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Improving PBBM with Surface pH Driven Dissolution: Case Studies for Palbociclib and Ibuprofen

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This poster was developed with the support of the Enabling Technologies Consortium (ETC) – www.etconsortium.org. ETC is comprised of pharmaceutical and biotechnology companies collaborating on issues related to pharmaceutical chemistry, manufacturing, and control with the goal of identifying, evaluating, developing, and improving scientific tools and techniques that support the efficient development, and manufacturing of pharmaceuticals.

PURPOSE

The Current Approach:

- Dissolution rate of ionizable compounds is historically treated in a simplified manner based on the solubility of the drug in bulk intestinal fluid at a static pH. Modeling dissolution provides important insight across multiple applications:

❑Formulation Optimization
❑Effect of Proton Pump Inhibitors (PPI)
❑Cross species predictions (dog vs. human)
❑Food Effect Modeling
❑Drug-Drug Interactions
❑Virtual Bioequivalence

The Problem:

- Ionizable drugs and/or excipients can change the pH at their own surface as they dissolve in weak intestinal bicarbonate buffer and gastric fluid leading to inaccurate dissolution predictions when assuming bulk pH.

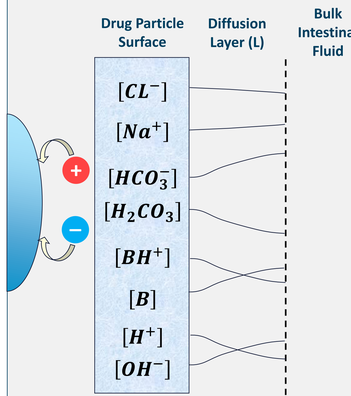
The Solution:

- Improve existing chemical equilibrium approaches in literature[1,2] to dynamically calculate the surface pH based on a drugs pKa(s) and important gastrointestinal fluid species.

OBJECTIVES

Test the newly developed mechanistic calculation of surface pH with PBPK models for ibuprofen (acidic) and palbociclib (basic) to verify that accounting for surface pH improves predictions of in vivo dissolution.[3,4]

METHODS



Equilibrium of all acidic ionized species

(similar equation for bases)

$$H_k A <=> H_{k-1} A + H^+, k = 1, \ldots, nA$$

$$K_a^{(k)} = \frac{[H_{k-1}A][H^+]}{[H_k A]}$$

Charge Flux Neutrality:

$$\sum_{i=1}^{N_i^+} Z_i^+ D \frac{d[I_i^+]}{dL} + \sum_{j=1}^{N_j^-} Z_j^- D \frac{d[I_j^-]}{dL} = 0$$

H Proton
k stoichiometry
A Acid
Ka Equilibrium Constant

N Number of ionic species
Z Charge
D Diffusivity
I Ion Concentration
L Diffusion layer

The GastroPlus® Version 9.9 Advanced Compartmental and Transit Model (ACAT) was improved by adding full mechanistic surface pH calculations that make fewer simplifying assumptions than existing models such as not assuming sink conditions, including all pKa(s), and all ionic species.[1,2] Utilizing this modified ACAT model, we built a PBPK model for ibuprofen and palbociclib. We then tested the model across multiple dosing scenarios and PPI administration.

Key Enhancements & Model Parameters

- **ACAT Model:**
  Surface pH is calculated accounting for all pKas and dissolved species for the mathematical solution of pH vs. time. All equilibrium equations are solved simultaneously with electroneutrality and salt equilibrium (Ksp) while not assuming sink conditions

- **Ibuprofen Model:**
  Systemic model parameterized with IV data and 20 µm particle size fit to in vitro dissolution. Nonlinear CYP2C9 metabolism was applied to gut and liver. Surface pH model was tested against equilibrium pH at doses of 400, 800, and 1200 mg.[5,6]

- **Palbociclib Model:**
  - **Metabolism:**
    Model incorporated nonlinear CYP3A4 metabolism in gut and liver with 25.8% linear clearance added to account for SULT2A1 metabolism.[7] A mean particle radius of 7.7 µm was determined in DDDPlus V6 utilizing in vitro dissolution data.
  - **Lysosomal Trapping:**
    MembranePlus™ V3 was utilized to calculate palbociclib unbound fraction in enterocytes (Fu = 2%) to justify the fitted value of 1.73% in the PBBM model. This is further backed by literature studies of palbociclib lysosomal trapping.[8]
  - **Dosing Scenarios:**
    Palbociclib simulations were performed and compared against literature data for 125 mg in fasted and fed states with/without proton pump inhibitor rabeprazole.[9]

