Nose-to-Brain Delivery of Novel Fingolimod-Ibuprofen Salt for Pain Relief in Multiple Sclerosis

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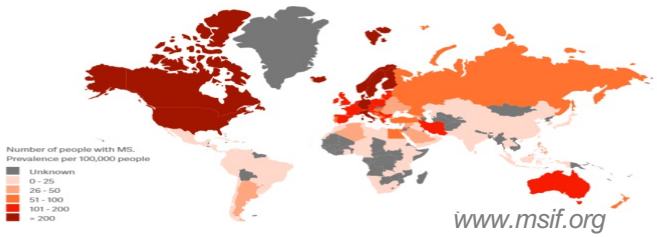
NEXT-GENERATION DELIVERY INNOVATIONS

Agenda

- Project Background
- Preparation and Characterization of Novel Fingolimod Salts
- Dry Powder Formulation Development of Fingolimod-Ibuprofen Salt
- Highlights and Significance of the Study

Background: Multiple Sclerosis

2.9 million people live with multiple sclerosis (MS) worldwide[1]



Limitations of Current Oral Treatments:

- First-pass metabolism
- Systemic side effects
- Delayed onset of action

Gilenya® (Fingolimod hydrocloride): first-line oral treatment for MS

Mechanism of Action[2]:

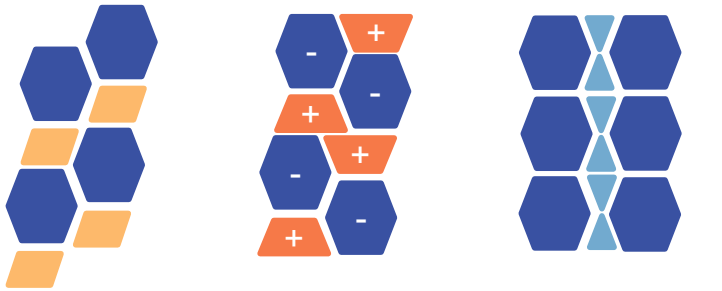
- Metabolized to fingolimod-phosphate (active form)
- Mimics sphingosine 1-phosphate (S1P), a natural lipid mediator
- Binds to S1P receptors, modulating immune cell trafficking

Reference:
[1] https://www.healthline.com/health/multiple-sclerosis/
[2] Chun, J *et al*, 2010. Clin. Neuropharmacol. 33, 91.

Background: Crystal Engineering & Particle Engineering

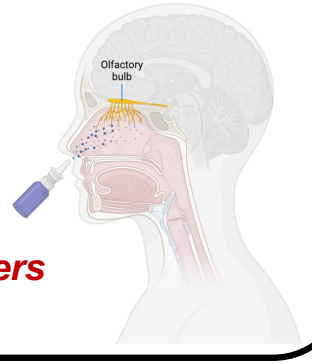
An Alternative Strategy for Treating Multiple Sclerosis

Multicomponent Crystals (MCC)



Particle Engineering

Nose-to-Brain Delivery



Inhalable dry powders

Aims

- Design, prepare and characterize novel crystalline forms of fingolimod
- Fabricate fingolimod-based dry powder formulations using ball milling
- Study the effect of particle size of dry powder formulations on aerosol deposition within the nasal cavity

Results: Prediction and Resolution of Novel Solid-States of Fingolimod

Unpublished Research

Hansen Solubility Parameters (unit: MPa$^{1/2}$)

Compound	δD	δP	δH	Total HSP
Fingolimod	18.3	3.9	9.9	21.2
Ibuprofen	16.9	4.3	10.6	20.4
Flurbiprofen	17.5	3.3	6.8	19.1

