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# DEVELOPMENT AND EVALUATION OF MUCOADHESIVE FLUNARIZINE NANOEMULSION FOR NOSE-TO-BRAIN DRUG DELIVERY IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

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**Abstract**

Alzheimer's disease is a progressive neurodegenerative disorder characterised by memory loss and cognitive impairment. The delivery of therapeutic agents to the brain is significantly restricted by the blood–brain barrier (BBB), limiting drug effectiveness. Flunarizine, a lipophilic calcium channel blocker, exhibits potential neuroprotective activity; however, its oral bioavailability is limited due to extensive first-pass metabolism. The present study aimed to develop and evaluate a mucoadhesive nanoemulsion of Flunarizine for intranasal (nose-to-brain) drug delivery to enhance brain targeting and therapeutic efficacy. Nanoemulsions were formulated using sesame oil as the oil phase, Tween 80 as the surfactant, PEG 400 as the co-surfactant, and distilled water as the aqueous phase, employing the vortexing–sonication method. A total of nine formulations (F1–F9) were developed using an L9 Taguchi orthogonal array design. The prepared formulations were evaluated for physicochemical parameters such as pH, drug content, entrapment efficiency, particle size, polydispersity index, zeta potential, and in-vitro drug diffusion.Among the formulations, F3 demonstrated optimal characteristics, including suitable particle size, high entrapment efficiency, stability, and enhanced drug release. Drug release kinetics indicated that the optimised formulation followed zero-order kinetics with a diffusion-controlled release mechanism. The findings suggest that the developed mucoadhesive Flunarizine nanoemulsion is a promising approach for intranasal drug delivery, offering improved brain targeting and therapeutic potential in the management of Alzheimer's disease.



## INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder that primarily affects the elderly population and is characterised by memory impairment, cognitive decline, and behavioural disturbances [1]. It is one of the leading causes of dementia worldwide and poses a significant burden on healthcare systems. The pathological features of AD include amyloid-β plaque accumulation, neurofibrillary tangles, synaptic dysfunction, and neuronal loss, ultimately leading to progressive deterioration of brain function [2]. A major challenge in the treatment of central nervous system (CNS) disorders, including Alzheimer's disease, is the presence of the blood–brain barrier (BBB)[3]. The BBB is a highly selective physiological barrier composed of endothelial cells with tight junctions that restrict the entry of most drugs into the brain. This protective mechanism significantly limits the therapeutic effectiveness of many pharmacological agents administered via conventional routes [4]. Flunarizine, a lipophilic calcium channel blocker, possesses neuroprotective, anti-ischemic, and anti-migraine properties. It acts by inhibiting calcium influx into neuronal cells, thereby reducing neuronal excitotoxicity and oxidative stress [5]. Despite its potential benefits in neurodegenerative disorders, the clinical application of Flunarizine is limited by poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability, resulting in inadequate drug concentrations in the brain [6]. To overcome these limitations, alternative drug delivery strategies that enhance brain targeting are essential. Intranasal drug delivery has emerged as a promising non-invasive approach for delivering drugs directly to the brain [7]. Drugs administered via the nasal route can bypass the BBB and reach the brain through olfactory and trigeminal neural pathways, leading to rapid onset of action and improved bioavailability. Additionally, this route avoids hepatic first-pass metabolism, further enhancing drug effectiveness [8]. Nanoemulsion-based drug delivery systems have gained considerable attention due to their ability to improve the solubility and bioavailability of poorly water-soluble drugs. Nanoemulsions are thermodynamically stable systems with droplet sizes typically ranging from 20 to 200 nm, providing a large surface area for absorption and enhanced permeation across biological membranes [9-11]. Furthermore,

the incorporation of mucoadhesive agents into nanoemulsion systems can prolong the residence time of the formulation in the nasal cavity, thereby enhancing drug absorption and improving brain targeting efficiency [12].

Therefore, the present study aims to develop and evaluate a mucoadhesive nanoemulsion formulation of Flunarizine for intranasal administration. This approach is expected to overcome the limitations associated with conventional delivery methods and enhance therapeutic efficacy in the management of Alzheimer's disease.

