Brain Bound! Nose-to-Brain Delivery with In-situ Intranasal Gels

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Gupta Lab
Innovations in Drug Delivery and Discovery

St. John's University
College of Pharmacy and Health Sciences

Research Focus

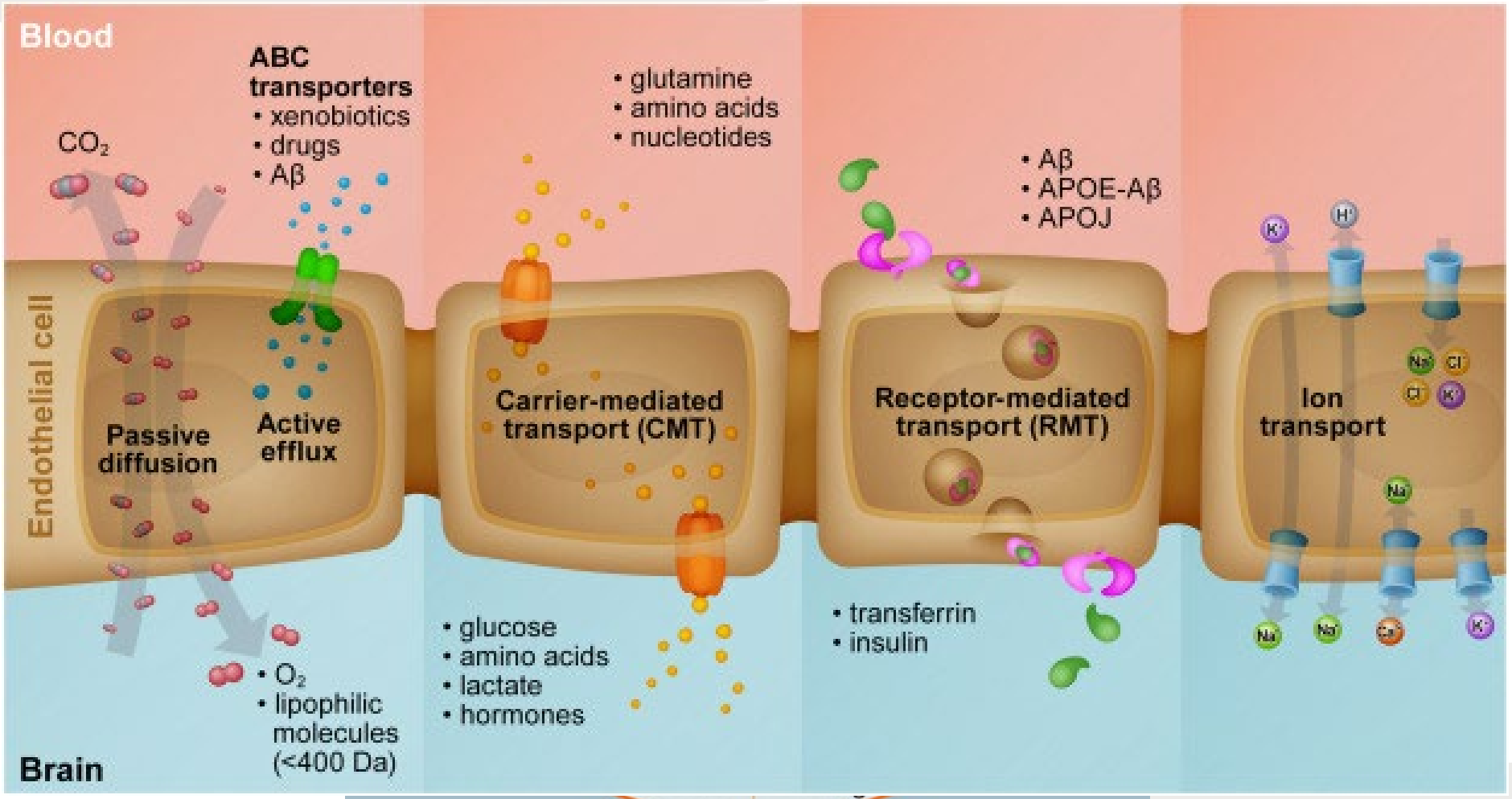
Gupta Lab
Innovations in Drug Delivery and Discovery

Drug Repurposing	• High throughput screening • FDA-approved therapies
Local Deposition & Enhanced Bioavailability	• Local delivery of therapies • Solubility & bioavailability enhancement • Inhibition of efflux transport
Scalable Nanomedicine	• Hot Melt Extrusion • High Pressure Homogenizer • Spray Drying

Disorders of the Brain

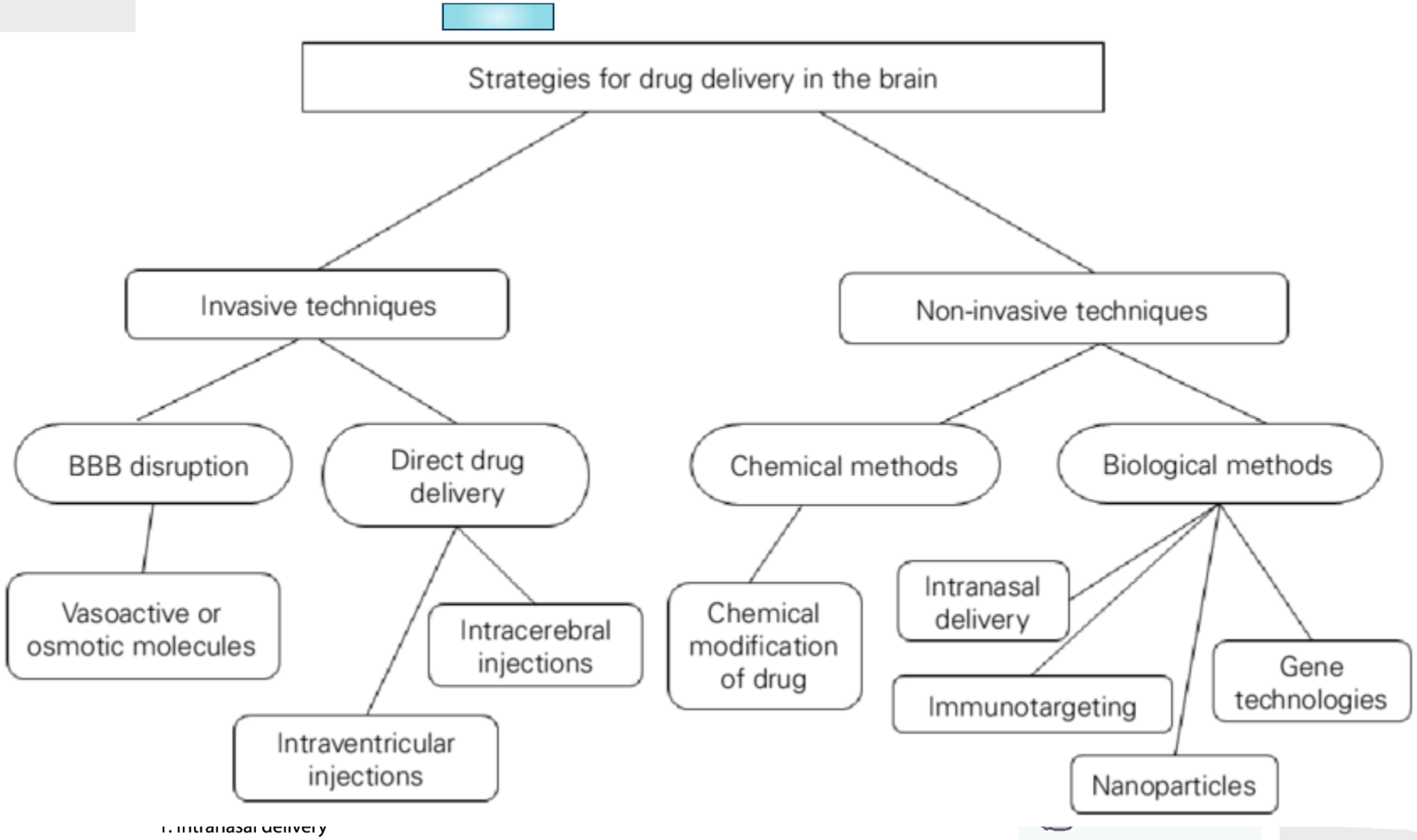
- A wide range of diseases affecting the brain and nervous system
  - It can impact brain function, leading to functional loss and disabilities
- Over 1 in 3 people around the world are affected by a neurological condition
  - >2 billion patients, >11 million deaths
  - Over 4.9 billion cases projected by 2050
  - Not including brain cancers, which are more deadly than most other cancers
- Cause significant disability
  - >18% increase in DALYs since 1990
  - Leading cause of overall global disease burden

