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Targeting Neuroinflammation and Tau/APP Pathology via Intranasal Delivery of Azilsartan Medoxomil Nanoemulgel in AlCl3-induced Alzheimer's Dementia Model

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Abstract

Background: Cognitive impairment and dementia have become a global burden, distressing millions of elderlies, accounting for progressive loss of neurons in the brain affecting higher multiple cortical centers, and impacting social life. The renin-angiotensin system and its receptors, widely distributed within the brain, offer potential to treat dementia via diminishing oxidative stress, neuronal inflammation, and increasing blood-brain barrier (BBB) integrity. The present study delves into the formulation and optimization of thermoresponsive azilsartan medoxomil (AZL-M) loaded in situ nanoemulgel for targeted nose-to-brain delivery to the brain due to low BBB permeability and validated through in vivo models.

Methods: A Box-Behnken design was used to optimize formulation parameters such as droplet size, gelation temperature, and drug release. The optimized nanoemulgel was characterized for physicochemical properties and evaluated for ex-vivo nasal mucosal toxicity, in-vitro cytotoxicity, and ROS reduction. In-vivo efficacy of intranasal application of the optimized formulation was assessed in an $AlCl_3$-induced Alzheimer's model.

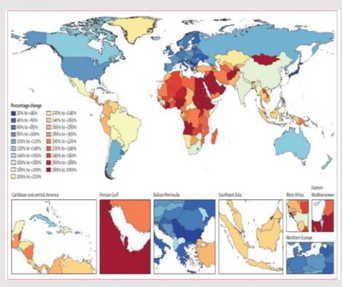
Results: Formulation-F20 showed optimal gelation at 33.4°C, pH-6.21, droplet size of 160nm, 60.4% drug release in 8h, high permeation, and flux, with confirmed safety and cell viability. TEER studies confirmed the integrity of RPMI-2650 monolayers, and while apparent permeability values of AZL-M solution and nanoemulgel were comparable, the nanoemulgel exhibited significantly higher cumulative permeation across the nasal epithelial barrier. In-vivo studies showed that nanoemulgel significantly improved cognitive performance and neuronal survival. At the molecular level, AZL-M treatment led to a marked reduction in brain inflammatory cytokines TNF-α and IL-1β, along with downregulation of Alzheimer's-specific markers including phosphorylated tau, amyloid precursor protein, and NF-κB. Simultaneously, a significant upregulation of brain-derived neurotrophic factors indicated enhanced neurotrophic support and synaptic plasticity.

Conclusion: The intranasally delivered AZL-M-loaded nanoemulgel showed potential as a safe and effective therapy for Alzheimer's dementia by attenuating neuroinflammation and Alzheimer's pathology markers.

Introduction

Definition of the problem

- ✓ Currently more than 55 million people have dementia worldwide.
- ✓ In India, 8.8 million Indians older than 60 years live with dementia.
- ✓ Seventh leading cause of death [1].



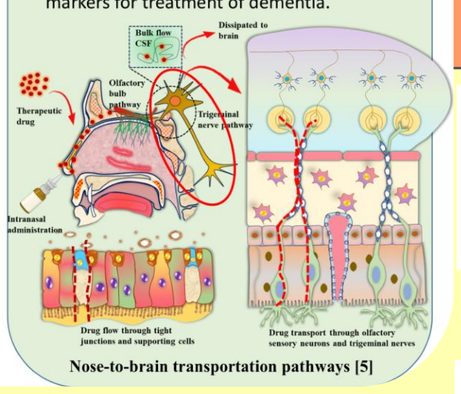
Percentage change between 2019 and 2050 in all-age number of individuals with dementia [2]

Knowledge gap

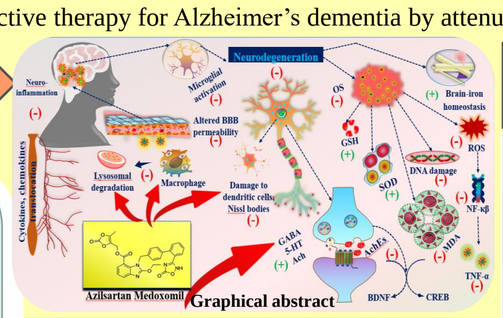
- Addressing memory decline in dementia and other neurodegenerative diseases comes with limited medications and increased toxicity profile.
- Angiotensin receptor blockers offers potent neuroprotective activity, but faces poor bioavailability and blood-brain barrier penetration [3, 4].
- Direct delivery of ARBs with suitable formulation to improve efficacy and evaluate impact on memory decline in animal models.

