. Results and Discussion

Preformulation investigations confirmed characteristic physicochemical properties of *p*-cymene as a volatile aromatic monoterpene. Solubility studies demonstrated that orange oil exhibited superior solubilization capacity, while Tween 80 and Carbitol demonstrated satisfactory emulsification efficiency. [8, 19, 20]

FTIR analysis confirmed absence of significant chemical interaction between *p*-cymene and selected excipients. HPLC chromatographic analysis confirmed purity of the selected drug sample with 98.33% area purity.

Pseudoternary phase diagram studies demonstrated successful formation of transparent nanoemulsion regions using different Smix ratios. Thermodynamic stability and dispersibility studies indicated that surfactant-to-co-surfactant ratio significantly influenced formulation stability and physiological compatibility.[16, 21, 22]

The optimized formulations demonstrated satisfactory dispersibility behavior in simulated nasal fluid and acceptable thermodynamic stability characteristics. Dynamic Light Scattering analysis confirmed successful formation of nanosized droplets suitable for intranasal delivery applications. Smaller globule size may contribute to enhanced surface area and improved permeation characteristics.[23, 24]

Recent investigations have highlighted that intranasal nanoemulsion systems improve nose-to-brain transport, prolong nasal residence time, and enhance therapeutic bioavailability[25].

Nanoemulsion systems containing higher aqueous phase proportion are generally favorable for oil-in-water nanoemulsion formation and improved intranasal compatibility.[25, 26] Among investigated systems, LP3 formulation demonstrated comparatively better aqueous phase proportion and satisfactory physicochemical stability suitable for oil-in-water nanoemulsion formation.

5. Conclusion

The present investigation successfully developed and optimized *p*-cymene-loaded nanoemulsion using aqueous titration method. FTIR and HPLC analyses confirmed compatibility and purity of the drug sample. Optimized formulations demonstrated satisfactory thermodynamic stability, dispersibility, and nanosized globules suitable for intranasal delivery applications.

The developed nanoemulsion system may represent a promising carrier for enhanced intranasal delivery of *p*-cymene. Further studies involving nanoemulgel development, ex vivo permeation, and in vivo evaluation are recommended.

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Conflict of Interest

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The authors declare that there is no conflict of interest regarding the publication of this research work.

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