Challenges in Therapeutic Delivery to the Brain



Zhao *et al.*, Drug Delivery, 2023

Enabling Drug Delivery to the Brain

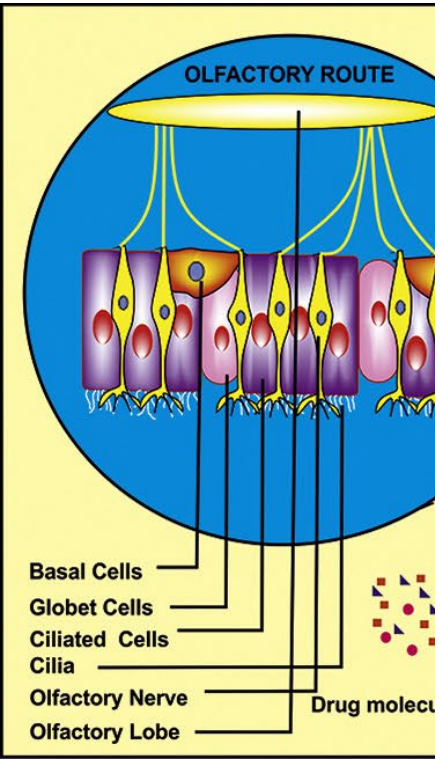


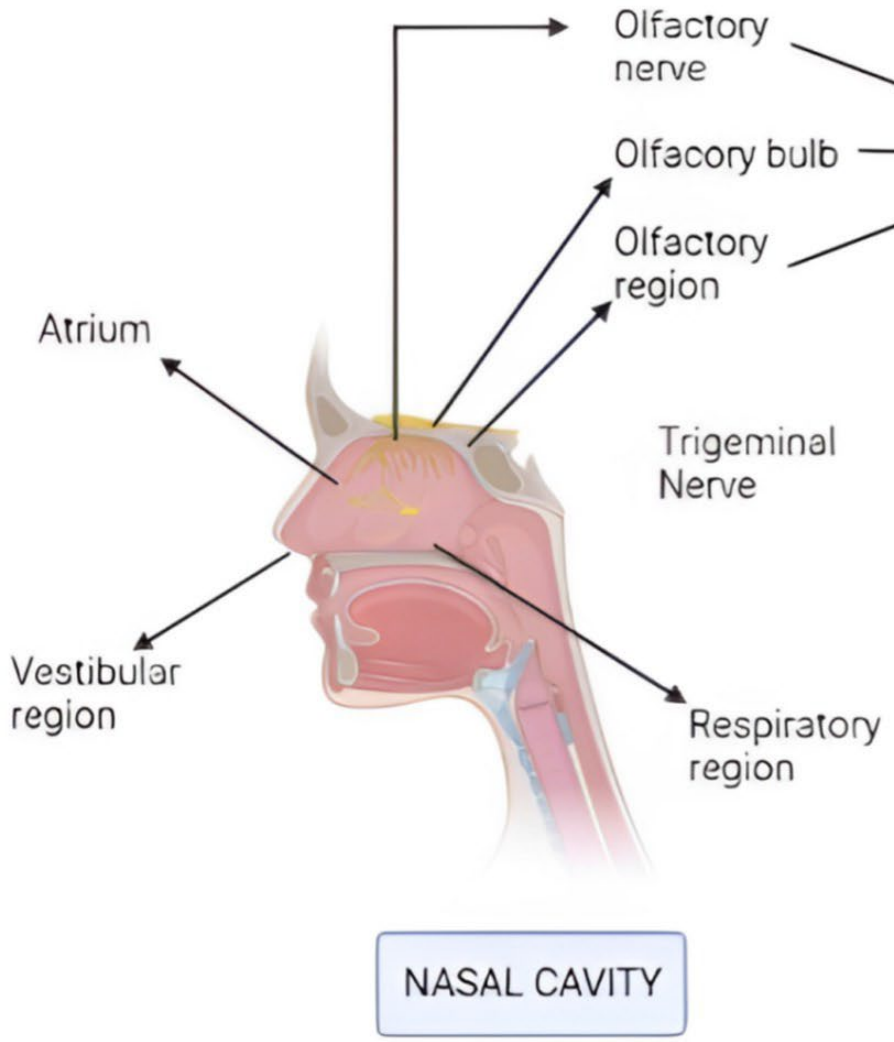
Haumann *et al., CNS* Drugs, 2020

Intranasal Route of Drug Delivery

- **Non-invasive:** A non-invasive method of delivering drugs to the body through nose
- **Rapid Absorption**: Bypasses the gastrointestinal tract and hepatic first-pass metabolism
- **Direct Brain Access**: Facilitates drug delivery to the central nervous system through the olfactory and trigeminal pathways
- **Versatile Formulations**: Suitable for a wide range of drugs, including peptides, proteins, and small molecules
- **Potential for Self-Administration**: Patients can often self-administer, enhancing convenience and accessibility
- **Low Dosage Requirements**: Typically requires smaller doses compared to oral or intravenous routes

Nasal Route to Access Brain!