RESULTS

The ibuprofen PBPK model was calibrated based on IV bolus and rapidly dissolving or solubilized formulations (sodium salt and liquid-gel capsules). Tissue-to-plasma partition coefficients were calculated based on Lukacova method with fitted Rbp to provide the correct volume of distribution. Ibuprofen model parameters are listed in Table 1. Particle size was estimated as 20 µm from in vitro dissolution data in USP2 apparatus at 100 rpm in 900 mL of 50 mM Phosphate buffer at pH 6.8.[10]

Palbociclib model was calibrated based on 4 hr IV infusion and the oral simulation with and without PPI were based on literature data of Yu. Particle size for palbociclib based on in vitro dissolution using DDDPlus Version 6 (Simulations Plus, Inc.) as shown in Figure 1. Palbociclib model parameters are listed in Table 1.

Table 1: *Model input values for Ibuprofen and Palbociclib*

Model Input	Ibuprofen	Palbociclib
S+LogP*	3.65	2.01 (AP13)
Exp LogD	3.5 @ pH 8.1 (BioByte Starlist)	0.99 @ pH 7.4 (NDA 207,103)
S+pKa	4.52 (acid)	8.85, 3.41, 1.56, 1.1, -0.68, -2.49 (Base)
Exp.	4.55 (acid) (BioByte Starlist)	7.106, 4.882, 2.18 (fitted to solubility data)
S+Sw	0.12 mg/mL @ pH 3.93	8.81×10^{-3} mg/mL @ pH = 8.94
Exp Sw	0.021 mg/mL @ pH 1.2[12]	0.0922 mg/mL @ pH 9.03
S+FaSSIF	0.33 mg/mL	0.82 mg/mL
Exp FaSSIF	0.718 mg/mL (Sim+ Meas.)	0.04 mg/mL
S+FeSSIF	1.87 mg/mL	1.01 mg/mL
Exp FeSSIF	4.02 mg/mL (Sim+ Meas.)	
S+Peff	6.46×10^{-4} cm/s	0.94×10^{-4} cm/s
Exp Peff (Caco-2)	6.13×10^{-4} cm/s (BioByte Starlist)	2.982×10^{-4} cm/s (based on Caco-2)
Peff (fit)	10×10^{-4} cm/s	
S+PrUnbnd	2.72%	16.23%
Exp	0.561%[5]	14.7% (NDA 207,103)
S+Rbp	0.67	0.88
Rbp	0.45 (fit)	1.63 (exp – NDA 207,103)
Metabolism	Km (exp) = 33.75 uM CYP2C9[13] Vmax (fit) = 12 nmol/min/mg	Km (AP13) = 29.12 µM Clint (fit) = 32.5 uL/min/mg CL (SULT2A1) = 9.68 L/hr, Clren = 6 L/hr

* S+ refers to ADMET Predictor® Version 13 *In Silico* Predictions

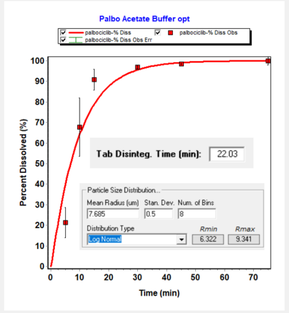


Figure 1*: DDDPlus In Vitro Dissolution Model for Estimation of Palbociclib Particle Radius in USP 2 Apparatus, 75 rpm, 900 mL Acetate buffer at pH 5.5.*[11]

Ibuprofen



Palbociclib



- **Ibuprofen (acid):**
  - ❑ **Equilibrium Bulk pH Model Issues:**
    Using model based on equilibrium bulk pH, Cmax is overpredicted and the Tmax is underpredicted due to overestimation of solubility and dissolution rate (Figures 2 and 3).
  - ❑ **Surface pH Model Improvements:**
    Surface pH is lower than bulk pH causing reduced solubility and dissolution rate as dose increases, resulting in more accurate prediction (Figures 2 and 3).

