Enabling Biopharmaceutics Risk Management Using gCOAS Oral Absorption Modelling

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Outline

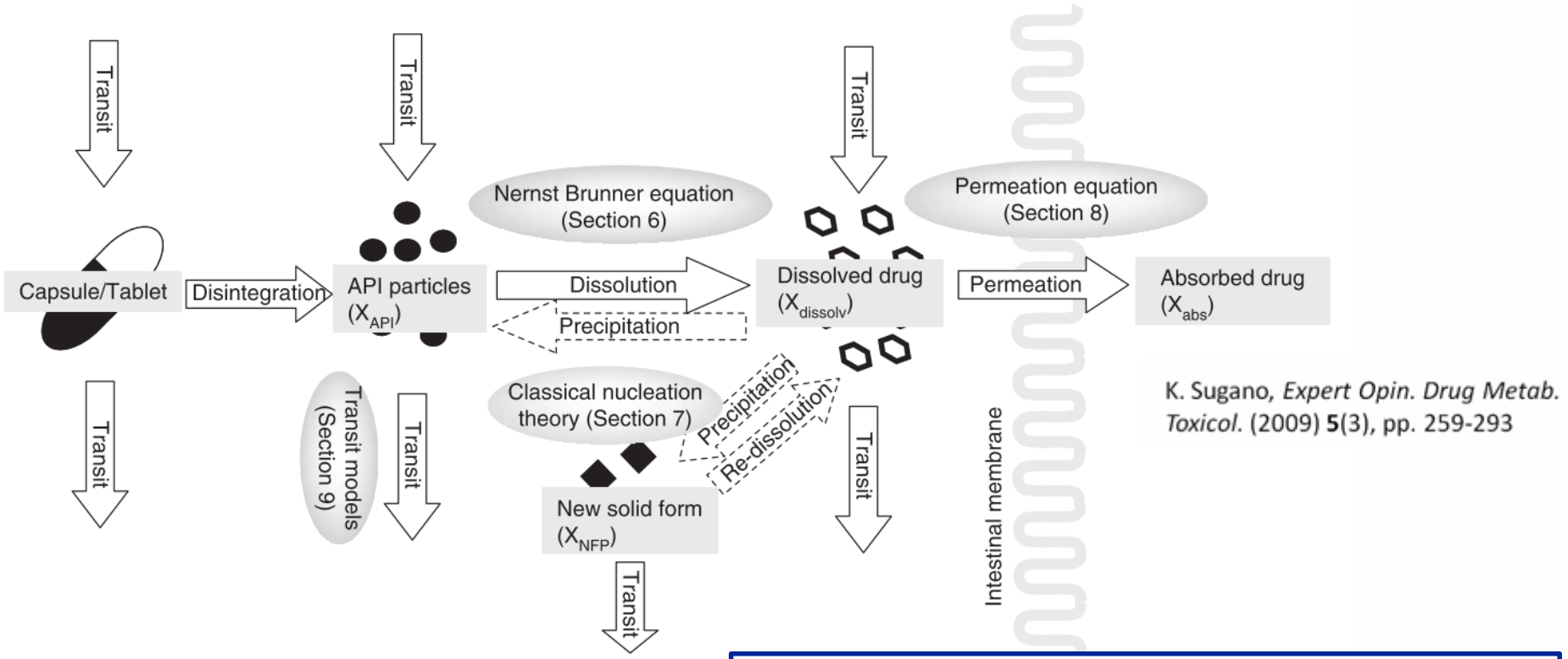
1. What is gCOAS?
2. Illustrative case study for biopharmaceutic risk management with gCOAS simulations
3. Conclusions & future plans for gCOAS

What is gCOAS?

- gCOAS - Computational Oral Absorption Simulation built in the gPROMS language in collaboration with PSE
- Motivation for developing gCOAS is understanding of FRACTION ABSORBED (Fa) and not PK or PK-PD prediction.
- Identification of key RISK FACTORS for absorption of drug molecules
  - Optimize molecular design
  - Co-optimize formulation design and bioperformance

Framework

- Framework populated with models from various sources
  - Framework based on K. Sugano's work, additional models and phenomenon added
- Open model architecture allows addition or modification of models for phenomena



- **Thermodynamics is fundamental**
- **Kinetics influences outcomes**

Knowledge of both is essential for optimizing the biopharmaceutics properties of a drug product through all stages of discovery & development

gCOAS: Created As Bottom Up Approach

- **gCOAS model has several advanced features for simulating oral absorption. Features include:**
  1. **Mass and charge balances** of drug species including **zwitterions** (ionic, non-ionic and micellar) and **physiological ions** in solution in the gastrointestinal (GI) tract
     - Enables evaluation of the impact of K_{sp} on drug precipitation and dissolution
  2. Drug dissolution is modeled incorporating **surface pH of solids**, changes in pH of GI tract, and **speciation** of drug in solution, including solubilization of various drug species into **bile micelles**
     - Enables the evaluation of micro-environment pH on dissolution and the influence of bile salts on absorption
  3. **Kinetic co-existence** of more than one solid form in the GI tract
     - Enables the evaluation of dissolution, precipitation and re-dissolution of precipitated form