## MATERIALS AND METHODS

### Materials

Flunarizine and Chitosan were obtained as gift samples from Yarrow Chem Products, Mumbai, India. Sesame oil was procured from Cargo Enterprises, New Delhi, India. Tween 80 and PEG 400 were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade and used as received.

### Preformulation Studies

#### Determination of λmax of Flunarizine

The maximum absorption wavelength (λmax) of Flunarizine was determined using a UV–Visible spectrophotometer (Shimadzu UV-1800). Accurately weighed 10 mg of Flunarizine was dissolved in phosphate buffer (pH 7.4), and the volume was made up to 10 mL to obtain a stock solution. Further dilution was carried out to obtain a suitable concentration. The solution was scanned in the wavelength range of 200–400 nm, and the λmax was recorded[13].

#### Preparation of Calibration Curve

Standard solutions of Flunarizine were prepared in phosphate buffer (pH 7.4) at different concentrations (5–25 µg/mL). The absorbance of each solution was measured at the determined λmax using a UV–Visible spectrophotometer. A calibration curve was constructed by plotting concentration versus absorbance [14].

#### Drug–Excipient Compatibility Studies

Compatibility studies between Flunarizine and selected excipients were carried out using Fourier Transform Infrared (FTIR) spectroscopy (Bruker Alpha II). The spectra of pure drug, excipients, and their physical mixture were recorded over a range of 4000–400 $cm^{-1}$ and analysed for any possible interactions [15].

### Formulation of Flunarizine Nanoemulsion

#### Preparation of Nanoemulsion

Flunarizine nanoemulsions were prepared by the vortexing–sonication method. The required amount of Flunarizine was dissolved in sesame oil with mild heating. Tween 80 and PEG 400 were added to the oil phase with continuous stirring.

Chitosan was dissolved in a small quantity of dilute acid and then added to distilled water to prepare the aqueous phase. The aqueous phase was slowly added to the oil phase under continuous vortexing to form a coarse emulsion. The resulting emulsion was subjected to sonication to obtain a nanoemulsion with reduced droplet size [16,17].

### Evaluation of Nanoemulsions

#### pH Measurement

The pH of the prepared nanoemulsions was measured using a calibrated digital pH meter. Approximately 10 mL of the formulation was taken in a beaker, and the electrode was immersed in the sample. Measurements were performed in triplicate [18].

#### Viscosity Determination

Viscosity of the formulations was determined using a Brookfield digital viscometer (Model DV-E). Approximately 25 mL of the sample was placed in a beaker and analysed using spindle LV-2 at 50 rpm at room temperature [19].

#### Drug Content Estimation

An aliquot (1 mL) of nanoemulsion was diluted with phosphate buffer (pH 7.4), sonicated to ensure complete drug extraction, and filtered. The absorbance was measured at λmax using a UV–Visible spectrophotometer. Drug content was calculated using the calibration curve [20].

#### Determination of Entrapment Efficiency

Nanoemulsion samples were centrifuged at 15,000 rpm for 30–40 minutes at 4°C. The supernatant containing free drug was collected and analysed spectrophotometrically at λmax. Entrapment efficiency was calculated using the formula:

#### Particle Size and Polydispersity Index (PDI)

Particle size and PDI of the optimised formulation were determined using Dynamic Light Scattering (DLS) (Malvern Zetasizer). The sample was diluted appropriately with distilled water and analysed at 25°C.

#### Zeta Potential Analysis

Zeta potential was measured using a Zetasizer based on electrophoretic light scattering. The sample was diluted and placed in a capillary cell. Measurements were carried out at 25°C.

#### In-vitro Drug Diffusion Study

In-vitro drug diffusion studies were carried out using a Franz diffusion cell apparatus. A dialysis membrane (MWCO 12,000–14,000 Da) was used as the diffusion barrier. The membrane was soaked in distilled water for 12 hours and equilibrated in phosphate buffer (pH 7.4). The receptor compartment was filled with buffer and maintained at 37 ± 0.5°C with continuous stirring. The nanoemulsion formulation was placed in the donor compartment. At predetermined time intervals, samples were withdrawn from the receptor compartment and replaced with fresh buffer. The samples were analysed using a UV–Visible spectrophotometer at λmax [21-23].

