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Formulation, Evaluation, and Optimization of Nanostructured Lipid Carriers Containing Memantine and Donepezil-Loaded In-Situ Gel for Improvement of Alzheimer's Disease

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Abstract : *Alzheimer's disease is a progressive neurodegenerative disorder associated with memory loss, cognitive decline, and reduced ability to perform daily activities. Conventional oral delivery of drugs may be limited by the blood–brain barrier and systemic clearance. The objective of this work is to explore a nose-to-brain delivery approach in which memantine hydrochloride and donepezil hydrochloride are co-loaded into nanostructured lipid carriers (NLCs) and incorporated into an intranasal in-situ gelling system. The proposed methodology includes drug and excipient selection, physicochemical characterization, analytical method development, NLC preparation and optimization, and evaluation of particle size, polydispersity index, zeta potential, entrapment efficiency, pH, viscosity, gelation, in-vitro drug release, nasal compatibility, and stability. The formulation observations reported in the supplied draft indicate that F3 and F4 were clear, while F1 and F2 were hazy; the reported pH range was 5.5–5.7. Gelation temperatures ranged from 21 ± 1.2°C to 28 ± 1.4°C, and gel melting temperatures ranged from 80 ± 1.7°C to 91 ± 1.3°C, with F4 showing the lowest gelation and highest melting temperature. These findings support further systematic evaluation of the proposed intranasal NLC in-situ gel.*

Keywords: Alzheimer's disease; memantine; donepezil; nanostructured lipid carriers; in-situ gel; intranasal drug delivery; nose-to-brain delivery

I. INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the gradual deterioration of memory, cognitive function, learning ability, and the capacity to perform daily activities. It is one of the leading causes of dementia, particularly among older adults. The disease is associated with the accumulation of amyloid-beta plaques, the formation of neurofibrillary tangles due to abnormal tau protein, synaptic dysfunction, and neuronal loss. Disturbances in neurotransmitter systems, particularly cholinergic and glutamatergic neurotransmission, contribute to the cognitive impairment observed in affected individuals.

Donepezil and memantine are two drugs commonly used to manage the symptoms of Alzheimer's disease. Donepezil is an acetylcholinesterase inhibitor that increases the availability of acetylcholine in the brain, thereby supporting learning and cognitive function. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that regulates excessive glutamate-mediated activity and may help maintain cognitive and functional abilities in patients with moderate-to-severe Alzheimer's disease. These drugs act through different mechanisms to help manage symptoms and support quality of life.

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Although donepezil and memantine act through different mechanisms, their combination may provide complementary symptomatic benefits in some patients. Neither drug cures Alzheimer's disease nor completely prevents its progressive course.

In-situ gel formulations are liquid preparations that undergo gel formation after administration in response to physiological conditions such as temperature, pH, or ionic composition. Intranasal in-situ gels may prolong contact with the nasal mucosa, reduce rapid mucociliary clearance, and provide sustained drug release. Suitable polymers and mucoadhesive agents can be selected to achieve appropriate gelation properties, viscosity, drug-release characteristics, and nasal compatibility.

1.1 Mechanism of Action of Donepezil and Memantine

Donepezil – Acetylcholinesterase inhibitor: Donepezil inhibits acetylcholinesterase, the enzyme that normally breaks down acetylcholine in the brain. This inhibition increases acetylcholine levels in the synaptic cleft and supports communication between nerve cells (Guo et al., 2020).

Memantine – NMDA receptor antagonist: Memantine blocks NMDA-type glutamate receptors when they are excessively activated. Glutamate is an excitatory neurotransmitter involved in learning and memory, while excessive activity may contribute to neuronal dysfunction and damage (Atri et al., 2013).

II. OBJECTIVES

- To conduct a literature review on Alzheimer's disease and the pharmacological actions of memantine and donepezil.
- To formulate and optimize nanostructured lipid carriers (NLCs) containing memantine and donepezil.
- To characterize prepared NLCs for particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency.
- To develop an intranasal in-situ gel incorporating optimized drug-loaded NLCs using suitable polymers.
- To evaluate the in-situ gel for pH, viscosity, gelation properties, and in-vitro drug release.
- To investigate nasal compatibility, stability, and brain-targeting potential via intranasal delivery.