gCOAS: Created As Bottom Up Approach

- **Features include:**
  4. **Nucleation and crystal growth kinetics** include calculating the supersaturation with respect to the relevant species forming the solid phase
     - Enables the evaluation of rate of precipitation and the resulting particle size distribution of the solid phase
  5. **A population balance approach** is used to represent the particle size distribution of each solid phase either present in the drug product or formed during transit through the GI tract
     - Enables detailed assessment of behavior of a population of particles based on the analysis of a single particle in a local condition, minimizing computational time for maximum information on particle size changes

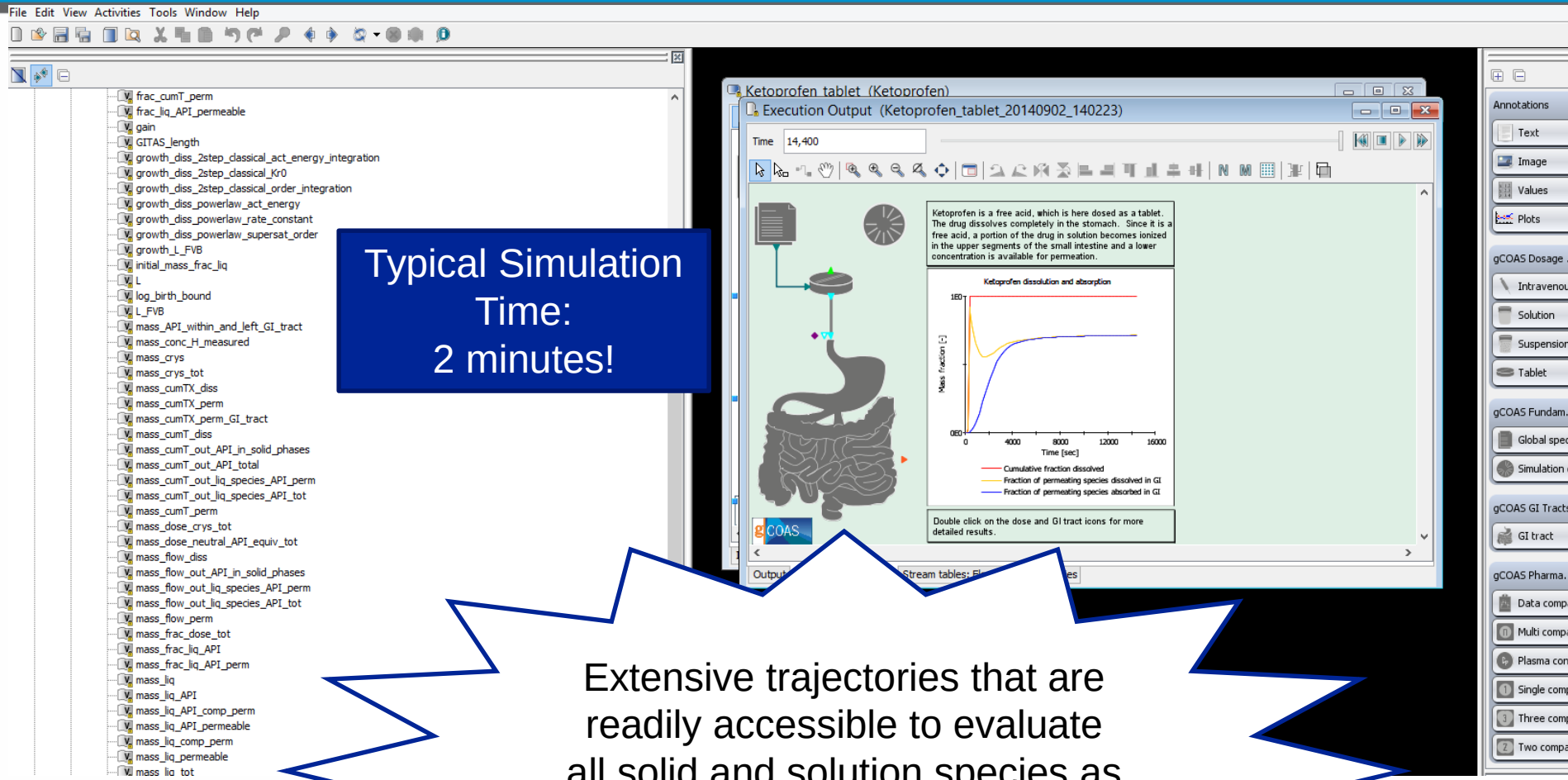
gCOAS: Created As Bottom Up Approach

- **Features include:**
  6. Selection of **permeable species** (ionized vs. unionized) in solution
     - Enables the evaluation of relative contributions of unionized and ionized forms of drug to the permeation and fraction dose absorbed
  7. The GI tract is modeled based on anatomical segments including **fluid movement kinetics** (water secretion and absorption)
     - Enables evaluation of drug dissolution, precipitation and absorption in a dynamically changing environment
  8. Incorporates a **standard feeding paradigm**
     - Enables the evaluation of partially fed state (in between meals) on oral absorption of drugs and provides ability to evaluate difference in oral absorption of doses administered at different times during the day