1 - DIRECT PATHWAY

Olfactory nerve pathway

↓

Direct drug delivery to the brain

↑

Trigeminal nerve pathway

2 - Indirect pathway

Respiratory epithelim

↓

Systemic circulation

↓

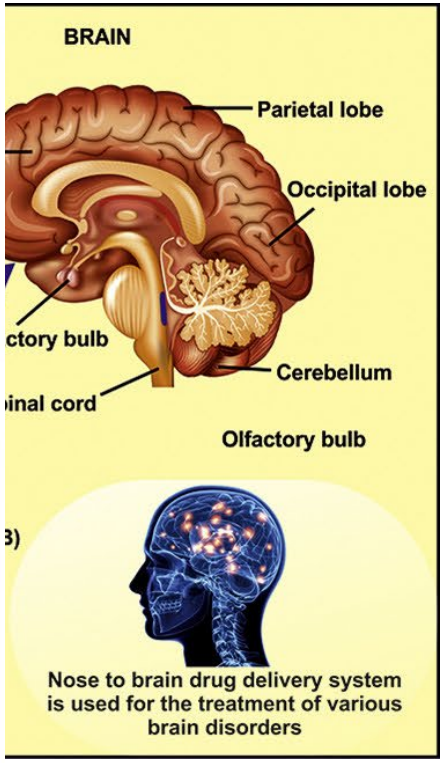
Counter current exchange

↓

Carotid arterial blood flow

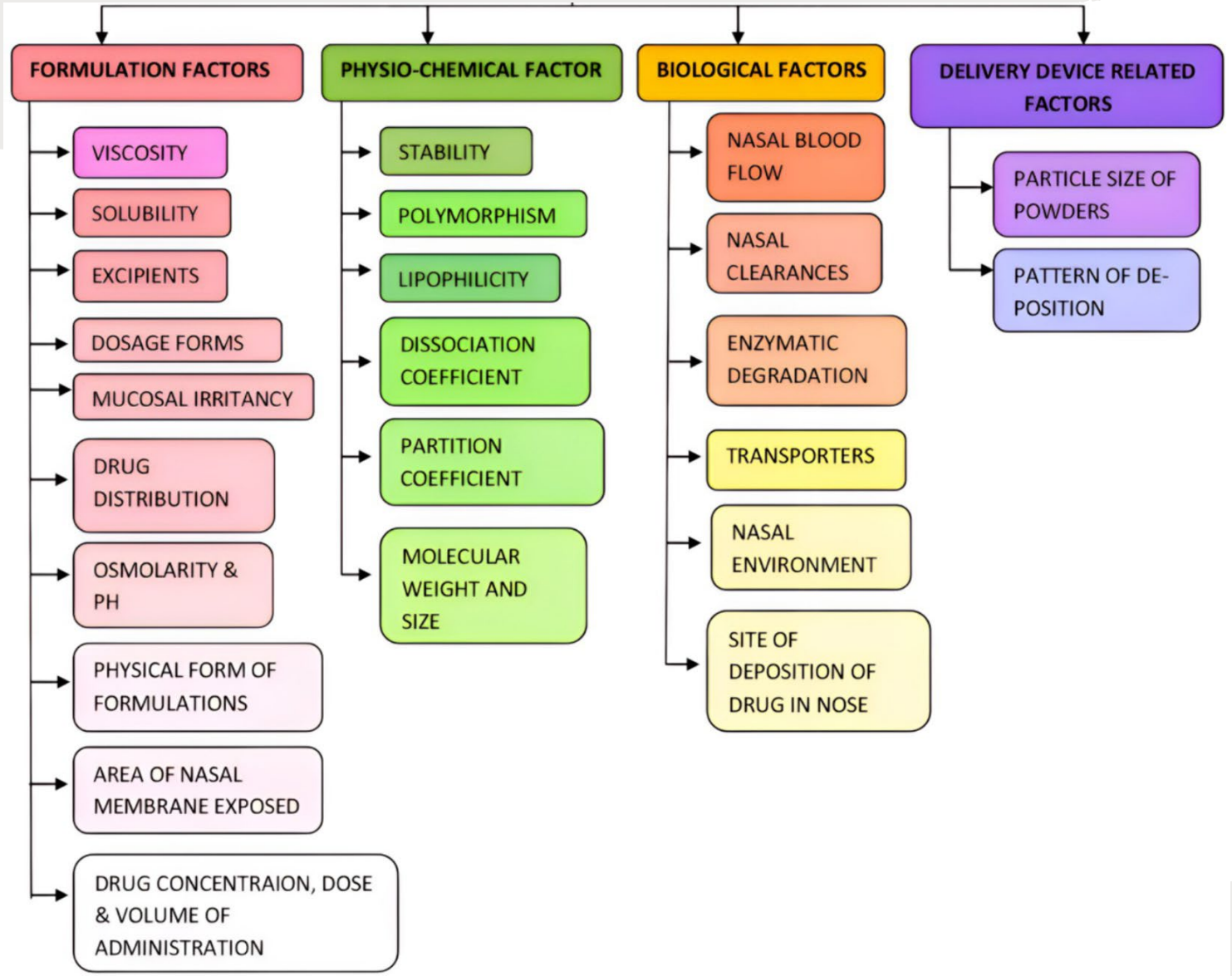
↓

Indirect drug delivery to the brain



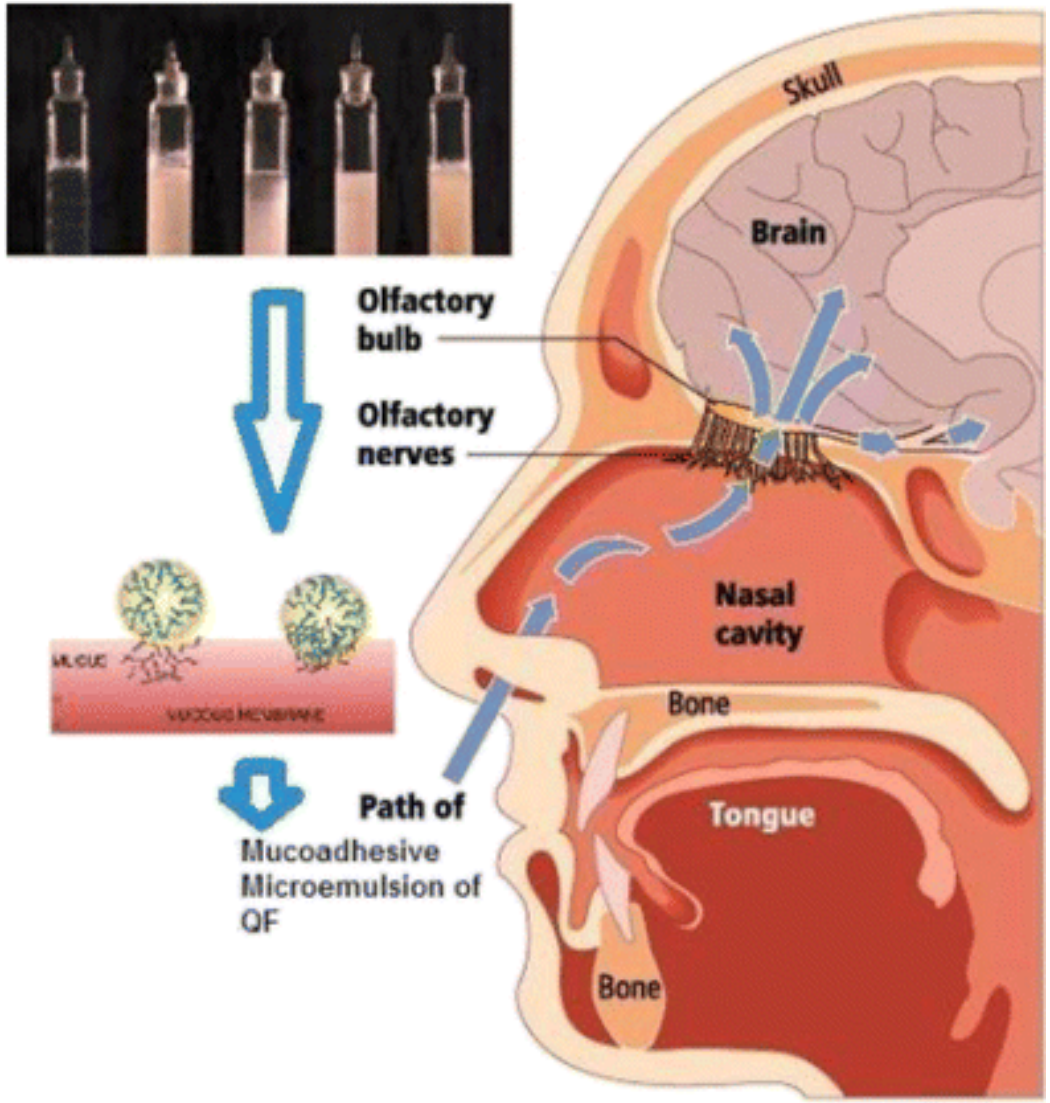
Aderibigbe B, Pharmaceutics, 2018; Agrawal M *et al.*, J Control Rel, 2018; Kisku *et al.*, Frontiers in Medicine, 2024

Challenges of Nasal Drug Delivery



Kisku *et al.*, *Frontiers in Medicine*, 2024

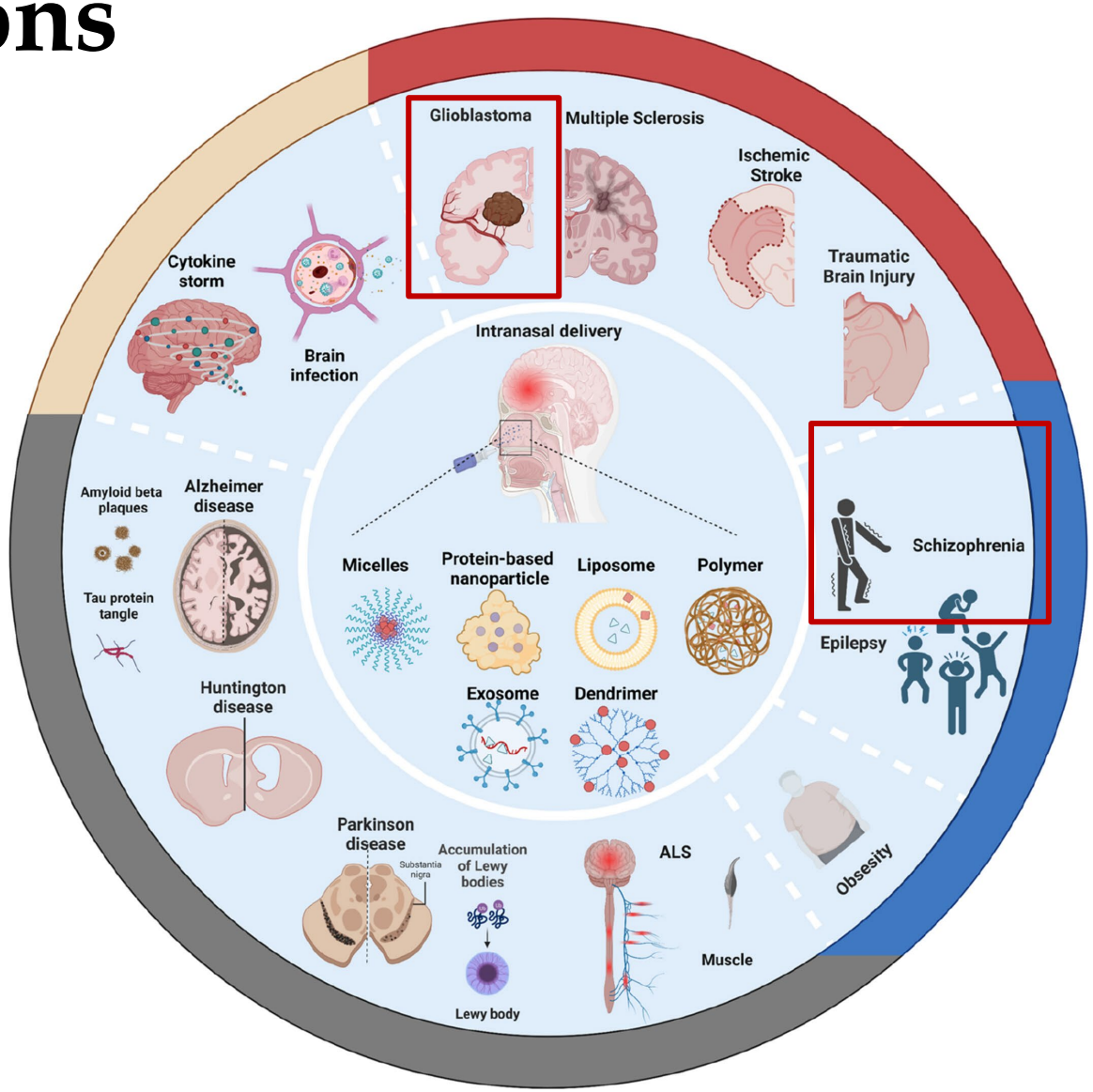
In-situ Gels for Nose-to-Brain Delivery



- Based on bioadhesive polymers that form gels upon contact with nasal mucosa
- Increase retention of drug in nasal cavity
- Capable of encapsulating a variety of delivery systems and hence aid in bypassing blood-brain barrier
- Biodegradable