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

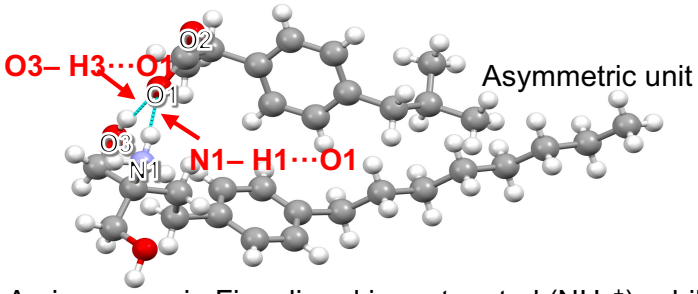
$$\Delta\delta_t = |\delta_{t2} - \delta_{t1}|$$

$$\Delta\delta_{FIN-IBU} = 0.76 \text{ MPa}^{1/2}$$

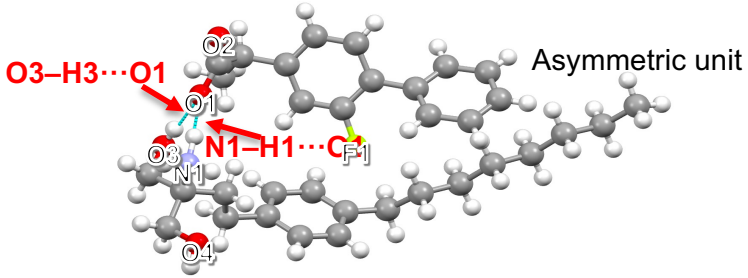
$$\Delta\delta_{FIN-FLU} = 2.11 \text{ MPa}^{1/2}$$

A Δδt value below 7 MPa$^{1/2}$ implies drug miscibility and a great chance of cocrystal/salt formation[1]

Fingolimod-Ibuprofen Salt (FIN-IBU)



Fingolimod-Flurbiprofen Salt (FIN-FLU)



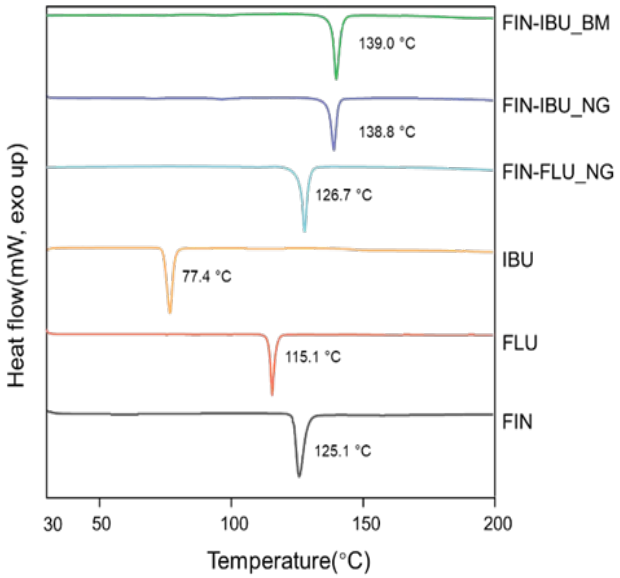
Amine group in Fingolimod is protonated (NH_3^+), while the carboxylic acid group in Ibuprofen/Flurbiprofen is deprotonated (COO^-).

Reference:
[1] Mohammad *et al.* Int J Pharm. 2011 Apr 4;407(1-2):63-71.