## RESULTS AND DISCUSSION

### Determination of λmax of Flunarizine

The spectrum obtained showed several peaks, among which the major absorption peak was observed at 253 nm, which was selected as λmax for further analysis.

### Construction of Calibration Curve

A standard calibration curve of Flunarizine was prepared using phosphate buffer (pH 7.4). Standard solutions with concentrations of 5, 10, 15, 20, and 25 µg/mL were prepared.

The absorbance of each solution was measured at 253 nm using a UV–Visible spectrophotometer. A calibration curve was plotted between concentration and absorbance.

Table 1: Absorbance Values for Calibration Curve of Flunarizine

| Concentration (µg/mL) | Absorbance at 253 nm |
|---|---|
| 5 | 0.311 |
| 10 | 0.428 |
| 15 | 0.619 |
| 20 | 0.736 |
| 25 | 0.802 |

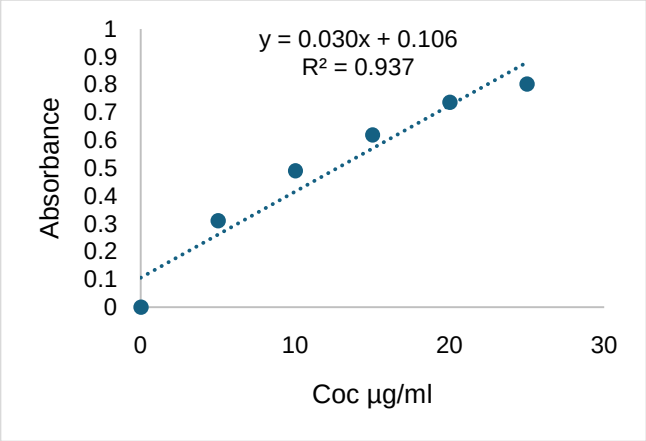


Figure 1: Calibration Curve of Flunarizine

**Drug–Excipient Compatibility Studies**

Drug–excipient compatibility studies were carried out using Fourier Transform Infrared (FTIR) spectroscopy (Bruker Alpha II). The FTIR spectra of pure Flunarizine, individual excipients, and the physical mixture of drug with excipients were recorded in the range of 4000–400 $cm^{-1}$. The obtained spectra were analyzed for any changes in characteristic peaks. The results indicated no significant shifts or disappearance of peaks, confirming the absence of chemical interaction between Flunarizine and the selected excipients, thereby indicating compatibility.

**Formulation Studies**

**4Preparation of Flunarizine Nanoemulsion**

An L9 Taguchi orthogonal matrix design was employed to optimize formulation variables. A total of nine formulations (F1–F9) were prepared by varying the concentrations of oil, surfactant, and co-surfactant. The nanoemulsions were prepared using the vortexing–sonication method. Initially, sesame oil (oil phase) was heated gently, and the required amount of Flunarizine was dissolved in it. Tween 80 (surfactant) and PEG 400 (co-surfactant) were then added with continuous stirring. Chitosan was dissolved separately in a small quantity of dilute acid and subsequently added to distilled water to prepare the aqueous phase. The aqueous phase was added slowly to the oil phase under continuous vortexing to form a coarse emulsion. The obtained emulsion was further subjected to sonication to produce a nanoemulsion with reduced droplet size.

**Formulation Design Using L9 Taguchi Orthogonal Matrix**

**Table 2: Composition of Flunarizine Nanoemulsion Formulations (F1–F9)**

| Formulation | Sesame Oil (%) | Tween 80 (%) | PEG 400 (%) | Chitosan (%) | Water (%) | Total (%) |
|---|---|---|---|---|---|---|
| F1 | 5.0 | 10.0 | 5.0 | 2 | 78.0 | 100 |
| F2 | 5.0 | 20.0 | 12.5 | 2 | 60.5 | 100 |
| F3 | 5.0 | 30.0 | 20.0 | 2 | 43.0 | 100 |
| F4 | 12.5 | 10.0 | 12.5 | 2 | 63.0 | 100 |
| F5 | 12.5 | 20.0 | 20.0 | 2 | 45.5 | 100 |
| F6 | 12.5 | 30.0 | 5.0 | 2 | 50.5 | 100 |
| F7 | 20.0 | 10.0 | 20.0 | 2 | 48.0 | 100 |
| F8 | 20.0 | 20.0 | 5.0 | 2 | 53.0 | 100 |
| F9 | 20.0 | 30.0 | 12.5 | 2 | 35.5 | 100 |

