Population Balance Modeling of Aggregation in Long-Acting Injectable Formulations Integrated with PBPK Modeling

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PURPOSE

- Long-acting injectable (LAI) formulations are critical for sustained drug delivery in a multitude of applications for birth control, psychological disorders, human immunodeficiency virus (HIV), and cancer.
- The injection depot site is a complex system due to:
  - Immune response
  - Low compound solubility
  - Particle agglomeration/size
  - Viscosity
  - Injection volume
  - Excipient effects
- Simulating agglomeration dynamics is essential for understanding the difficult-to-observe in vivo formulation behavior at the injection site[1].
- The objective of this study is to develop a population balance model (PBM) to describe in vivo agglomeration of once-monthly extended-release LAI suspension of Invega Sustenna®, paliperidone palmitate (PP), and integrate it with a physiologically based pharmacokinetic (PBPK) model to predict the in vivo performance.

METHODS

A population balance model (PBM) was implemented to calculate particle agglomeration within GastroPlus Version 9.9 beta version (Simulations Plus, Inc.):

- Finite difference method was utilized to solve equations of Smoluchowski[2] (Figure 1).
- Fixed pivot method was utilized to solve the system and conserve mass and particle number[3].
- Brownian motion, uniform, and sum of sizes aggregation kernels was implemented.
- The model was coupled with full dissolution equations in the intramuscular (IM) depot volume.
- Johnson dissolution model was used with mean particle size of 0.359 µm (SD = 1.4 µm) [4,5]
- A perfusion-limited PBPK model was calibrated against Paliperidone IV administration[6].
- Lukacova model was utilized to predict tissue partition coefficients.

Discrete Population Balance

$$\frac{dn_i}{dt} = \frac{1}{2}\sum_{j=1}^{i-1} K_{i-j,j} n_j n_{i-j} - n_i \sum_{j=1}^{\infty} K_{i,j} n_j$$

Collision Kernels

Brownian Motion

$$K_{i,j} = \frac{\beta 2kT}{3\mu}\frac{(r_i + r_j)^2}{r_i r_j}$$

Sum of Sizes

$$K_{i,j} = \beta(r_i + r_j)$$

Uniform

$$K_{i,j} = \beta$$

n	Number density (particles per unit volume)
N	Number of discrete particles tracked
i,j,k	Particle indices
K	Aggregation kernel
β	Fitted kernel rate constant
k	Boltzmann Constant
T	Temperature (37 C)
μ	Viscosity
r	Particle radius

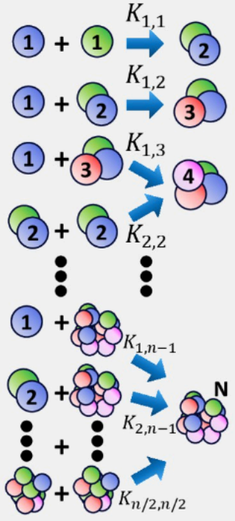

Figure 1: Discrete Population Balance Model for Aggregation

RESULTS

Paliperidone PBPK Model:

- Build the model based on input parameters listed in Table 1.
- Fit PBPK model with volume of distribution (V_d) and clearance (CL) based on IV Data (Fig. 2A)
- Validate PBPK model with oral solution (Fig. 2B)

Paliperidone Palmitate Intramuscular Model:

- Injection site: Deltoid muscle
- Paliperidone palmitate solubility utilized for dissolution
- Assumes esterases in muscle immediately convert paliperidone palmitate ester to free paliperidone[7]
- Compare models with/without particle agglomeration.

Simulation Results (No Particle Agglomeration):

- PBPK model mispredicted plasma concentration vs. time (Cp-time) profiles across all doses (Figure 3A).
- Drug immediately reached saturated solubility conditions at all doses from 25-150 mg resulting in flat Cp-time profile.
- Failed to capture sustained release observed in vivo

Population Balance Simulation Results:

- Accurately predicted Cp-time shape with all agglomeration kernels (Figures 3B-3D)
- Particles increased in size over time from 0.359 µm to an average of 110 µm by 2000 hours for 50 mg dose simulated with sum of sizes kernel (Figure 4).

Fitted Kernel Rate Constants:

- Brownian motion: 1 (unitless)
  - No fitting required, diffusion accurately predicted collision frequency.
- Uniform kernel: $4x10^{-11}$ mg²/s
- Sum of sizes kernel: $2x10^{-10}$ mg²/s

Cmax Error Range (Table 2)

- Reasonable accuracy for 25, 50, and 150 mg doses.
- 100 mg formulation exhibited larger error due to injection variability or subcutaneous leakage[11].