Features Highlighted in Presentation

- **Features include:**
  1. **Mass balances** of drug species including **zwitterions** (ionic, non-ionic and micellar) and **physiological ions** in solution in the gastrointestinal (GI) tract
  2. Drug dissolution is modeled incorporating **surface pH of solids**, changes in pH of GI tract, and speciation of drug in solution, including solubilization of various drug species into bile micelles.
  3. **Kinetic co-existence** of more than one solid form in the GI tract
  4. **Nucleation and crystal growth kinetics** include calculating the supersaturation with respect to the relevant species forming the solid phase
  5. **A population balance approach** is used to represent the particle size distribution of each solid phase either present in the drug product or formed during transit through the GI tract
  6. Selection of **permeable species** (ionized vs. neutral) in solution
  7. The GI tract is modeled based on anatomical segments including **fluid movement kinetics** (water secretion and absorption)
  8. Incorporates a **standard feeding paradigm**

gCOAS Interface



Typical Simulation Time:
2 minutes!

Extensive trajectories that are readily accessible to evaluate all solid and solution species as a function of time and position in GI tract

Case Study – Example to Illustrate gCOAS Influence on Risk Assessments

- Model Weak Base
  - MW: 386 g/mol
  - Log P: 3.5
  - pKa: 4.8
  - Intrinsic solubility: 0.2 µg/mL
  - Cl^- ion K_{sp}: $5x10^{-8}$ M^2
  - High Permeability:
    - Caco-2: 13.6 x 10^{-6} cm/sec
  - Dose: 5 mg free base
  - Particle size: 7 µm average
  - Permeating species: neutral form in solution (unionized)

- Low K_{sp}, may expect limitations on stomach solubility, Cl salt precipitation
- Solubility as a function of pH may influence
  - Precipitation of free base
  - Dissolution of solid phases
- Absorption likely to be limited by solubility/dissolution, not permeability

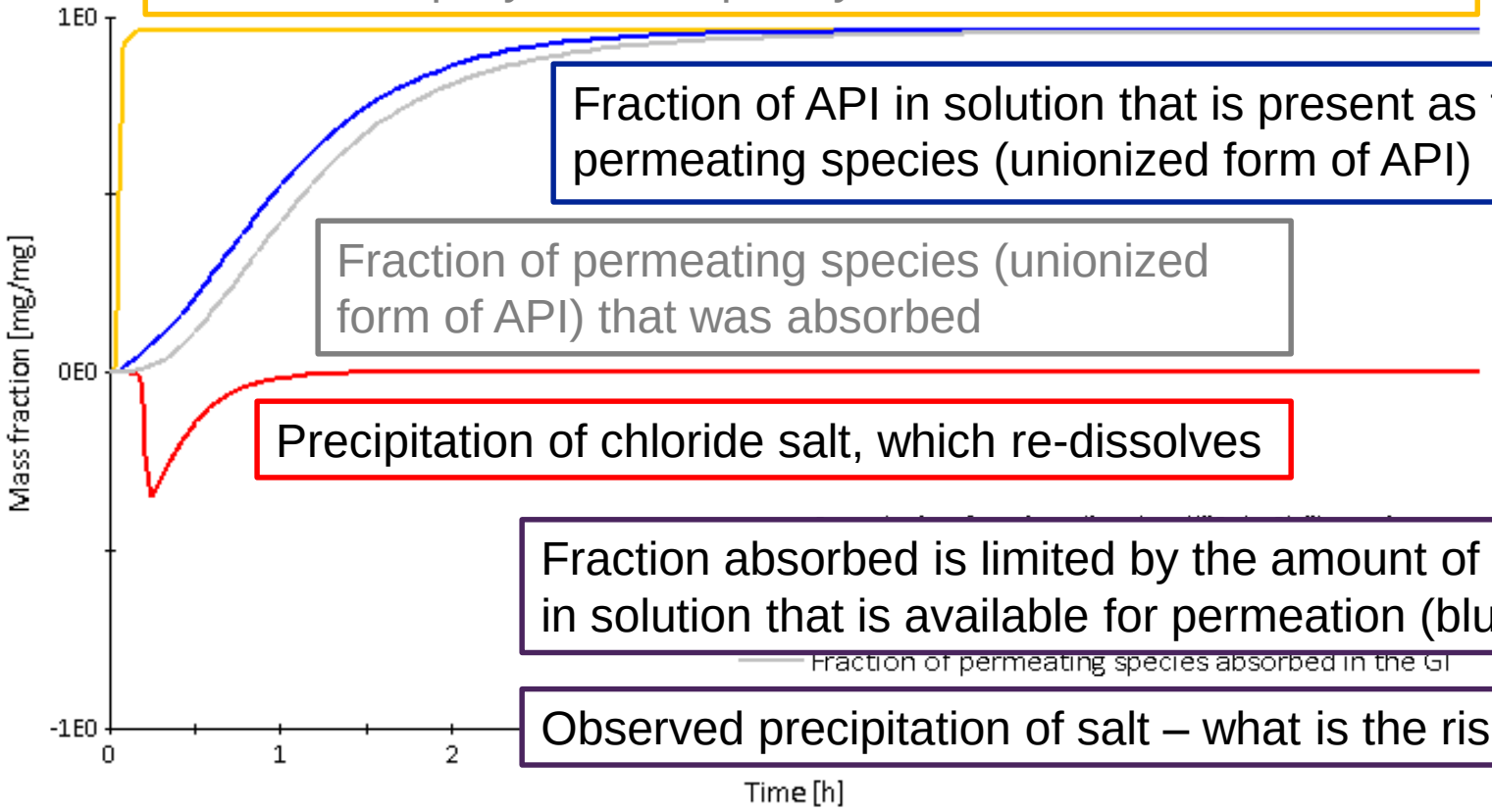
- **<u>What factors are most likely to influence the fraction absorbed?</u>**
  - Simulate, varying parameters to understand the risks to biopharmaceutic performance