**pH of Nanoemulsions**

All formulations exhibited pH in the range of 6.10–6.52, which is suitable for intranasal administration and compatible with the nasal mucosa. The slight variation is attributed to differences in excipient composition. Formulation F3 showed pH closest to physiological conditions, indicating better suitability and stability.

Table 3: pH of Flunarizine Nanoemulsion Formulations (F1–F9)

| Formulation | pH (Mean ± SD) |
|---|---|
| F1 | 6.10 ± 0.04 |
| F2 | 6.25 ± 0.05 |
| F3* | 6.52 ± 0.03 |
| F4 | 6.18 ± 0.06 |
| F5 | 6.34 ± 0.04 |
| F6 | 6.28 ± 0.05 |
| F7 | 6.21 ± 0.03 |
| F8 | 6.40 ± 0.04 |
| F9 | 6.30 ± 0.05 |

**Viscosity of Nanoemulsions**

Viscosity values ranged from 142 to 175 cP, indicating acceptable flow properties for nasal delivery. Increased viscosity in some formulations is due to higher surfactant and polymer content. F3 exhibited higher viscosity, which may enhance formulation stability and prolong nasal residence time.

Table 4: Viscosity of Flunarizine Nanoemulsion Formulations (F1–F9)

| Formulation | Viscosity (cP) |
|---|---|
| F1 | 142 ± 3 |
| F2 | 158 ± 4 |
| F3* | 175 ± 3 |
| F4 | 150 ± 2 |
| F5 | 165 ± 3 |
| F6 | 160 ± 4 |
| F7 | 148 ± 3 |
| F8 | 168 ± 2 |
| F9 | 162 ± 3 |

**Drug Content**

All formulations showed high drug content (91–98%), indicating uniform drug distribution. Minor variations may be due to formulation composition differences. F3 exhibited maximum drug content, suggesting efficient drug incorporation within the nanoemulsion system.

Table 5: Drug Content of Flunarizine Nanoemulsion Formulations (F1–F9)

| Formulation | Drug Content (%) |
|---|---|
| F1 | 91.24 ± 0.52 |
| F2 | 93.15 ± 0.48 |
| F3* | 98.42 ± 0.36 |
| F4 | 92.05 ± 0.41 |
| F5 | 94.32 ± 0.38 |
| F6 | 93.87 ± 0.45 |
| F7 | 92.60 ± 0.47 |
| F8 | 95.28 ± 0.39 |
| F9 | 94.64 ± 0.42 |

**Entrapment Efficiency**

Entrapment efficiency ranged from 72% to 89%, influenced by oil and surfactant concentration. Higher surfactant levels improve drug solubilization and encapsulation. F3 showed maximum entrapment efficiency, indicating optimal formulation composition.

Table 6: Entrapment Efficiency of Flunarizine Nanoemulsions (F1–F9)

| Formulation | Entrapment Efficiency (%) |
|---|---|
| F1 | 72.36 ± 0.62 |
| F2 | 75.84 ± 0.58 |
| F3* | 89.76 ± 0.45 |
| F4 | 74.21 ± 0.51 |
| F5 | 81.35 ± 0.49 |
| F6 | 79.64 ± 0.53 |
| F7 | 76.82 ± 0.55 |
| F8 | 84.28 ± 0.47 |
| F9 | 82.15 ± 0.50 |

**Particle Size and PDI (Optimised Formulation F3)**

The particle size of 376.4 nm confirms a nanoscale formulation suitable for enhanced permeation. The low PDI value (0.122) indicates uniform droplet distribution and system homogeneity, suggesting good formulation stability.

**Zeta Potential (Optimized Formulation F3)**

The zeta potential value of −39.3 mV indicates good electrostatic stability of the nanoemulsion system. The high negative charge prevents aggregation due to repulsive forces, ensuring long-term stability.