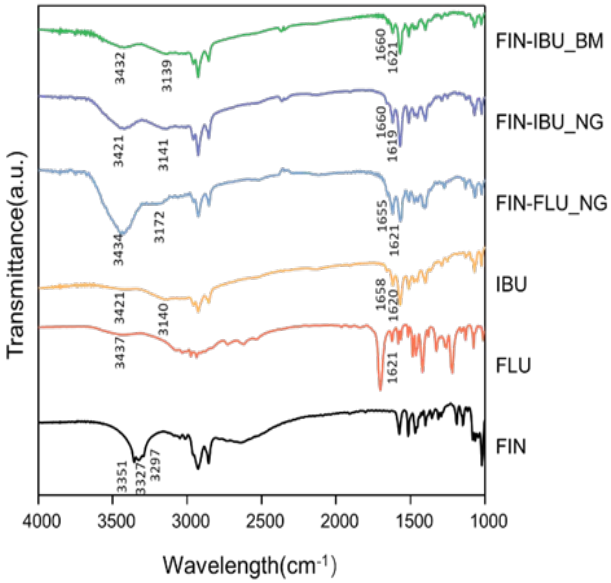
Unpublished Research

Results: Solid-State Characterization

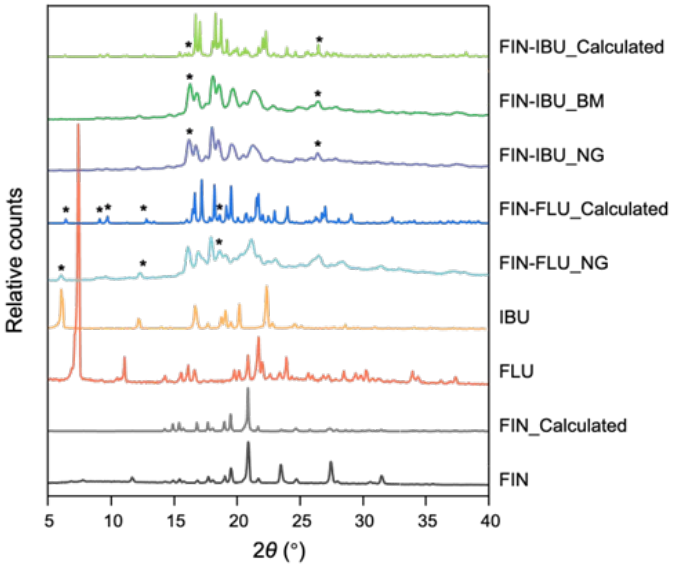
Differential Scanning Calorimeter (DSC)



Fourier-transform Infrared Spectroscopy (FT-IR)

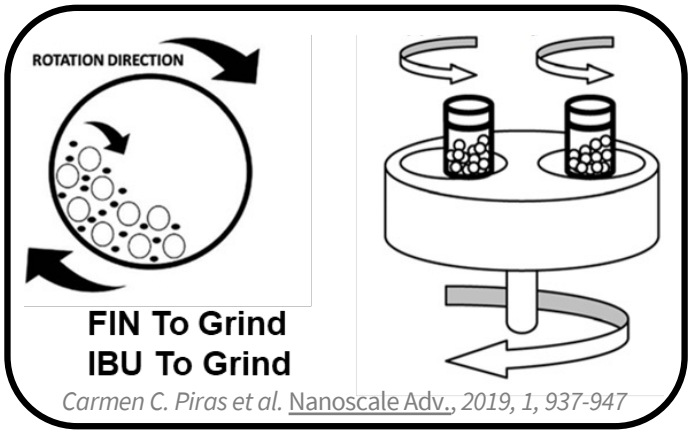


Powder X-ray Diffraction (PXRD)



Unpublished Research

Results: Development of FIN-IBU Dry Powder Formulations



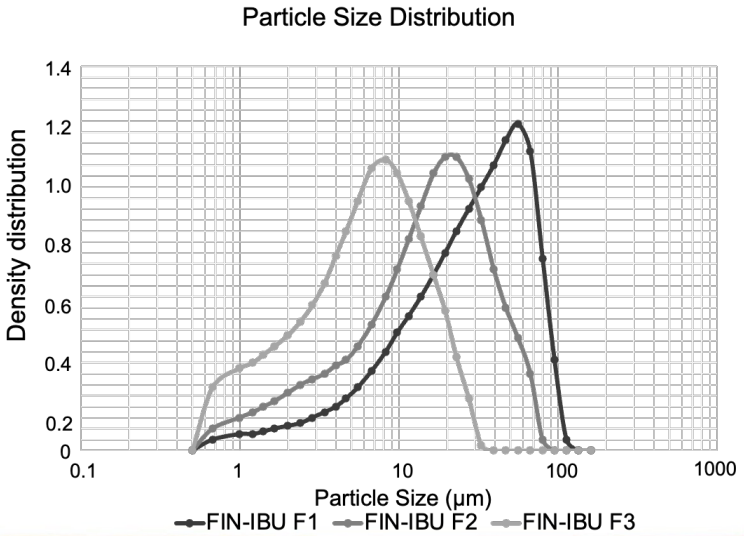
Carmen C. Piras et al. Nanoscale Adv., *2019, 1, 937-947*

