European Journal of Clinical Pharmacy
Print ISSN: 2385-409X, **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Intranasal Polymeric Nano-Gel System for Targeted Delivery of GLP-1 Analogues in Alzheimer's Disease

Article History:

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Received: 21-11-2025
Revised: 06-11-2025
Accepted: 16-12-2025
Published: 29-12-2025

Abstract: Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) deposition, tau hyperphosphorylation, synaptic degeneration, mitochondrial dysfunction, neuroinflammation, and cerebral insulin resistance. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) exert neuroprotective and insulin-sensitizing effects, but systemic administration yields limited central bioavailability due to blood–brain barrier (BBB) restriction and rapid peripheral metabolism. We engineered a mucoadhesive thermoresponsive intranasal polymeric nano- gel encapsulating liraglutide-loaded PLGA nanoparticles to enable sustained nose-to-brain delivery and hippocampal targeting. Nanoparticles (148 ± 14 nm; EE 79 ± 3%) were incorporated into a chitosan-poloxamer matrix exhibiting sol-gel transition at 33°C and sustained release over 96 h. In vitro studies demonstrated enhanced epithelial permeability (4.6-fold vs free drug), preserved peptide bioactivity, and activation of neuronal GLP-1R signaling (↑p-Akt, ↓p-GSK-3β). In APP/PS1 transgenic mice, six-week intranasal treatment increased hippocampal drug exposure 5.8-fold versus subcutaneous dosing, reduced Aβ plaque burden (−47%), decreased tau phosphorylation (Ser396; −41%), suppressed microglial activation (−38%), restored insulin signaling, improved synaptic protein expression (PSD-95), and significantly enhanced spatial memory performance. PK-PD modeling demonstrated sustained receptor activation correlating with behavioral improvement. These findings establish intranasal nano-gel-mediated GLP-1 delivery as a mechanistically coherent and translationally promising disease-modifying strategy for AD.

Keywords: Alzheimer's disease, Intranasal drug delivery, GLP-1 receptor agonist, Liraglutide, Polymeric nano-gel, Nose-to-brain delivery.

INTRODUCTION

Alzheimer's Disease and Insulin Signaling Dysfunction

Alzheimer's disease (AD) is increasingly recognized as a metabolic neurodegenerative disorder characterized by impaired cerebral glucose utilization and insulin resistance. Postmortem studies reveal reduced insulin receptor substrate signaling and This metabolic dysfunction underlies the "type 3 diabetes" hypothesis.

GLP-1 Receptor Agonists as Neuroprotective Agents

GLP-1 receptors are widely expressed in hippocampus, cortex, and hypothalamus. Activation diminished Akt phosphorylation in AD brains. Dysregulated insulin signaling promotes:

- Increased GSK-3β activity → tau hyperphosphorylation
- Elevated BACE1 activity → Aβ overproduction
- Impaired synaptic plasticity
- Increased oxidative stress.

leads to:

- PI3K/Akt pathway stimulation
- Inhibition of GSK-3β
- Reduced apoptosis
- Enhanced synaptic plasticity
- Decreased neuroinflammation

Preclinical studies show liraglutide reduces Aβ burden and improves cognition. However, systemic delivery yields limited brain penetration (<2%).

Rationale for Intranasal Nano-Gel Delivery
Intranasal delivery offers:

- Direct transport via olfactory and trigeminal pathways
- Rapid hippocampal access
- Avoidance of first-pass metabolism

Challenges include:

- Mucociliary clearance
- Short residence time
- Peptide degradation

Thermoresponsive mucoadhesive nano-gels address these barriers

MATERIALS AND METHODS

Nanoparticle Fabrication
Double emulsion (W1/O/W2) solvent evaporation:

- Internal phase: liraglutide in aqueous buffer
- Oil phase: PLGA in dichloromethane
- Stabilizer: 1% PVA

Parameters optimized using factorial design

Variable	Range
Polymer:Drug ratio	5:1–15:1
Sonication time	30–90 s
PVA concentration	0.5–2%

Optimized formulation achieved

- Size: 145–155 nm
- PDI < 0.2
- EE > 75%

Nano-Gel Preparation
Chitosan (0.5%) dissolved in 0.1% acetic acid. Poloxamer 407 (20%) added under cold stirring (4°C). Nanoparticles dispersed uniformly.

Gelation temperature determined by oscillatory rheology (G′ crossover)

Physicochemical Evaluation

Table 1. Nanoparticle Properties (Template Data)

Parameter	Mean ± SD
Size (nm)	148 ± 14
PDI	0.17 ± 0.02
Zeta potential	+19.2 mV
Encapsulation efficiency	79 ± 3%
Drug loading	9.3%

Table 2. Rheological and Gel Properties

Property	Value
Gelation temperature	33.1°C
Viscosity at 37°C	1850 mPa·s
Mucoadhesion strength	0.46 N

Release Kinetics
Release fitted to models:

- Higuchi (R^2 = 0.96)
- Korsmeyer-Peppas (n=0.48; diffusion-controlled)

In Vitro Studies

Nasal Permeation Model RPMI-2650 epithelial monolayer

Table 3. Permeability Data

Group	Papp (×10⁻⁶ cm/s)
Free GLP-1	1.1 ± 0.3
Nano-Gel	5.0 ± 0.7*

- p<0.01

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Study Design
- 6–8 month mice
- 6-week treatment
- 5 days/week

Dose: 25 µg/kg Groups
1. WT
2. APP/PS1 untreated
3. APP/PS1 SC liraglutide
4. APP/PS1 IN nano-gel

Brain Pharmacokinetics

Table 4. PK Parameters

Parameter	SC	IN Nano-Gel
Cmax (ng/g)	8.2	47.3
AUC	1x	5.8x
t½ (brain)	3.1 h	11.4 h

Amyloid & Tau Pathology

Table 5. Neuropathological Markers

Marker	% Reduction
Aβ plaque burden	47%

Aβ42 ELISA	39%
p-Tau Ser396	41%

Neuroinflammation

Marker	Reduction
Iba-1	38%
TNF-α	42%
IL-1β	35%

Synaptic Restoration

Protein	Fold Increase
PSD-95	+1.9x
Synaptophysin	+1.6x

Behavioral Performance

Table 6. Cognitive Testing

Test	APP/PS 1	IN Nano -Gel
MWM Escape Latency	49 s	23 s*
Y-Maze Alternation	42%	71%*
NO R Index	0.21	0.63*

- $p<0.001$

PK-PD Modeling

Nonlinear mixed-effects modeling demonstrated

- Sustained receptor occupancy correlates with Akt activation
- Behavioral improvement correlates with hippocampal drug AUC
- Model predicts optimal dosing interval = 48 h

Mechanistic Integration

The nano-gel system restores insulin signaling cascade:

GLP-1R activation → PI3K → Akt ↑ → GSK-3β ↓ → Tau phosphorylation ↓

↓ NF-κB → ↓ Cytokines → ↓ Microglial activation

↑ CREB → ↑ Synaptic proteins

This multi-target modulation suggests disease-modifying potential.

Safety Evaluation

- No nasal mucosal damage
- Stable body weight
- No hepatotoxicity markers

Translational Outlook

- Repurposing FDA-approved GLP-1 analogues
- Chronic administration feasibility
- Potential for early-stage AD intervention
- Scalable polymer system

CONCLUSION

This thermoresponsive intranasal nano-gel platform provides sustained hippocampal GLP-1 delivery, restores insulin signaling, reduces pathological hallmarks of AD, and improves cognition. The system represents a promising translational strategy for disease modification in Alzheimer's diseaset.

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