

Semi-Mechanistic Pharmacokinetic model of intranasal Fingolimod hydrochloride administration in mice

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BACKGROUND

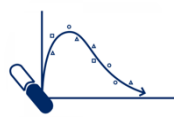
Fingolimod hydrochloride (FH) is a sphingosine-1-phosphate (S1P) receptor modulator approved for the treatment of multiple sclerosis (MS). Despite its high apparent oral bioavailability (~93%), its slow absorption ($T_{max} = 8-12$ h) and extensive hepatic metabolism pose significant challenges, prolonging the time to reach peak concentrations and affecting systemic exposure. However, the absolute bioavailability could not be determined due to the reversible metabolism of FH to its active phosphate form. Intranasal (IN) administration offers a promising alternative, enabling rapid nose-to-brain delivery while bypassing hepatic metabolism and reducing peripheral side effects [1-3]. To better understand the pharmacokinetics (PK) of fingolimod following nasal film and oral solution administration, we developed a pharmacokinetic model using R programming language [4]. PK modeling allows us to better understand the underlying kinetics of FH exposure and assess the delivery efficiency of different administration schemes.

METHODS

 : C57BL/6 J Mice administered either nasally or orally

 : Two different nasal formulations, F3 and F4 nasal films and oral FH solution in water for injection.

F3 containing **3%** hydroxypropyl methylcellulose (**HPMC**), **F4** containing **3%** **HPMC** and **6%** methyl-beta-cyclodextrin (**Me-β-CD**). The F3 and F4 nasal formulations were developed through an optimization process in previous work [5]

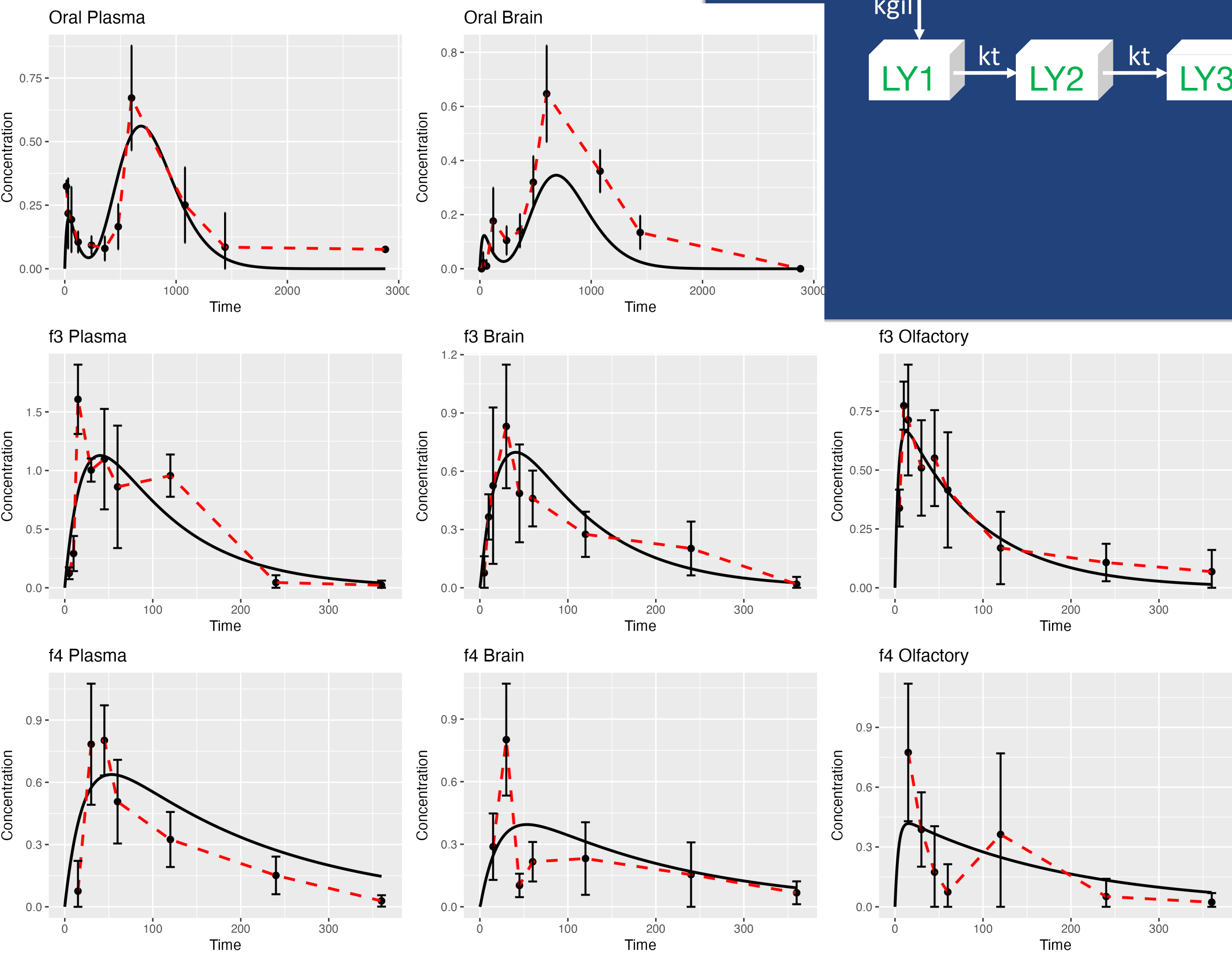
 : **FH concentration-time data** from the PK study were all averaged across individuals and fitted simultaneously to a semi-mechanistic PK model. The serum concentration-time profiles generated after oral administration included a **fast absorption phase and a second**, more pronounced peak occurring **8-10 hours post administration**.