Planetary Ball Milling

- Induce mechanochemical reaction
- Enable precise control over particle size for optimizing drug formulation properties

Ball Milling Processing Parameters

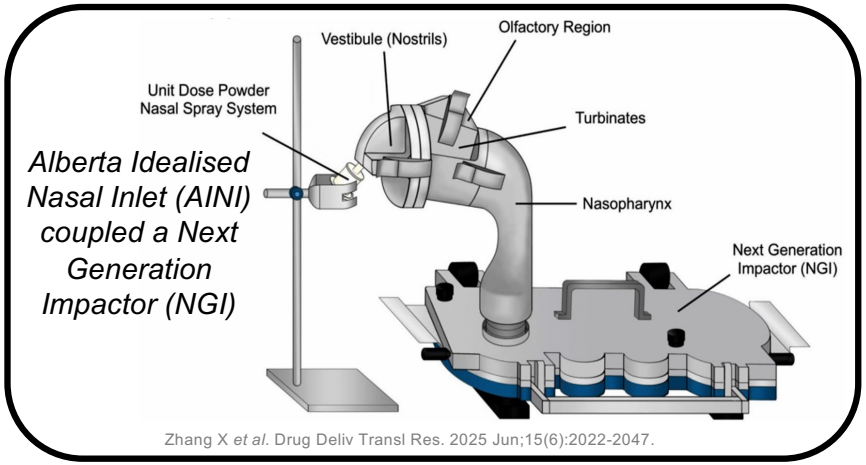
Formulation	Ball size (mm)	Milling time (min)	Rotation speed (rpm)	$Weight_{Sample}$: $Weight_{ball}$
F1	12	10	500	1:65
F2	12	30	500	1:65
F3	0.5	30	1000	1:10