Issues to be addressed

- ✓ Development of nanoemulsion based *in situ* gel
- ✓ Delivering azilsartan, a non BBB permeable drug, directly to the brain through nose to brain route.
- ✓ Assessment of behavioural and biochemical markers for treatment of dementia.

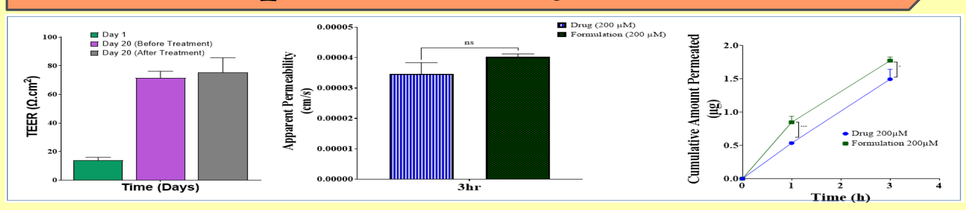


Nose-to-brain transportation pathways [5]



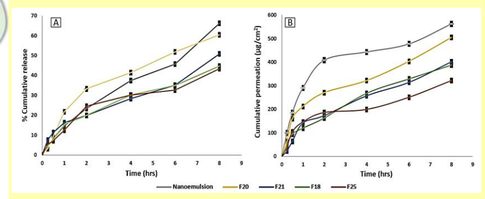
Graphical abstract

In vitro permeability in cell lines



RPMI-2650 cell monolayers formation, TEER measurement for AZL-M permeation across RPMI-2650 cell monolayer

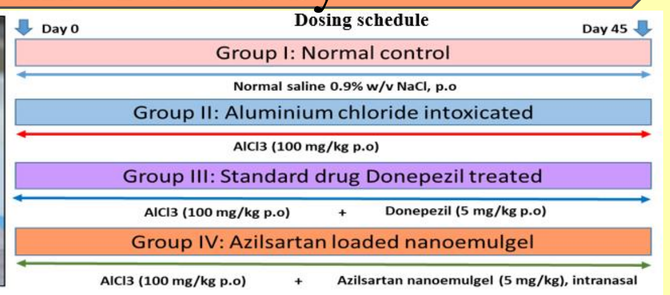
Characterization



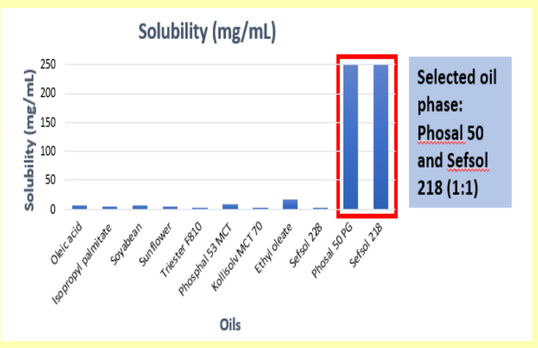
In vitro release and ex-*vivo* permeation of different optimized gels