Patel N *et al.*, J Pharm Innovation, 2015

Intranasal Delivery to the Brain – Disease Applications



Xu K *et al.*, WIREs, 2024

Case Study – I

Nanoformulations Mediated Enhanced Brain Delivery of Quetiapine for Schizophrenia Treatment

Gadhave D et al., Int J Pharmaceutics, 2023
Gadhave D et al., Int J Biol Macromol, 2024

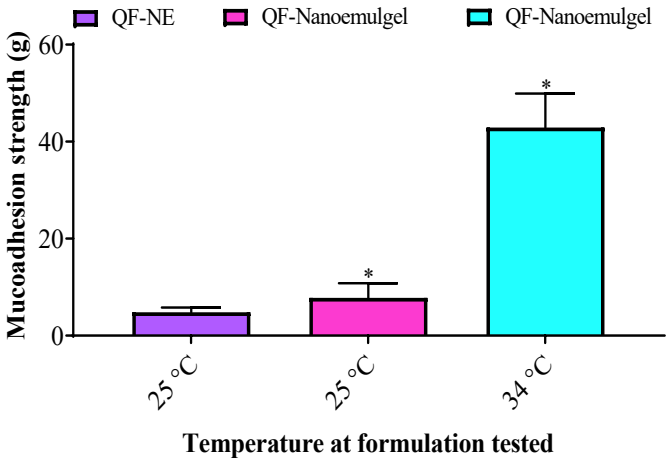
Schizophrenia & Quetiapine

- A mental health condition affecting how people think, feel and behave
- Caused by an imbalance in chemical signals, genetics, environment, etc.
- Approximately 1 in 300 people (24 million patients worldwide)
- Currently treated with antipsychotic medications
- Quetiapine (QF):
  - Limited oral bioavailability (<9%)
  - >10 million annual prescriptions in the US (>2 million unique patients) in 2023
  - Highly hydrophobic and significant liver metabolism
  - Serious off-target hematological effects

QF-encapsulated *in-situ* Gels

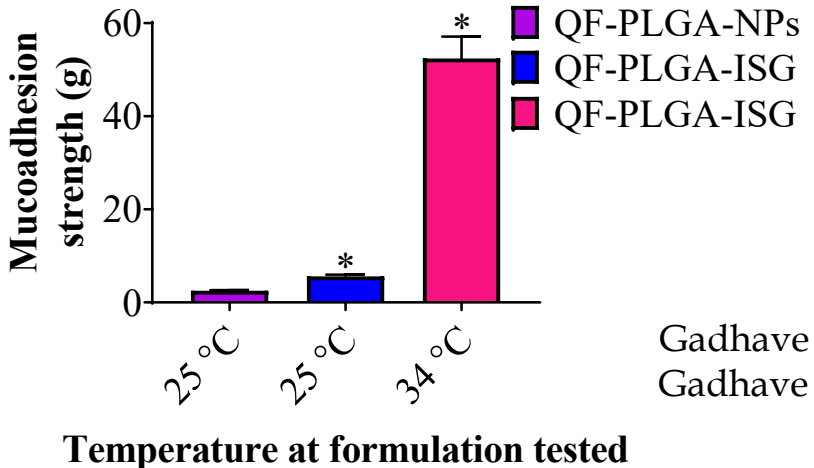
- **Nanoemulgel**
  - Nanoemulsion formulation
  - Chitosan/Poloxamer-407 mediated in-situ gel formulation

Formulations	Physicochemical characterization			
	Globule size (nm)	Polydispersity Index	Zeta potential (mV)	Transmittance (%)
QF-NE	15.0 ± 0.3	0.05 ± 0.001	−18.3 ± 0.2	99.6 ± 0.4
QF-Nanoemulgel	20.4 ± 0.7	0.121 ± 0.01	+21.5 ± 0.9	98.5 ± 1.2



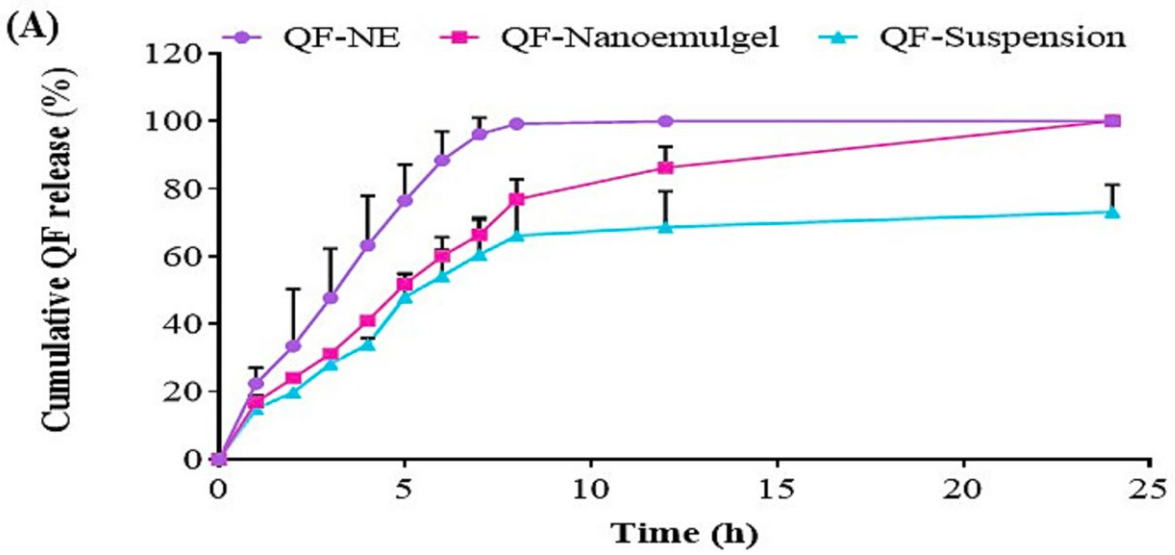
- **Mucoadhesive PLGA NPs**
  - Resomer 50:50 PLGA
  - Chitosan/Poloxamer-407 mediated in-situ gel formulation

Formulations	Physicochemical Characterization		
	Particle Size (nm)	PDI	ζ-Potential (mV)
QF-PLGA-NPs	154.3 ± 1.2	0.122 ± 0.01	-17.8 ± 0.6
QF-PLGA-ISG	162.2 ± 1.4	0.124 ± 0.02	+20.5 ± 0.7



Gadhave D *et al.*, Int J Pharmaceutics, 2023
Gadhave D *et al.*, Int J Biol Macromol, 2024