Simulation Results: Absorption - Fasted GI Physiology

Fraction Dissolved = 0.96
Fraction Absorbed = 0.96

Dosed as free base, Fasted

Free base rapidly and completely dissolves in fasted stomach



Fraction of API in solution that is present as the permeating species (unionized form of API)

Fraction of permeating species (unionized form of API) that was absorbed

Precipitation of chloride salt, which re-dissolves

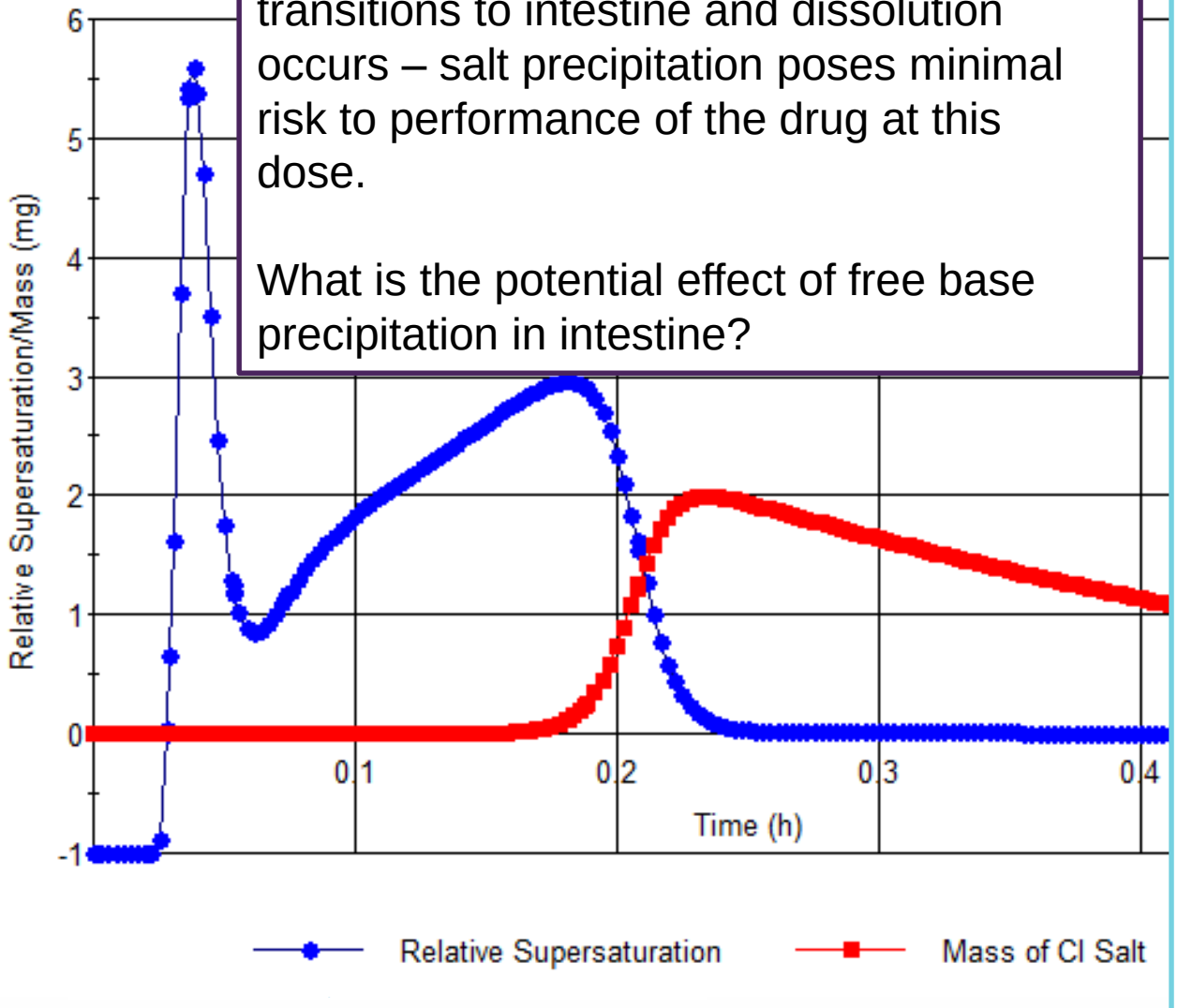
Fraction absorbed is limited by the amount of neutral API in solution that is available for permeation (blue curve).