III. NEED FOR THE STUDY

- Alzheimer's disease is a progressive neurodegenerative disorder associated with memory loss and cognitive impairment.
- Conventional delivery systems face challenges in achieving effective brain drug delivery and sustained therapeutic effects because of the blood–brain barrier.
- The combination of memantine and donepezil is intended to provide complementary symptomatic management.
- NLCs incorporated into an in-situ gel may enhance drug encapsulation, improve formulation stability, reduce rapid clearance, and support controlled nose-to-brain drug delivery (Cunha et al., 2021; Sonawane & Pokharkar, 2024).

IV. REVIEW OF LITERATURE

Recent studies demonstrate potential advantages of intranasal NLC-based hydrogel formulations. Chaudhari et al. (2024) developed thermoreversible in-situ gels for nasal delivery of donepezil and reported low nasal mucosal irritation and favorable gelation temperatures. Guo et al. (2020) conducted a network meta-analysis comparing memantine, donepezil, and combination therapy in Alzheimer's disease.

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Cunha et al. (2021) discussed lipid-based nanosystems integrated into in-situ hydrogels for nose-to-brain drug transport. Atri et al. (2013) evaluated the efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease who were already receiving donepezil.

V. MATERIALS AND METHODS

The supplied document describes a planned formulation and evaluation workflow. Specific quantities, grades, manufacturers, equipment settings, and a complete experimental protocol were not provided; these details should be added from the laboratory records before journal submission.

1. Selection of suitable drug candidates and excipients for NLC preparation, followed by procurement of drugs and excipients.
2. Physicochemical and analytical characterization of the drugs, including melting point, solubility, partition coefficient, FTIR, and HPLC.
3. Development and validation of an HPLC analytical method for the selected drugs, including preparation of calibration curves in water and dissolution media.
4. Screening of surfactants and solid lipids, followed by drug–excipient compatibility studies.
5. Preparation of NLC formulations using an appropriate experimental design and selected combinations of surfactant and solid lipid.
6. Evaluation of NLCs by visual inspection, pH, viscosity, particle size, PDI, and zeta potential; entrapment efficiency is also identified as an objective.
7. In-vitro drug-release studies and selection of an optimized batch, followed by accelerated stability testing.
8. Preparation of a hydrogel using a suitable experimental design and evaluation by viscosity, visual inspection, spreadability, pH, gelation behavior, and drug-release testing.

VI. RESULTS

The supplied draft reports the following observations for the in-situ gel formulations. Individual formulation-wise numerical values were not supplied, so only the reported ranges and qualitative comparisons are presented.

Evaluation parameter	Reported observation	Interpretation in source draft
Visual appearance	F1 and F2: hazy; F3 and F4: clear and transparent	F3 and F4 showed clearer appearance.
pH	5.5–5.7 across formulations	Reported as compatible with nasal mucosa in the draft.
Gelation temperature	21 ± 1.2°C to 28 ± 1.4°C	All formulations showed thermoreversible gelation.
Gel melting temperature	80 ± 1.7°C to 91 ± 1.3°C	F4 showed the highest reported melting temperature.
Overall observation	F4 had the lowest gelation temperature and highest gel melting temperature	The draft interprets F4 as having greater thermal stability and a stronger gel network.

Table 1. Summary of in-situ gel evaluation observations reported in the supplied draft.

VII. DISCUSSION

The reported clarity observations distinguish F3 and F4 from the hazy F1 and F2 formulations. The pH range of 5.5–5.7 is described in the source draft as potentially compatible with the nasal mucosa. The reported gelation and melting temperature ranges indicate thermoreversible behavior across the formulations. F4 was identified as having the lowest gelation temperature and highest gel melting temperature, which the source draft associates with greater thermal

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stability and a stronger gel network. However, the supplied document does not provide formulation-wise raw data, statistical analysis, NLC particle-size results, PDI, zeta potential, entrapment efficiency, or drug-release profiles. These data should be included before making comparative or definitive claims about the optimized formulation.

VIII. CONCLUSION

The proposed research focuses on the formulation, evaluation, and optimization of nanostructured lipid carriers co-loaded with memantine hydrochloride and donepezil hydrochloride and incorporated into an intranasal in-situ gelling system. The approach is intended to use the nose-to-brain route and sustained, controlled release to potentially improve drug delivery in the management of Alzheimer's disease. The planned work, including physicochemical characterization, NLC optimization, in-vitro evaluation, and stability studies, provides a framework for further investigation. Additional experimental details and complete quantitative results are required to establish the performance and suitability of the final formulation.

IX. CONFLICT OF INTEREST

The authors should confirm and insert their conflict-of-interest declaration before submission. No declaration was provided in the supplied source document.

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