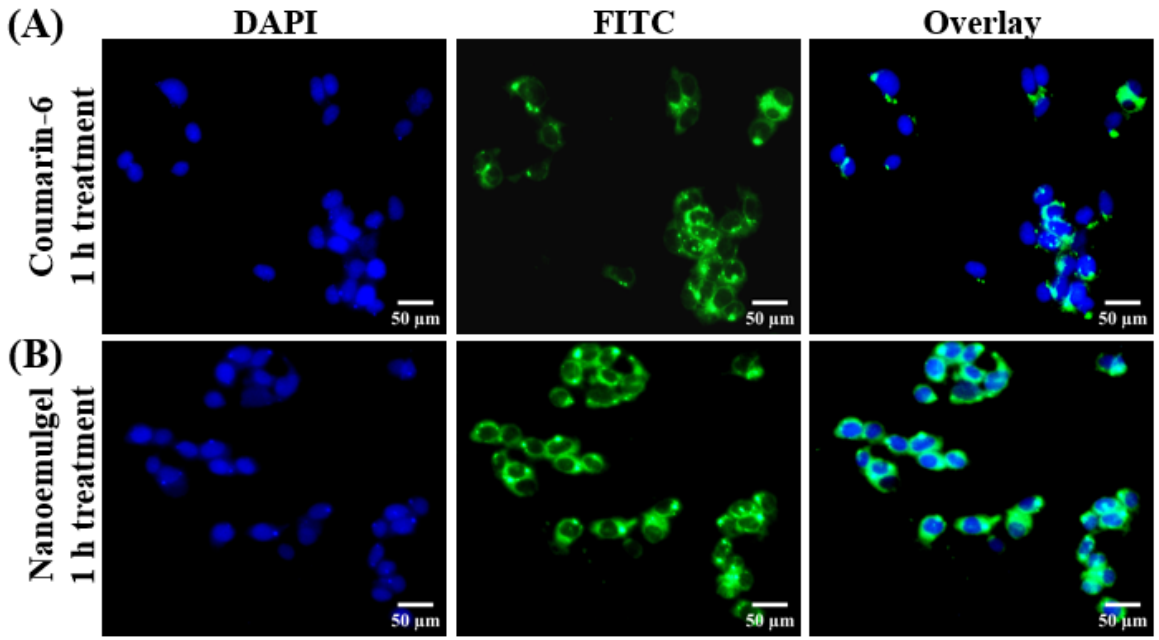
QF-loaded Nanoemulgel Characterization

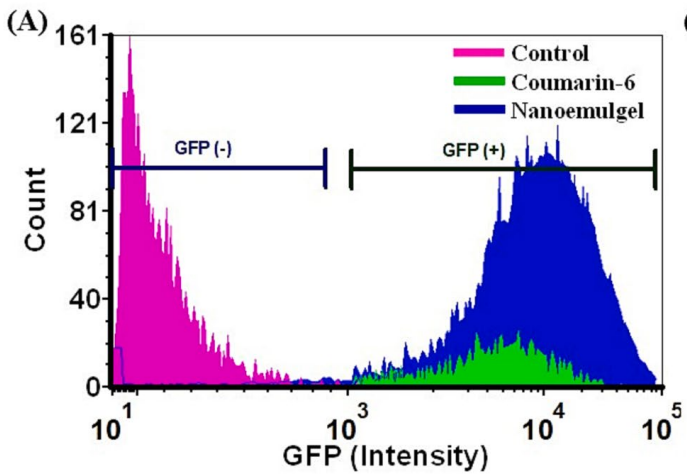


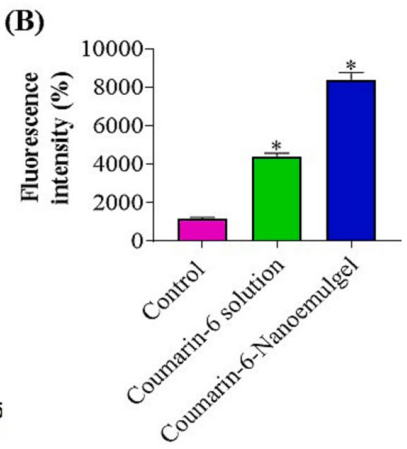
(B)

Release kinetic models	Formulations		
	QF-NE (R^2)	QF-Nanoemulgel (R^2)	QF-Suspension (R^2)
Zero-order	0.993	0.989	0.983
First-order	0.937	0.983	0.972
Higuchi	0.946	0.947	0.926
Hixon-Crowel cube root	0.977	0.98	0.987
Korsmeyer-Peppas	0.938	0.916	0.903
n = Release exponent	(n = 0.755)	(n = 0.705)	(n = 0.725)

QF-NE: Quetiapine hemifumarate nanoemulsion, *QF-Nanoemulgel:* Quetiapine hemifumarate chitosan poloxamer nanoemulgel, R^2: Regression coefficient

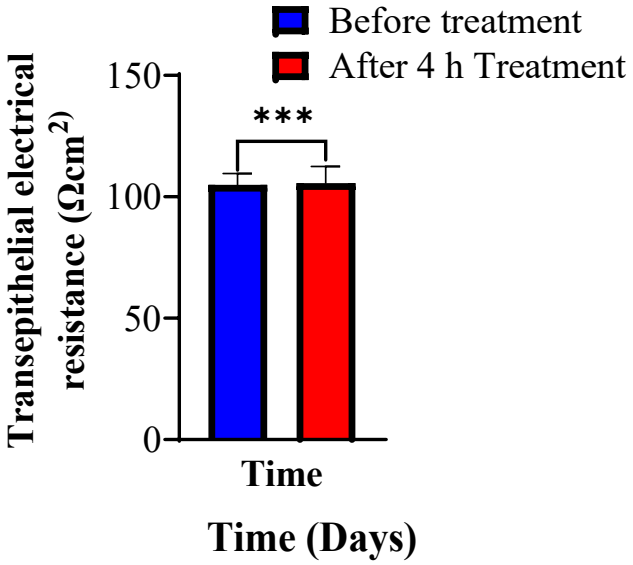


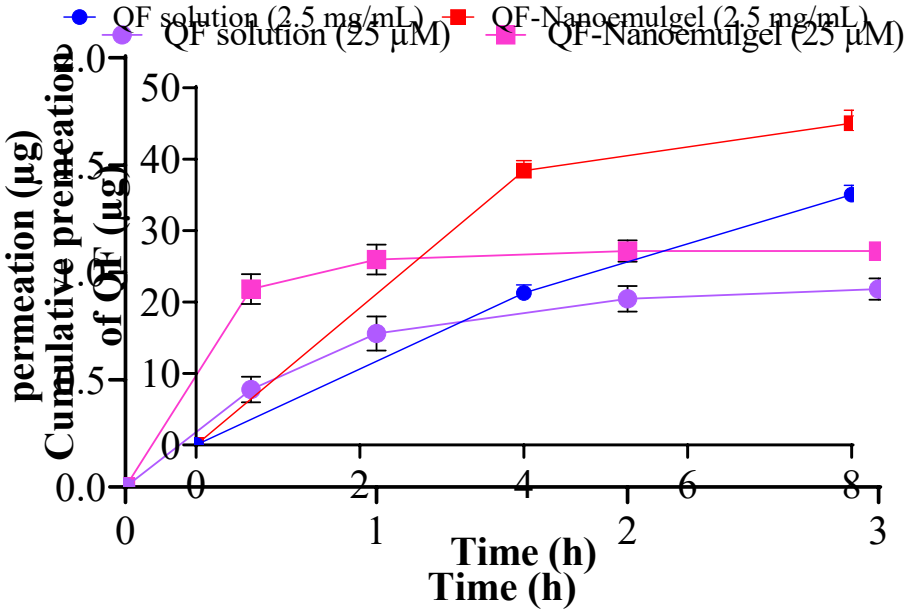


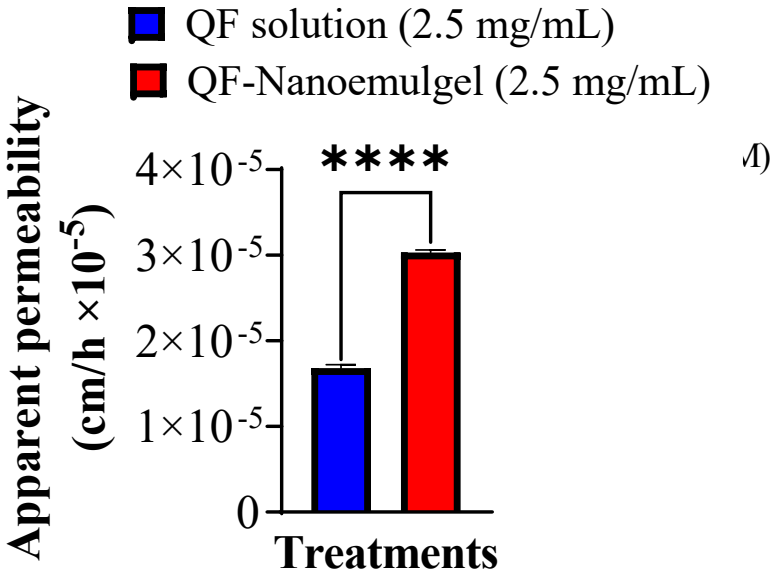


Enhanced Permeation across Nasal Epithelium (Nanoemulgel)

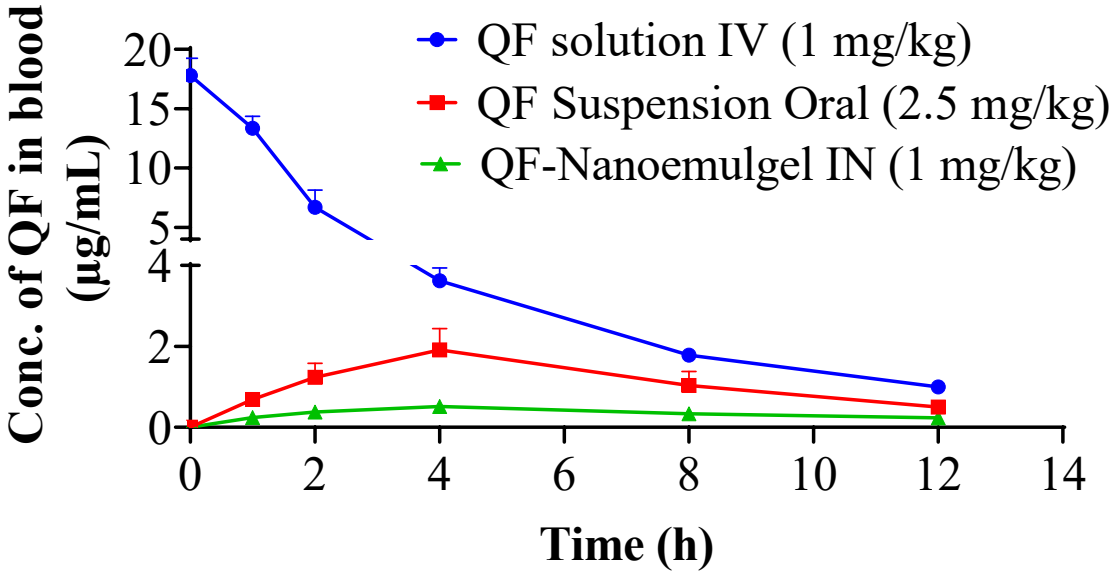
EpiNasal® 650 Nasal Epithelial Tissue Model