Observed precipitation of salt – what is the risk?

Salt Precipitation Influenced by Ksp

After precipitation in stomach, salt transitions to intestine and dissolution occurs – salt precipitation poses minimal risk to performance of the drug at this dose.

What is the potential effect of free base precipitation in intestine?



In stomach, free base dissolves and converts from the unionized species to the ionized species in solution.

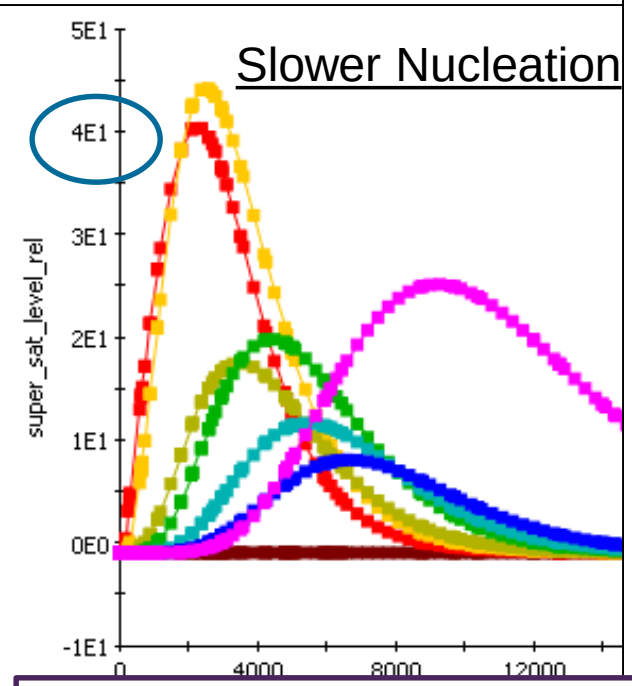
This creates a supersaturated solution relative to the solubility of the salt (Ksp with Cl ions present in stomach), which varies as water is ingested and HCl is secreted by the stomach.

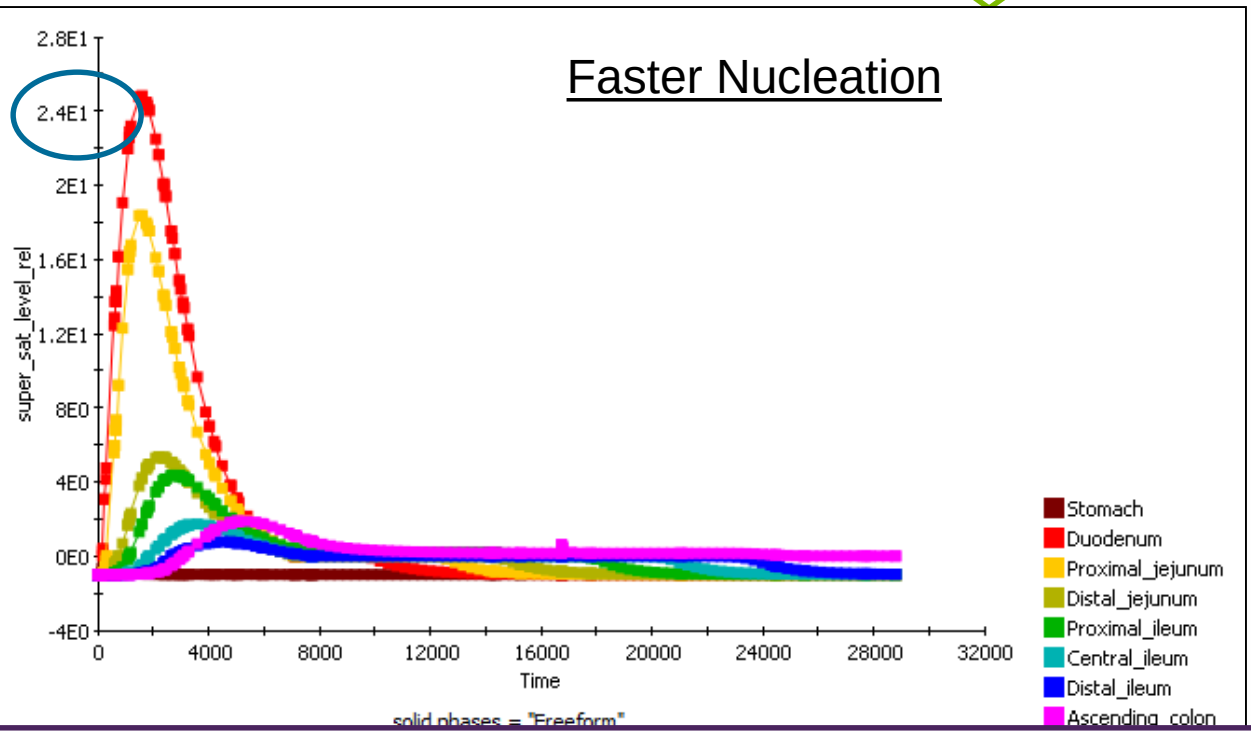
Supersaturation leads to nucleation of the salt and crystal growth, reducing supersaturation of Cl salt to 0