In vivo study

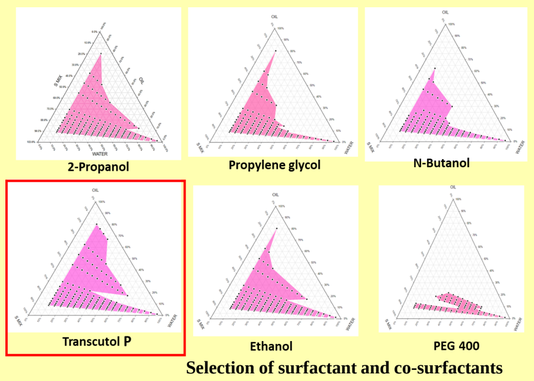
Intranasal delivery



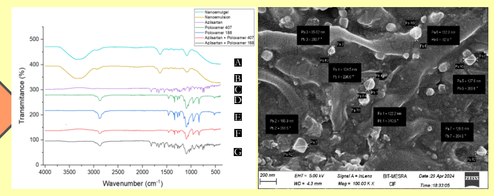
Pre-formulation studies



Solubility of oils

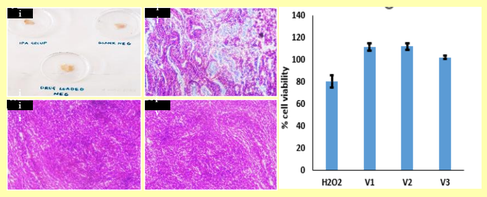


Selection of surfactant and co-surfactants



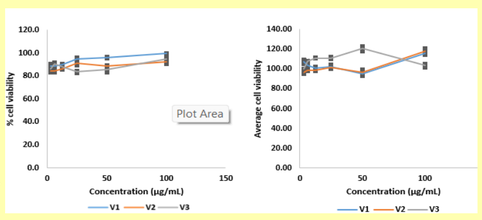
FTIR

FESEM



Ex vivo toxicity study

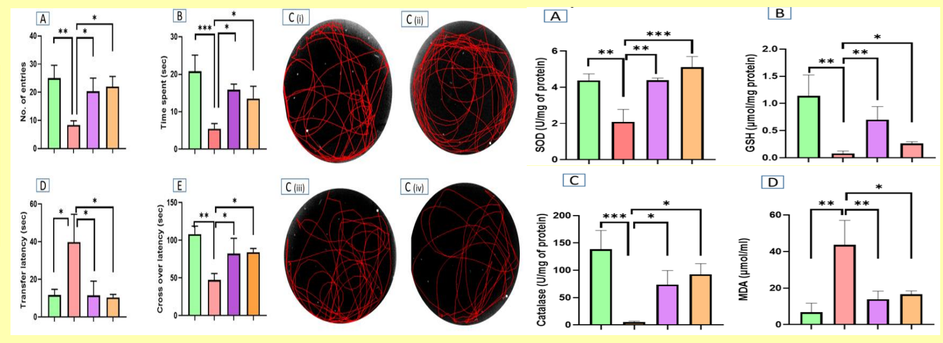
In vitro ROS



In vitro cytotoxicity study

Behavioural studies

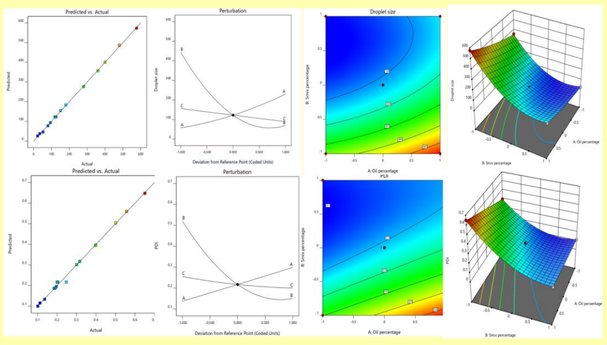
Biochemical studies



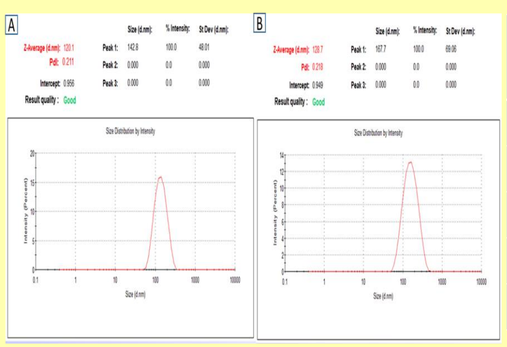
Behavioural studies; Morris water maze (A-C); Passive avoidance (D); Elevated plus maze (E) tests