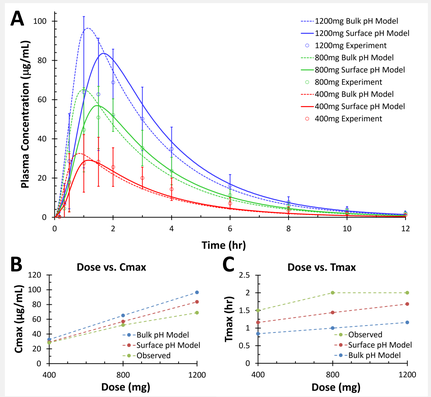


Figure 2: A) *Observed (points) and predicted (lines) for 400, 800, 1200 mg doses of ibuprofen from Lockwood study;* ***B)*** *Dose vs. Cmax; and* ***C)*** *Dose vs. Tmax with bulk pH (equilibrium) and surface pH (dynamic) solubility model.*

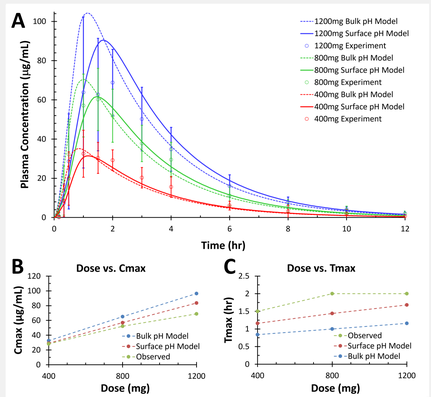


Figure 3: A) *Observed (points) and predicted (lines) for 400, 800, 1200 mg doses of ibuprofen from Albert study;* ***B)*** *Dose vs. Cmax; and* ***C)*** *Dose vs. Tmax with bulk pH (equilibrium) and surface pH (dynamic) solubility model.*

- **Palbociclib (base):**
  - ❑ **Model Comparison:**
    Figure 4 shows that both models yield similar results, but the surface pH model does improve Cmax ratio slightly as shown in Table 2.
  - ❑ **Clinical Outcomes:**
    Coadministration with a PPI increases stomach pH to 6.5, reducing solubility and lowering Cmax ratio to 0.2 and 0.63 in fasted and fed state (see Table 2).

Table 2: *Model input values for Ibuprofen and Palbociclib*

	PPI Cmax Ratio		
	Obs.	**Surface PH**	**Bulk PH**
Fasted	0.2	0.23	0.26
Fed	0.63	0.64	0.66

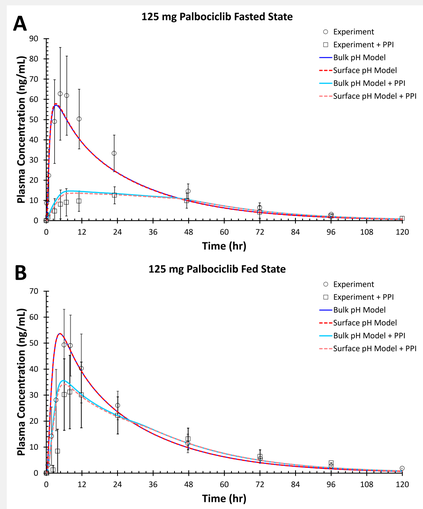


Figure 4: *Observed (points) and predicted (solid lines – bulk pH model, dashed lines - surface pH model) for 125 mg palbociclib with and without PPI in the* ***A)*** *fasted state and* ***B)*** *fed state.*

CONCLUSIONS

The enhanced surface pH and solubility PBBM has been implemented and overcomes several limiting assumptions of previous models allowing for improved calculation of dissolution rate for self-buffering compounds. The model was validated by comparing simulations with and without surface pH for ibuprofen and palbociclib.

- **Ibuprofen**
  - ❑ **Improved Cmax and Tmax prediction with increasing dose due to lower surface pH and dissolution.**
- **Palbociclib**
  - ❑ **Modest or slight improvement in Cmax prediction in fed and fasted state. Small difference in absolute errors but still reduced by 15% in fasted state and 3% in fed state.**

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