Table 2: Cmax % Error - all Kernels

Dose (mg)	Brownian	Uniform	Sum of Sizes
25	-12.5	-15.8	-22.7
50	-0.92	1.72	-1.68
100	60.0	64.3	60.9
150	8.7	5.4	10.4

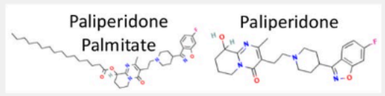

Table 1: Input Parameters for Paliperidone Intramuscular PBPK Model

Parameter	Value
S+LogP Experiment	2.29 2.39 (Invega-EMA[8])
S+pKa Experiment	7.74, 2.52 (base) 8.24[9], 2.6[8]
S+Sw (palmitate ester) [mg/mL]	8e-5 @ pH = 12.9
S+FaSSIF / S+FeSSIF [mg/mL]	0.091 / 0.258
S+Peff [cm/s]	$2.33x10^{-4}$
S+Fup % (human)	19.68
S+Rbp (human) Experiment	0.83 0.78-0.83[10]
Volume of Distribution (V_d) [L]	122
Clearance (CL) [L/hr]	3.5 + 0.918 (kidney + Liver)

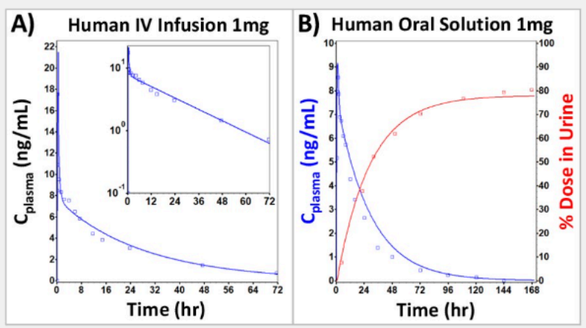

Figure 2: Observed vs. predicted plasma concentration vs. time for (A) 1 mg IV infusion of paliperidone and (B) 1 mg oral solution of paliperidone.

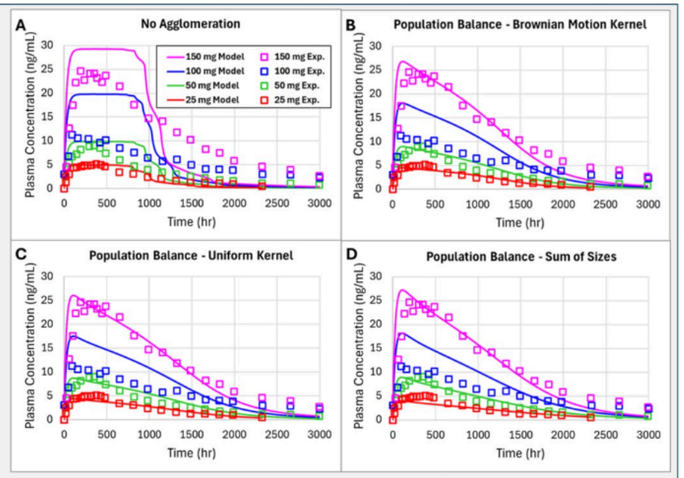

Figure 3: Predicted vs observed plasma concentration for 25, 50, 100, and 150 mg IM injection of paliperidone palmitate suspension A) with no agglomeration, B) Brownian Motion kernel, C) uniform kernel, and D) sum of sizes kernel.

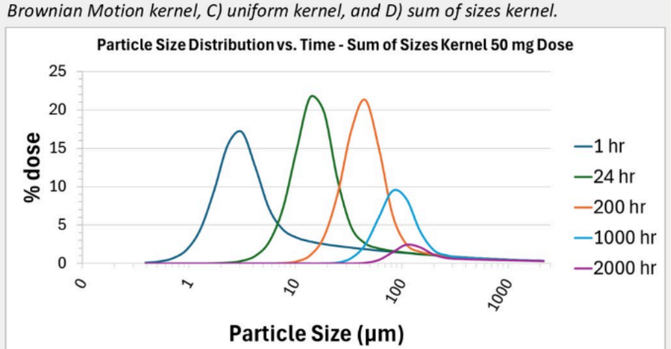

Figure 4: Evolution of particle size distribution for 50 mg paliperidone intramuscular injection utilizing sum of sizes aggregation kernel.

CONCLUSIONS

Key Accomplishment:

- PBM model successfully integrated within GastroPlus® PBPK platform to accurately predict LAI formulation performance.
- Showed that agglomeration may be a key mechanism for the sustained release from certain IM depot formulations.

Limitations Addressed:

- Flat Cp-time profile shape is inaccurately predicted when utilizing initial particle size due to constant saturated concentration in the depot volume.
- Cp-time profile shape corrected with PBM by increasing particle size vs. time and reducing dissolution rate.

Benefits of PBM to Predict Agglomeration:

- Allows dissolution rate to decrease over time as particle size increases due to agglomeration.
- Prevents saturation of depot volume at active pharmaceutical ingredient (API) solubility leading to slower, controlled dissolution and absorption.
- Aligns with literature reported observation of particle agglomeration occurring in vivo within the IM depot.

Future Work:

- Extend PBM to subcutaneous delivery route.
- Apply framework to LAI development and regulatory submissions.

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