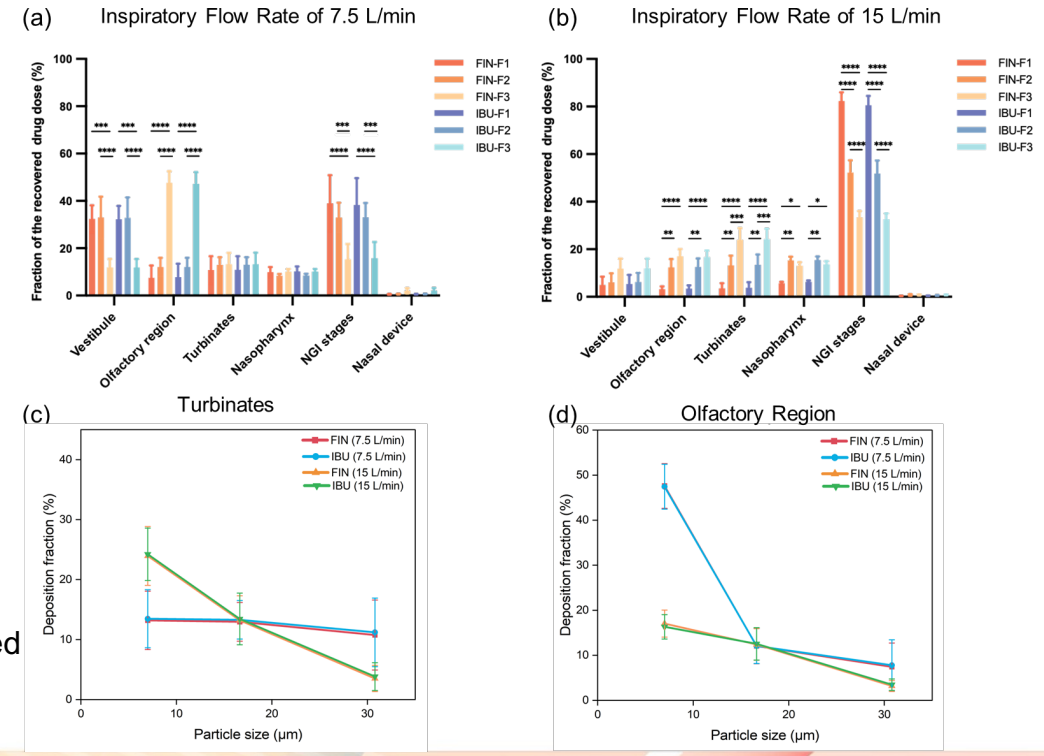
Unpublished Research

Results: *In vitro* Nasal Deposition Performance

Study the powder deposition of the formulations with varying particle size



Zhang X *et al.* Drug Deliv Transl Res. 2025 Jun;15(6):2022-2047.

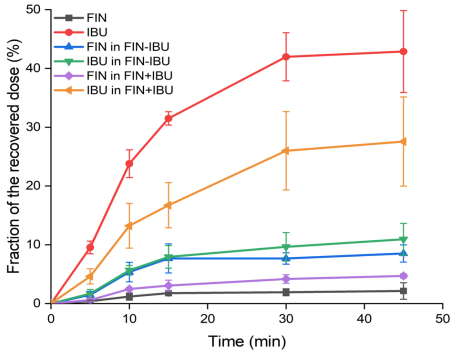


- The equimolar FIN-IBU salt formulation exhibited consistent deposition patterns of FIN and IBU
- Particle size critically influences powder deposition profile
- At flow rates of 7.5 L/min and 15 L/mins, FIN-IBU F3 exhibited superior olfactory deposition and turbinate deposition

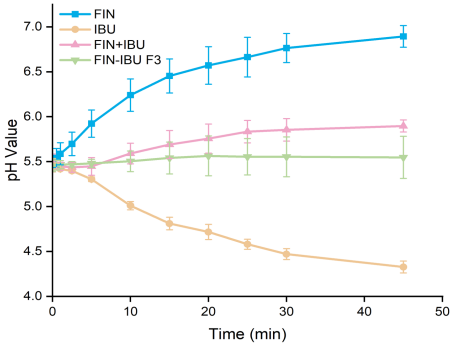
Unpublished Research

Results: *In vitro* Drug Release & Cell Viability

(a) The *in vitro* Drug Release Profile

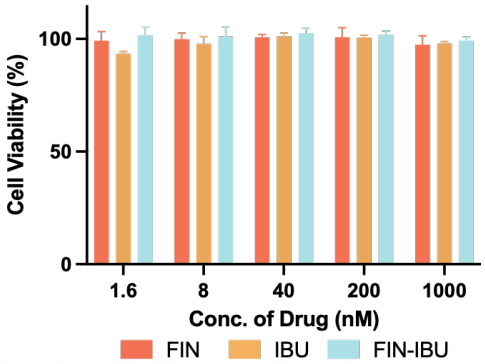


(b) pH Monitoring

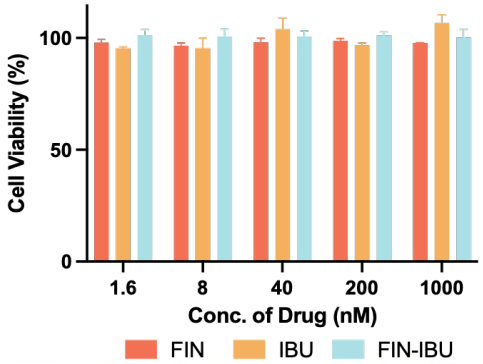


- Synchronized release of drugs during the initial 15 min
- FIN-IBU F3 maintains pH stability (5.46-5.56)