 :To capture this pattern, both blood and lymphatic absorption pathways were included in the model. Specifically, the model incorporates six compartments: blood, lymph, brain, olfactory bulbs, small intestine (SI) lumen and nasal cavity.

- **Perfusion-limited kinetics** were assumed for tissue partitioning.
- **Physiological parameters** were derived either directly from experimental measurements or obtained from the literature.
- The in vivo data were used to **estimate** the:
 - a) clearance rate from serum
 - b) absorption rate constants from small intestine (SI) lumen to blood and lymph
 - c) absorption rate from the nasal cavity to blood
 - d) serum-to-brain partition coefficient
 - e) parameters characterizing the direct nose-to-brain transport via the olfactory bulb

OBJECTIVES

- ✓ Estimate key pharmacokinetic parameters including serum clearance, absorption rate constants from nasal cavity and intestinal lumen, and brain partition coefficients.
- ✓ Quantify the contribution of distinct absorption pathways – gastrointestinal (via blood and lymphatic system) and intranasal (via bloodstream and olfactory bulbs) – to systemic and brain exposure.
- ✓ Assess how formulation composition (presence of methyl-beta-cyclodextrin) influences the efficiency of nose-to-brain delivery



RESULTS

- ✓ Several optimization schemes were tested to derive the best parameter solution. Specifically, **18 distinct optimization algorithms** were employed, along with **4 different objective functions**; i) the absolute average-fold error (AAFE), ii) the mean absolute percentage error (MAPE), iii) the simulations-observations discrepancy index [6], and iv) the root mean squared error (RMSE). The latter metric yielding the best results. To minimize dependence on initial values, the optimization problem was solved 1,000 times, each initiated with a unique random parameter set.
- ✓ The **lymph compartment** was divided into **7 subcompartments**, sharing the same transit rate (ktransit), to simulate the slower absorption component.
- ✓ The contribution of direct CNS uptake through the olfactory nerve was estimated to be **32% for the F3 film** compared to **41% for the F4 film**, while the clearance from the serum (CL) was 0.019 mL/min.

Pathway	Formulation	Absorption/Transport Rate (min ⁻¹)
GI Lumen → Lymph (kgil)	Oral	0.012
GI Lumen → Serum (kgis)	Oral	0.0009
ktransit (between lymph subcompartments)	Oral	0.010
Nasal Cavity → Serum (kns F3)	F3 Nasal Film	0.011
Nasal Cavity → Serum (kns F4)	F4 Nasal Film	0.005
Nasal Cavity → Olfactory Bulbs (knob F3)	F3 Nasal Film	0.00038
Nasal Cavity → Olfactory Bulbs (knob F4)	F4 Nasal Film	0.00022
Olfactory Bulbs → Brain (kobb F3)	F3 Nasal Film	0.00033
Olfactory Bulbs → Brain (kobb F4)	F4 Nasal Film	0.00015

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