Scenario: Will increase in nucleation rate influence Fa?

Dosed as free base, Fasted, Fast nucleation

Fraction Dissolved = 0.34
Fraction Absorbed = 0.34



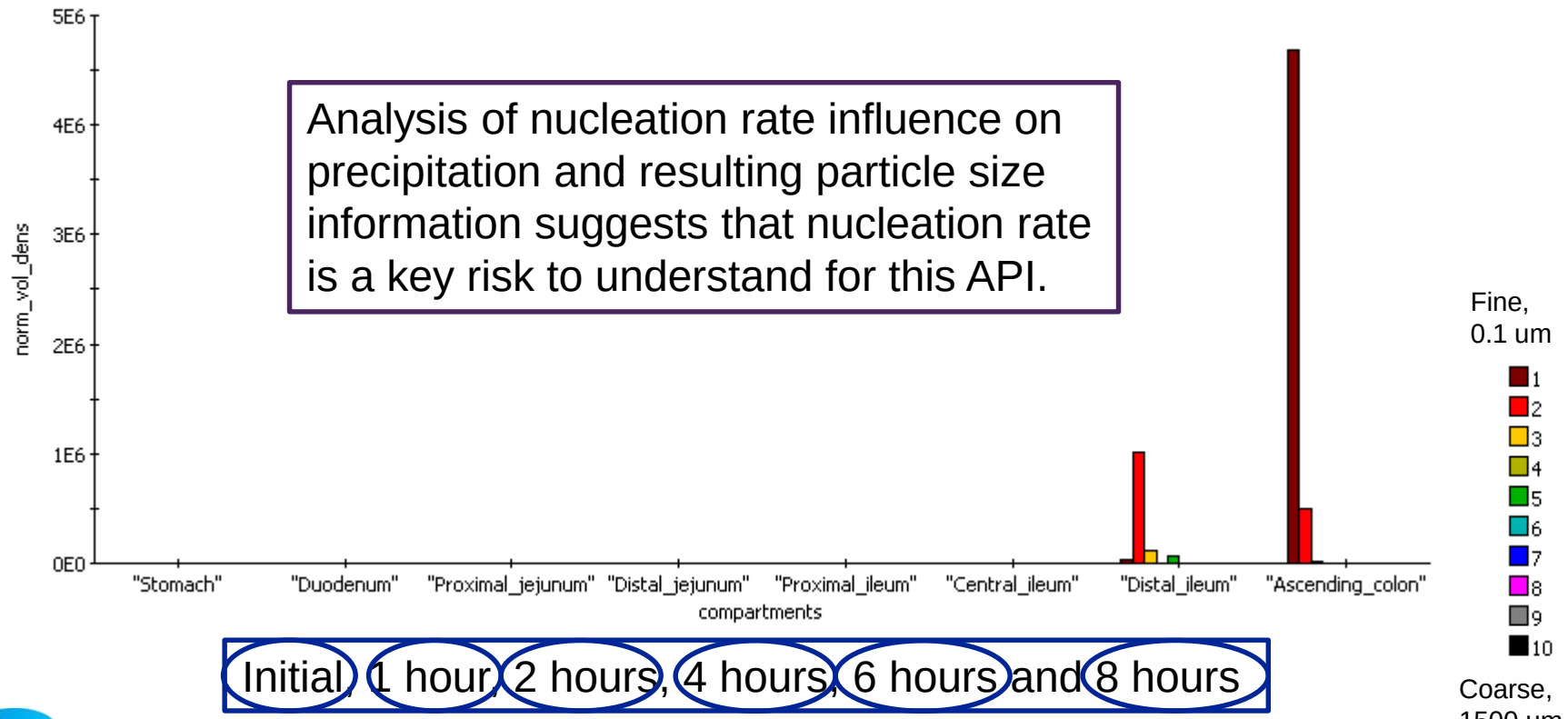


Slower nucleation rates attain higher levels of supersaturation in the intestine for a longer duration, leading to more drug absorbed.
Re-dissolution of precipitated free base is limited by the low solubility of the free form.

gCOAS can resolve the particle size changes upon precipitation to understand how this impacts particle re-dissolution.