Biochemical analysis of SOD (A); GSH (B); CAT (C); and MDA (D) levels from brain tissue homogenates

Quality by design approach (QbD)



Optimization of nanoemulsion components using BBD



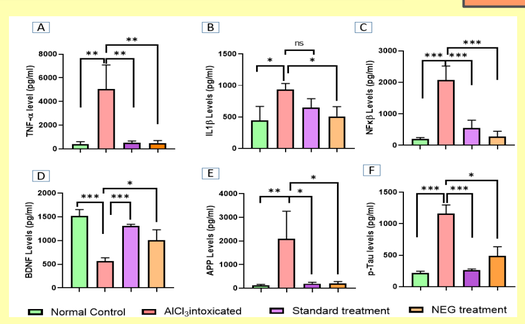
Particle size, PDI, and Zeta potential

Formulation code	pH	Viscosity (cP) at different temperature		Dynamic light scattering analysis			% Cumulative release	Cumulative permeation (µg/cm²)	Steady state flux (µg/h/cm²)	Mucoadhesive force (kg)
		37°C	15°C	Size (nm)	PDI	Zeta				
F18	5.34±1.01	2971.50±389.4	580.861±195.85	172.8±5.64	0.275±0.004	-9.34±1.201	44.641±0.002	388.108±0.052	48.513±0.052	0.338±0.018
F20	6.21±0.35	4578.39±541.2	190.153±6.42	160.1±3.72	0.210±0.001	-11.2±0.85	60.400±0.010	504.666±0.126	63.083±0.126	0.528±0.011
F21	6.13±0.42	4564.80±425.9	123.836±7.06	192.2±4.25	0.246±0.042	-10.6±1.45	50.851±0.006	401.815±0.017	50.227±0.017	0.294±0.022
F25	5.57±0.89	5926.67±740.2	853.853±215.98	200.4±4.28	0.349±0.012	-9.03±2.51	43.354±0.001	321.300±0.005	40.162±0.005	0.748±0.041
Nanoemulsion	6.02±0.05	61.279±6.534	66.485±5.364	127.6±2.72	0.218±0.002	-10.2±3.22	66.131±0.005	562.282±0.006	70.285±0.006	-

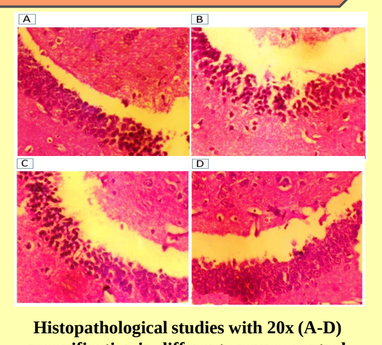
Selection of best suited *in situ* nanoemulgel based on all characterization parameters

Biomarker studies

Histopathological studies



Quantification of pathological markers TNF-α (A); IL-1β (B); NF-κβ (C); BDNF (D); APP (E); p-Tau (F)



Histopathological studies with 20x (A-D) magnification in different groups; control (A), disease (B), test (C), and standard (D)

Conclusion

- ✓ The study demonstrates that thermoresponsive in situ nanoemulgel mediated nose-to-brain delivery of azilsartan significantly attenuates memory decline in experimental animals. Behavioral assessments, biochemical and specific biomarkers parameters confirm the neuroprotective efficacy of this delivery method, highlighting its potential as a promising therapeutic approach for neurodegenerative diseases and dementia.

References

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5. Ghosh A, Majie A, Karmakar V, Chatterjee K, Chakraborty S, Pandey M, Jain N, Roy Sarkar S, Nair AB, Gorain B. In-depth Mechanism, Challenges, and Opportunities of Delivering Therapeutics in Brain Using Intranasal Route. AAPS PharmSciTech. 2024 May 6;25(5):96.

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CSIR-INDIA
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