**In-vitro Drug Diffusion Study**

All formulations exhibited sustained and time-dependent drug release. The initial slower release may be due to drug partitioning from oil droplets. Among all, F3 showed maximum drug release (92% at 10 h), likely due to optimised surfactant/co-surfactant ratio and reduced droplet size, enhancing diffusion and release rate.

Table 7: Cumulative Percentage Drug Release of Flunarizine Nanoemulsions (F1–F9)

| Time (h) | F1 (%) | F2 (%) | F3 (%) | F4 (%) | F5 (%) | F6 (%) | F7 (%) | F8 (%) | F9 (%) |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 1 | 2.05 | 2.81 | 9.53 | 4.10 | 7.76 | 1.20 | 9.20 | 1.25 | 1.06 |
| 2 | 2.25 | 15.50 | 11.08 | 3.35 | 8.80 | 4.30 | 11.30 | 9.70 | 6.66 |
| 3 | 9.60 | 22.60 | 26.70 | 10.03 | 11.30 | 7.30 | 13.15 | 21.60 | 11.30 |
| 4 | 15.70 | 35.70 | 33.50 | 15.21 | 17.03 | 0.01 | 16.60 | 36.90 | 15.21 |
| 5 | 24.00 | 39.60 | 42.06 | 15.36 | 25.50 | 28.50 | 29.30 | 61.20 | 25.16 |
| 6 | 29.60 | 41.30 | 42.53 | 29.25 | 28.40 | 30.50 | 41.03 | 63.30 | 29.55 |
| 7 | 54.63 | 62.70 | 62.03 | 42.10 | 28.50 | 45.03 | 47.00 | 67.10 | 33.53 |
| 8 | 67.23 | 78.20 | 75.90 | 52.50 | 48.60 | 55.60 | 61.70 | 76.70 | 41.03 |
| 9 | 77.20 | 80.66 | 89.10 | 63.20 | 54.20 | 68.40 | 68.70 | 77.20 | 55.50 |
| 10 | 90.26 | 86.20 | 92.90 | 77.20 | 75.90 | 79.80 | 77.30 | 78.60 | 67.90 |

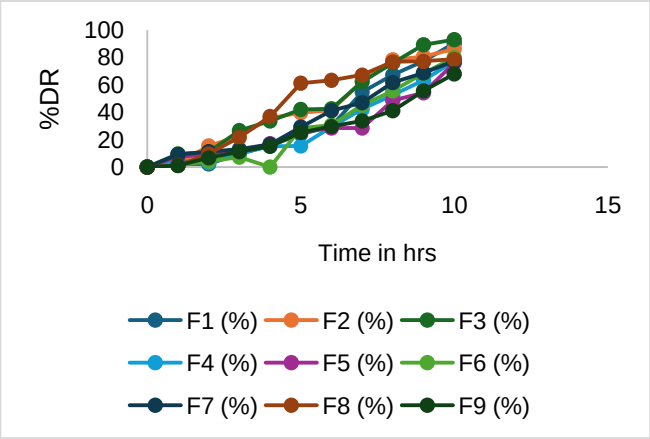


Figure 3: In-vitro Drug Release Profile of Flunarizine Nanoemulsions (F1–F9)

## CONCLUSION

The present study successfully developed a mucoadhesive Flunarizine nanoemulsion for intranasal drug delivery using an L9 Taguchi design. Among all formulations, F3 was identified as the optimized formulation based on superior physicochemical properties, high drug content, entrapment efficiency, and enhanced drug release profile. The optimized formulation exhibited nanoscale particle size, narrow size distribution, and good stability.Overall, the developed nanoemulsion system demonstrates significant potential for effective nose-to-brain delivery of Flunarizine, which may

improve therapeutic outcomes in the management of Alzheimer's disease.

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## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## INFORM CONSENT AND ETHICAL CNSIDERATIONS

Not applicable

## AUTHOR CONTRIBUTIONS

K. Mudrika carried out the experimental work, data collection, and manuscript preparation. A. Venkata Badarinath contributed to study design, supervision, data interpretation, and critical revision of the manuscript.

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