Particle Size Changes Upon Precipitation and Growth

Particles of free base dissolve in the stomach, creating supersaturation of the neutral API as the stomach contents enter the intestine and the pH shifts, resulting in precipitation of free base. As the particles move down the GI, re-dissolution of the particles occurs as API is absorbed.



Analysis of nucleation rate influence on precipitation and resulting particle size information suggests that nucleation rate is a key risk to understand for this API.

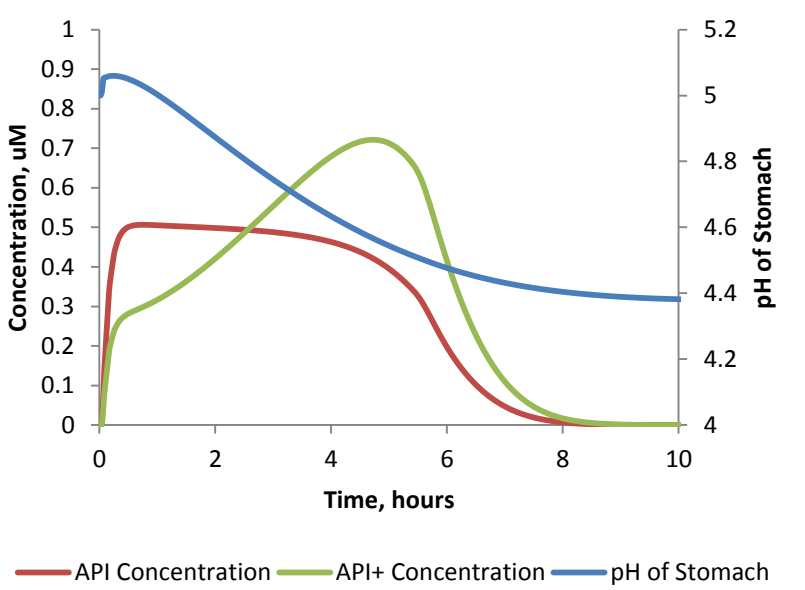
Initial, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours

Fed State: Impact of Stomach pH on Dissolution

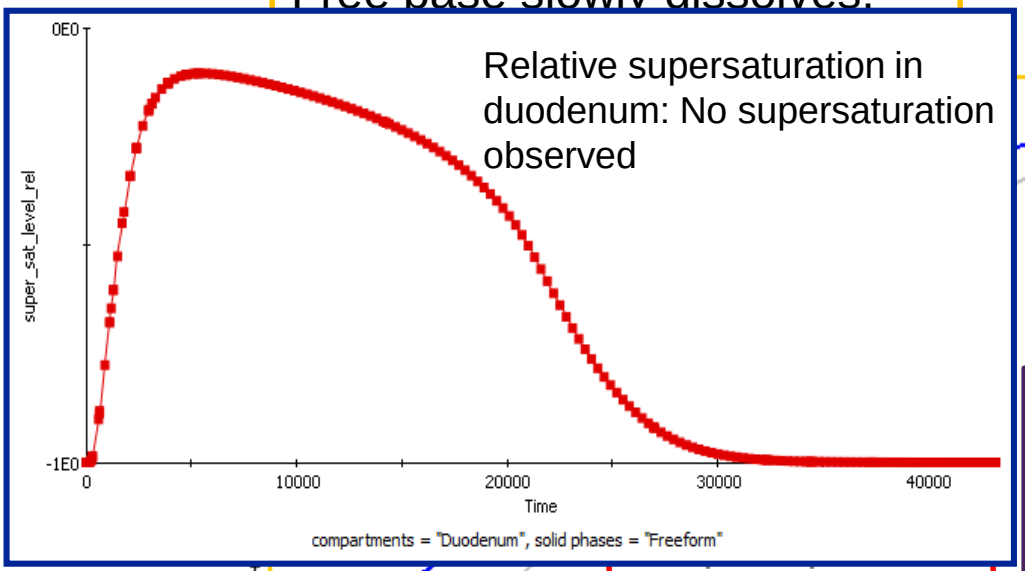
Fraction Dissolved = 0.20
Fraction Absorbed = 0.19

Dosed as free base, Fed

Dissolution of API is limited by the solubility of the API in high pH of the fed stomach



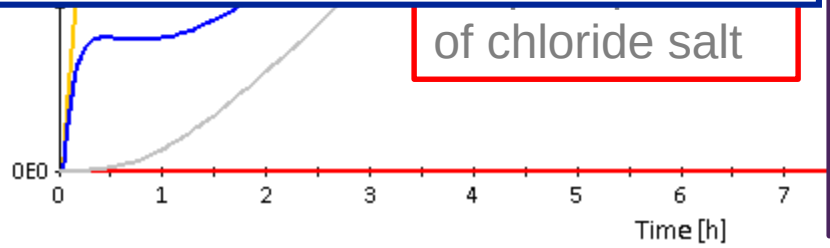
Free base slowly dissolves:



Relative supersaturation in duodenum: No supersaturation observed

Neutral form of API (permeating species) is absorbed throughout the GI

of chloride salt



Solubility in stomach limits the supersaturation in the intestine, leaving much of the drug undissolved as it enters the intestine. Despite higher bile concentrations in the fed state, less API is dissolved and absorbed; potential risk for negative food effect.