(c) Nasal epithelial RPMI 2650 cells



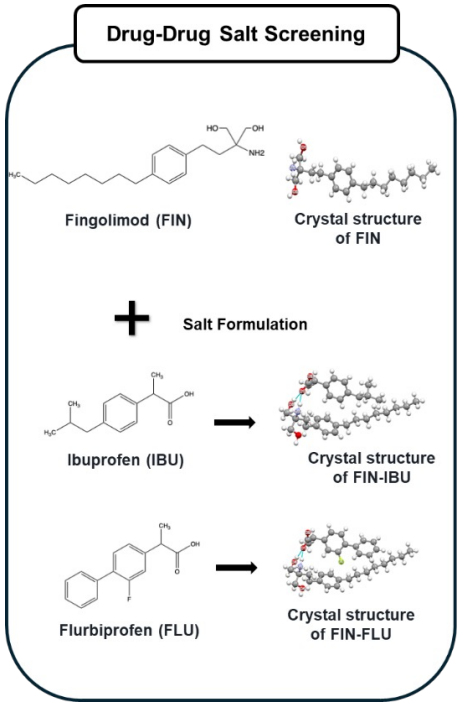
(d) Human neuroblastoma SH-SY5Y cells

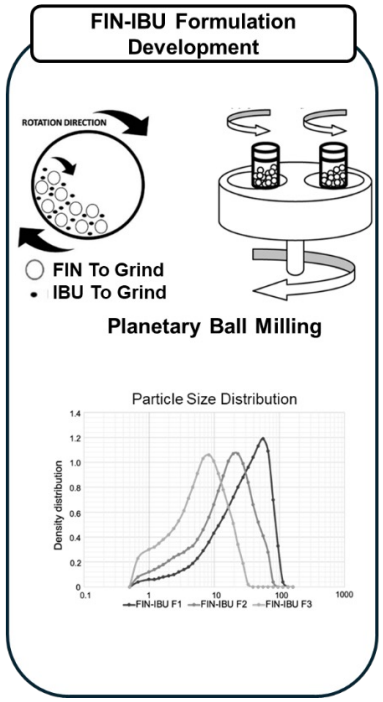


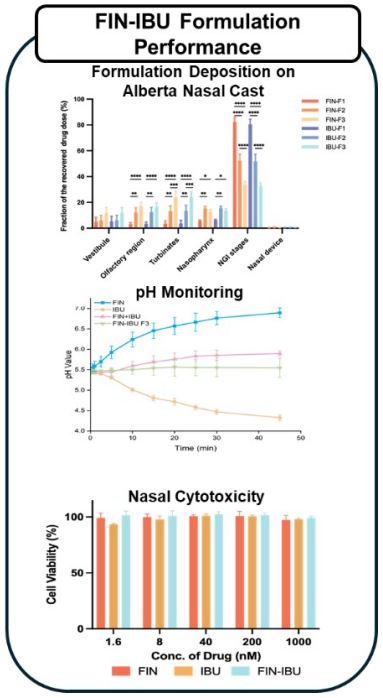
Minimal cytotoxicity in both RPMI 2650 and SH-SY5Y cell lines.

Unpublished Research

Highlights and Significance of the Study







- The structures of FIN and two drug-drug salts of FIN (FIN-IBU and FIN-FLU) were reported the first time
- Novel 1:1 FIN-IBU salt formulations were successfully fabricated via ball milling
- The FIN-IBU F3 with D_{50} of 7.00 µm exhibited superior deposition in olfactory region and turbinates
- The optimized formulation demonstrated a consistent and controlled drug release profile, showing stable pH and low irritation potential

Acknowledgement

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Thank you for listening.
Questions are warmly welcome!