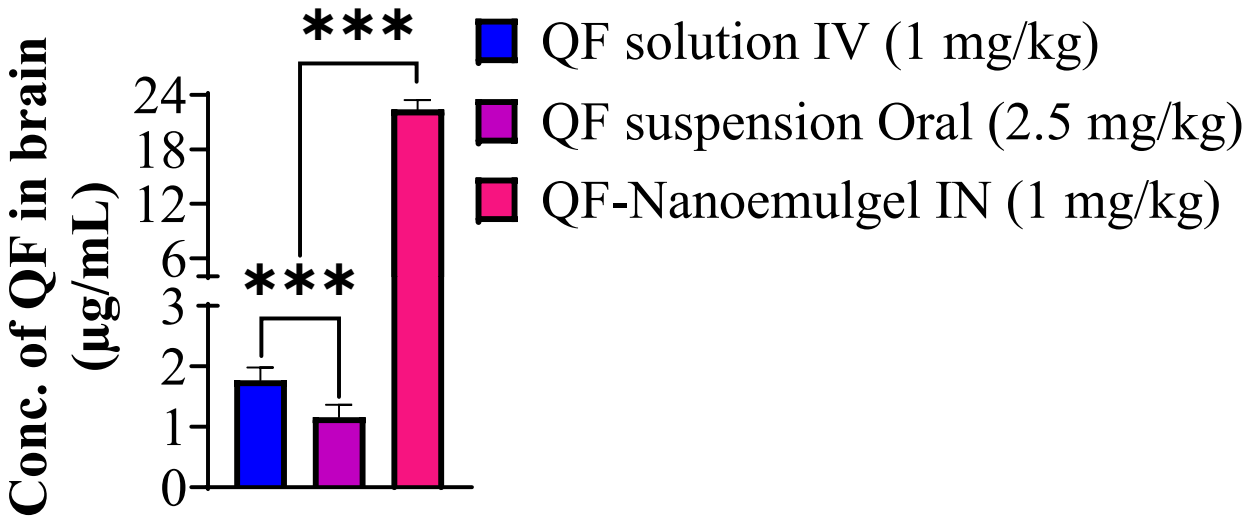






Single Dose Pharmacokinetics of QF-loaded Nanoemulgel





Case Study – II

Nintedanib-encapsulated Nanoemulgel for Glioblastoma Treatment

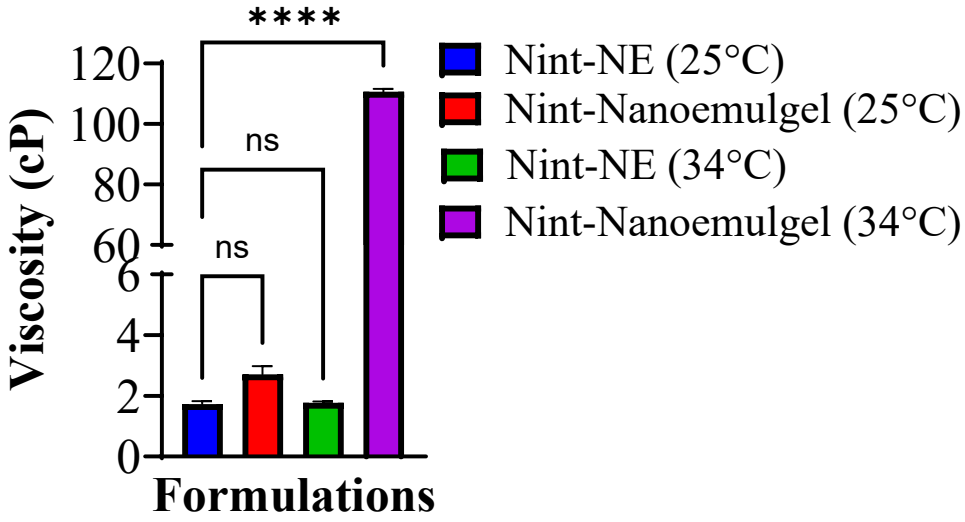
Gadhave D et al., Int J Pharmaceutics, 2025

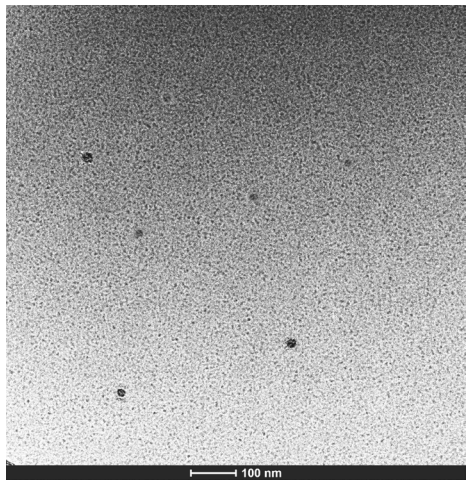
Glioblastoma & Nintedanib

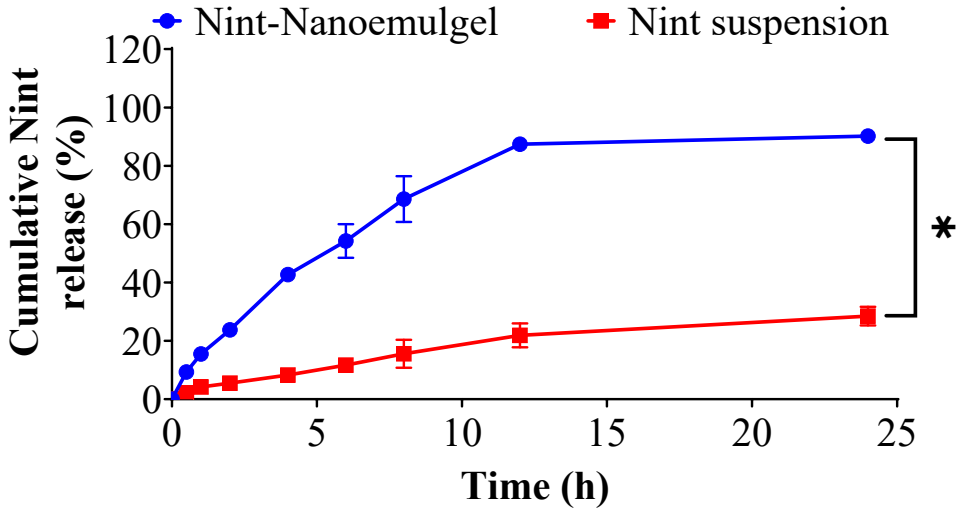
- The most common malignant brain tumor (about 48% cases)
- 2-year post-diagnosis survival = 17% (5% after 5 years)
- Presents unique treatment challenges due to localization in the brain, inherent resistance to therapy, tumor variability, and neurotoxicity associated with anti-cancer treatments
- Nintedanib
  - Multiple tyrosine-kinase inhibitor
  - Efficacy in preclinical models of glioblastoma
  - <5% oral bioavailability (efflux transport)
  - Does not cross blood brain barrier

