BEYOND EMPIRICAL BIOAVAILABILITY SCALING: A MECHANISTIC MODEL INCORPORATING PRE- AND POST-SYSTEMIC SATURABLE PROCESSES TO CHARACTERIZE NON-LINEAR PK OF ORALLY ADMINISTERED SMALL MOLECULES

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BACKGROUND & OBJECTIVES

BACKGROUND

- Non-linear PK in orally administered small molecules is commonly addressed using empirical adaptations such as dose-dependent bioavailability or clearance
- These approaches may not sufficiently capture all structural drivers of non-linearity and can lead to biased population predictions
- Mechanistic descriptions of saturable processes, including TMDD-related approximations, are well established for biologics but remain less commonly applied to small molecules with apparent distribution-driven non-linearity

OBJECTIVES

1. Apply a stepwise structural modeling strategy to diagnose non-linear PK
2. Compare empirical dose-dependent scaling vs.mechanistic representations of saturable processes
3. Evaluate a model structure incorporating both pre-systemic and systemic saturation

METHODS & MODELING STRATEGY

DATA & ANALYSIS

Early clinical PK data from an orally administered small molecule at five dose levels

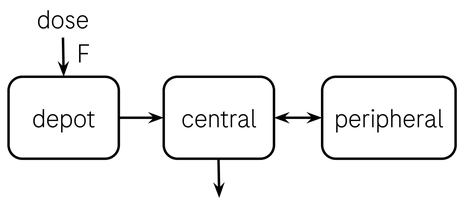
Models were fitted to individual concentration–time data in NONMEM

Dose-normalized mean concentration profiles were used to illustrate model performance

MODEL DEVELOPMENT: STEPWISE APPROACH

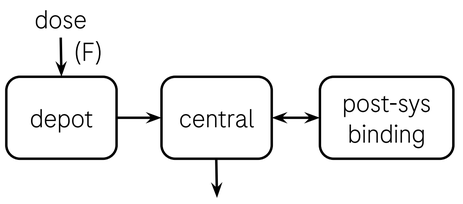
STEP 1
Empirical F scaling

2-compartment model with dose-dependent F



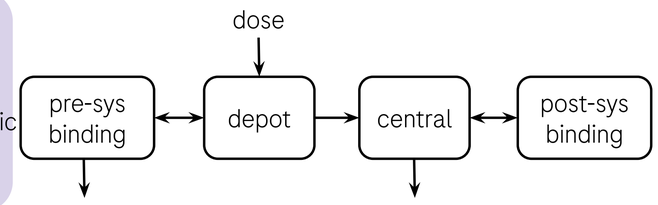
STEP 2
Post-systemic saturation

Including systemic binding (TMDD models, or Bmax function) with or without dose-dependent F



STEP 3
Pre- & post-systemic saturation

Including both pre- and post-systemic binding (TMDD models, or Bmax function), no dose-dependent F



EVALUATION METRICS

- Agreement between observation and prediction
- Systematic dose-dependent bias in population predictions (PRED) and random effects
- Plausibility of the parameter estimates
- Changes in objective function value (OFV)

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RESULTS: MODEL COMPARISON & PERFORMANCE