In-situ Nanoemulgel of Nintedanib

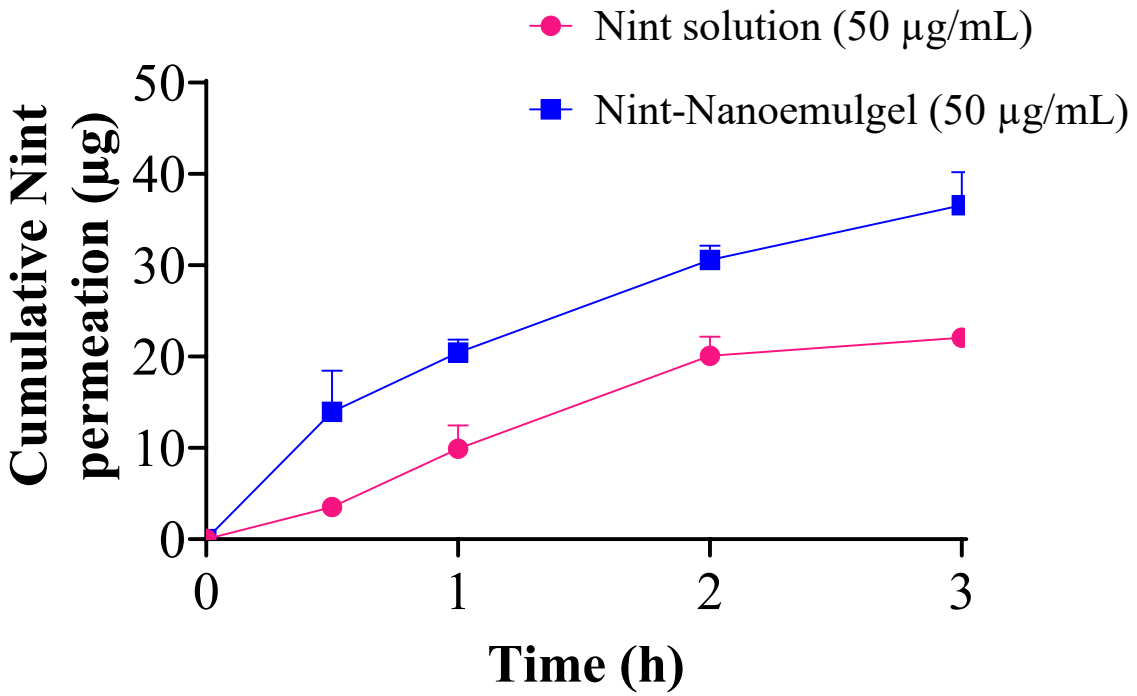
Formulation	Physicochemical Characterization					
	Globule size (nm)	Polydispersity Index	Encapsulation efficiency (%)	Zeta potential (mV)	Transmittance (%)	pH
Nint-NE	23.6 ± 1.8	0.19 ± 0.02	96.3 ± 2.7	-5.7 ± 1.1	98.9 ± 0.1	6.3 ± 0.4
Nint-Nanoemulgel	27.4 ± 0.8	0.17 ± 0.01	93.5 ± 3.5	-4.7 ± 0.6	98.2 ± 0.2	6.0 ± 0.2

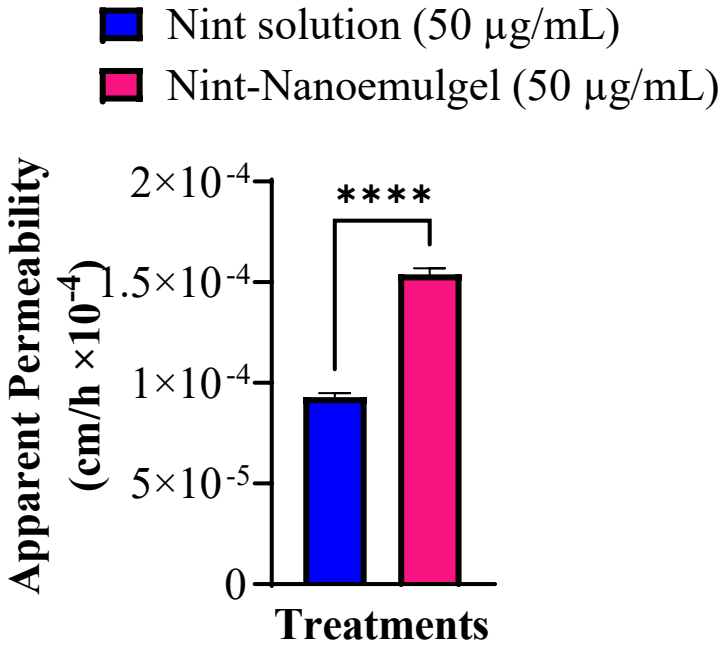






Enhanced Permeation & Reduced Efflux across Nasal Epithelium

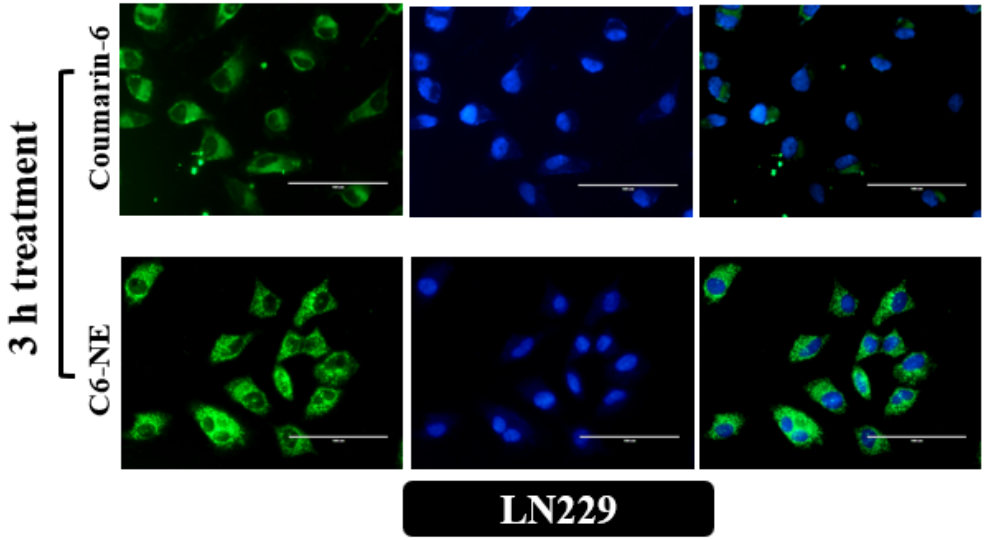


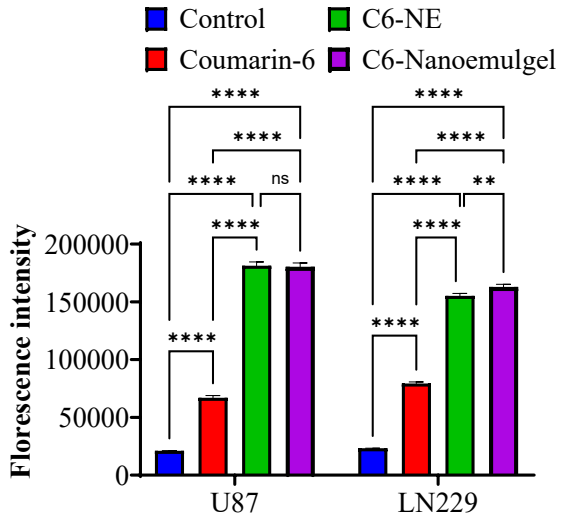


Formulation	P_{app} (cm/h × 10^{-x}) (A-B)	P_{app} (cm/h × 10^{-x}) (B-A)	Efflux ratio
Nint solution (50 ug/mL)	9.3×10^{-5}	1.9×10^{-5}	0.21
Nint-Nanoemulgel (50 ug/mL)	1.5×10^{-4}	1.4×10^{-5}	0.09

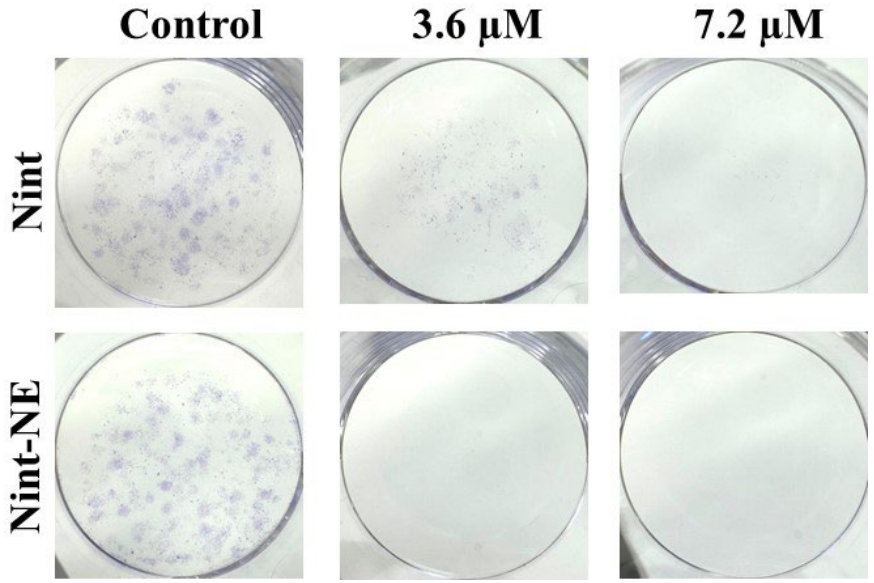
Nint solution: *Nintedanib solution*; Nint-Nanoemulgel: *Nintedanib nanoemulsion-loaded in-situ gel*; P_{app}: *Apparent permeability;* A-B: *Apical to Basolateral;* B-A: *Basolateral to Apical.*

Improved Cellular Uptake & Anticancer Properties of Nintedanib-loaded Nanoemulgels