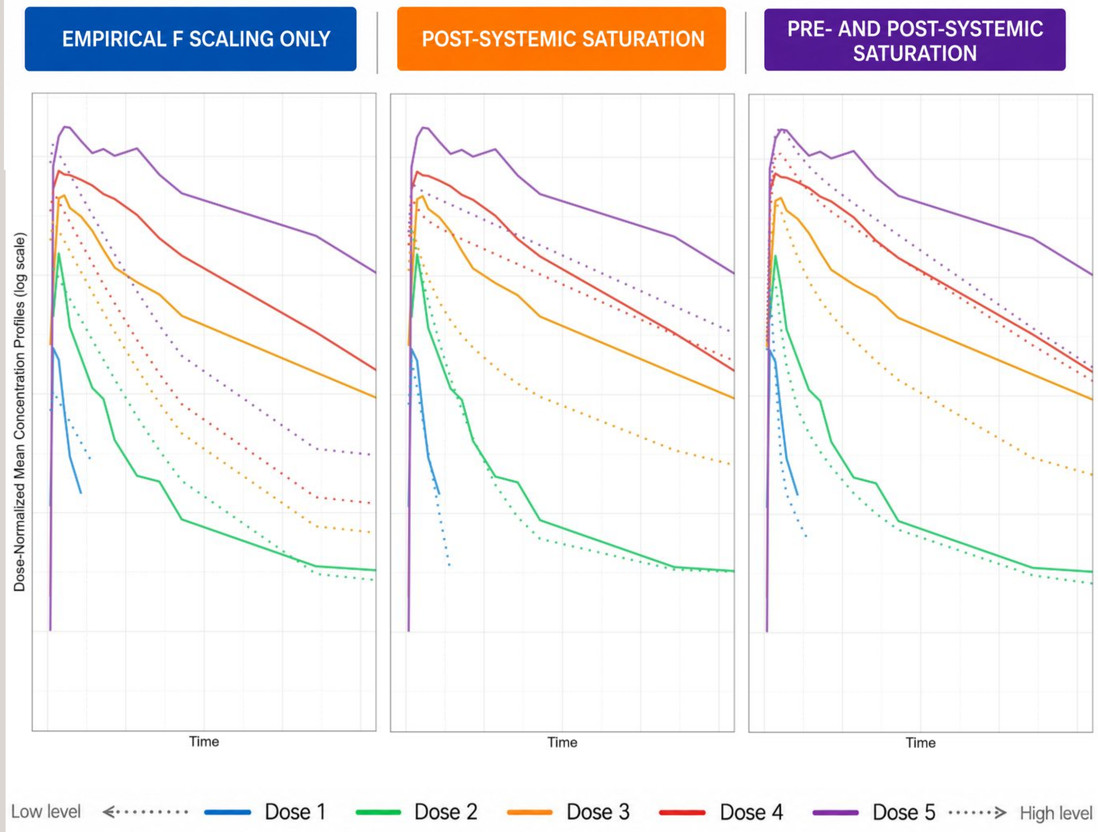
MODEL COMPARISON

Model	Bias across doses	Dose dependency in random effects	Parameters	ΔOFV (vs. models in previous step)
STEP 1: Empirical F scaling	Over-prediction at lower doses; under-prediction at higher doses	Obvious in distribution-related parameters	F decrease over doses (highest dose as reference)	(reference)
STEP 2: Post-systemic saturation with dose-dependent F	Good prediction at lower doses; under-prediction at higher doses	Not as obvious; remaining dependency in saturation parameter	F estimates remained comparable to STEP 1; saturable binding contributes meaningfully to the observed non-linearity	< -100
STEP 3: Pre- & post-systemic saturation; No empirical F scaling required	Improved prediction across dose levels	Not obvious; improved in saturation parameters	Both pre- and post-systemic binding contribute meaningfully to the observed non-linearity	< -100

EXAMPLES OF MODEL FIT

Dose-normalized mean concentration–time profiles across five dose levels

Solid lines: Observed | Dashed lines: Model-predicted



CONCLUSIONS

This framework of stepwise structural model exploration has supported the characterization of non-linear PK in orally administered small molecules

Empirical dose-dependent adaptations and post-systemic saturable processes alone did not fully resolve the dose dependency

Incorporating both pre- and post-systemic saturation adequately described the observed non-linear PK without the need for empirical parameter scaling

When empirical dose-dependent adaptations and post-systemic saturable processes alone are insufficient, a model incorporating both pre-systemic and systemic saturable binding processes may be considered as a practical alternative to empirical parameter scaling in clinical development, provided the processes are mechanistically plausible