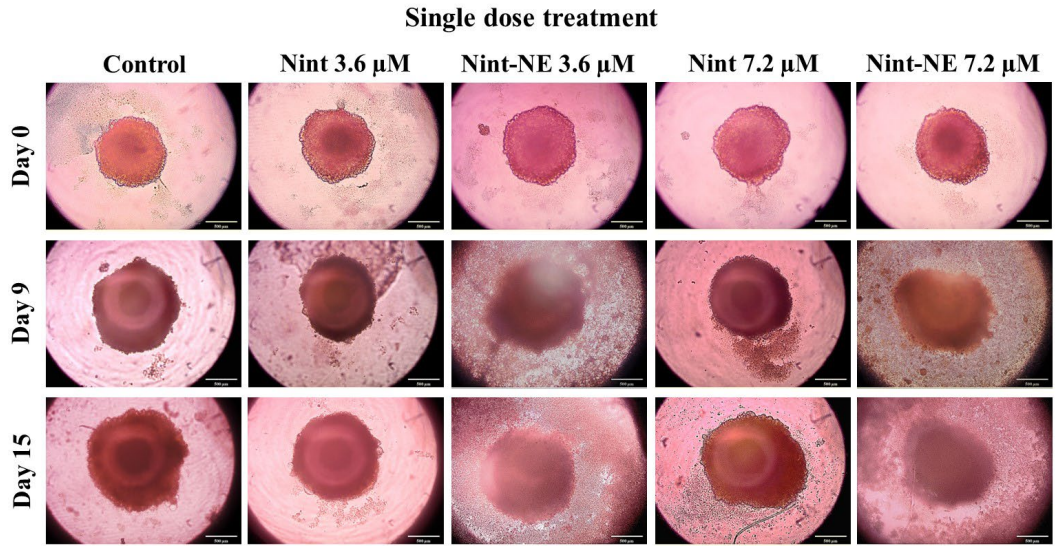


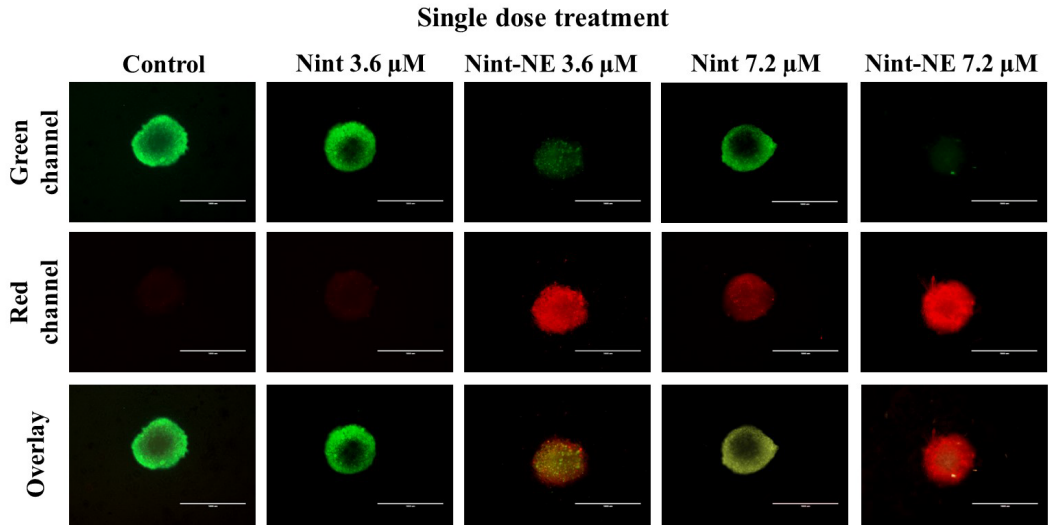


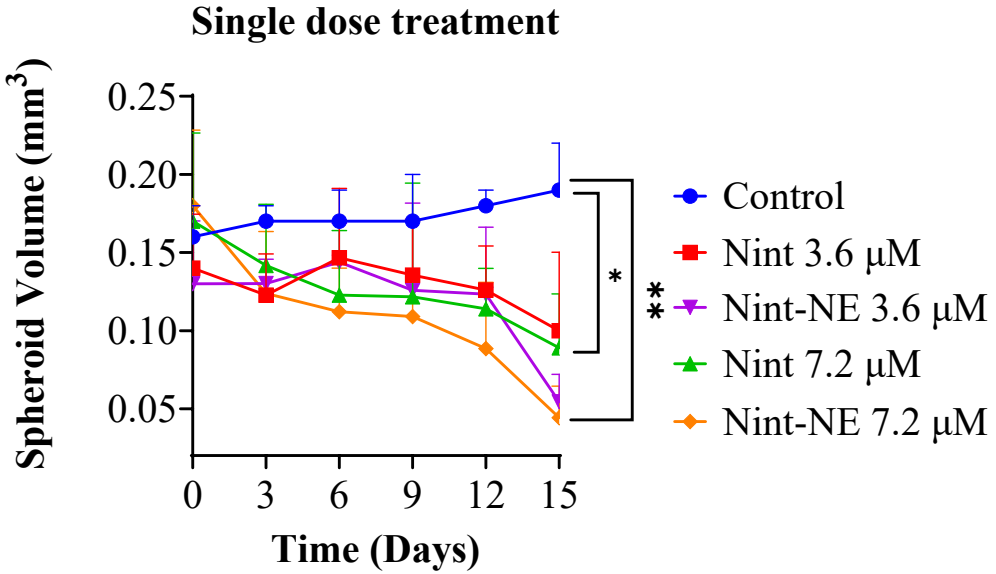
Sr. No.	Formulations	IC_{50} (µM) on different GBM cell lines		
		LN229	U87	U138
1	Nint (API)	13.7±1.8	7.7±1.8	7.5±2.4
2	Nint-NE	1.43±0.6	4.5±0.5	1.6±0.4
3	Nint-Nanoemulgel	5.3±2.1	3.7±0.8	3.6±1.4

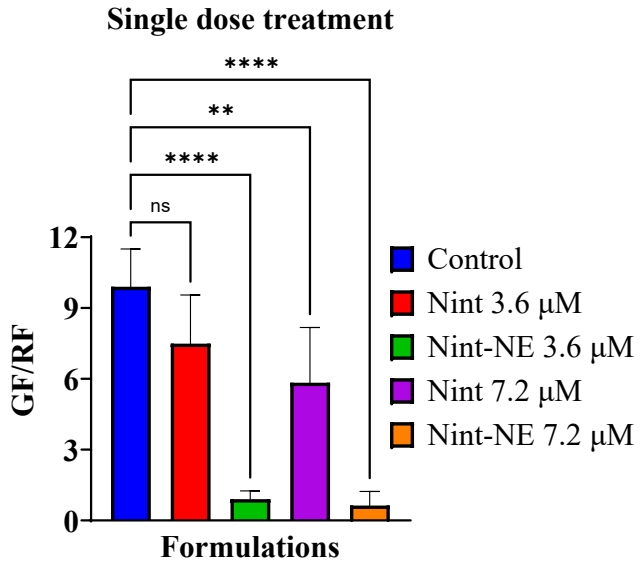


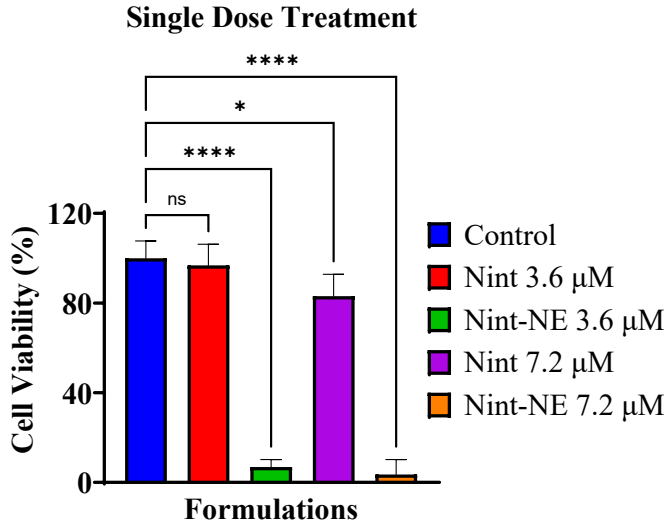
Improved Anticancer Properties of Nintedanib-loaded Nanoemulgels











Summary

- In-situ gels provide a viable alternative to conventional dosing
- Able to encapsulate multiple nano-delivery systems with controlled release of the encapsulated payload
- Facilitate enhanced permeation across nasal epithelium for quick entry into the brain, bypassing the BBB
- Localized brain accumulation while avoiding systemic circulation
- Enhanced in-vitro anti-cancer efficacy

Acknowledgments

St. John's University
College of Pharmacy and Health Sciences

NIH National Heart, Lung, and Blood Institute

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Cancer Institute

American Heart Association®

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