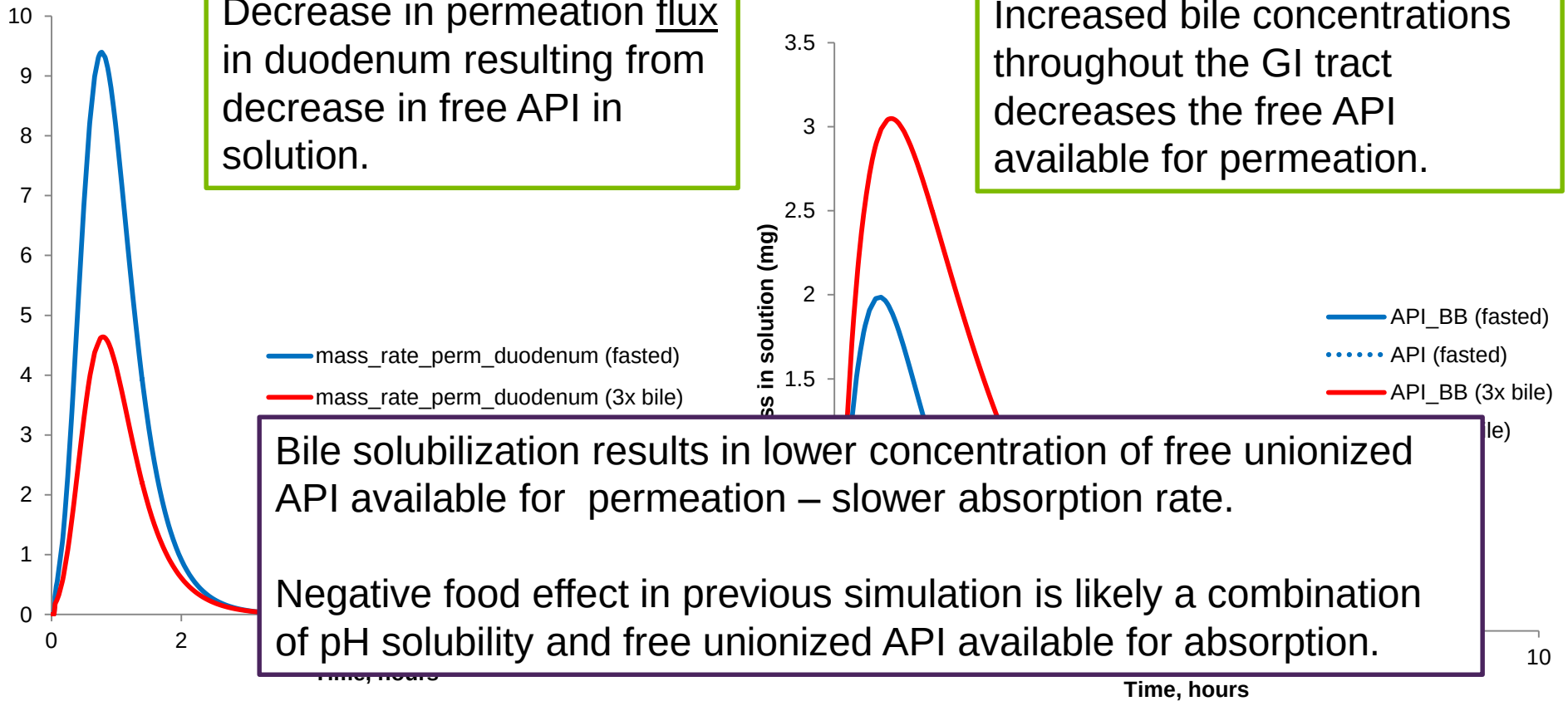
Impact of Bile Solubilization

Dosed as free base, Fasted, 3x Bile

Fraction Dissolved = 0.96
Fraction Absorbed (fasted) = 0.96
Fraction Absorbed (3x Bile) = 0.96

Decrease in permeation flux in duodenum resulting from decrease in free API in solution.

Increased bile concentrations throughout the GI tract decreases the free API available for permeation.



Bile solubilization results in lower concentration of free unionized API available for permeation – slower absorption rate.

Negative food effect in previous simulation is likely a combination of pH solubility and free unionized API available for absorption.

Summary of Biopharm Risk Management Strategy for Model Weak Base from gCOAS Simulations

Evaluated Risk Factor	gCOAS Evaluation Summary	Exposure Risk	Mitigation Strategy
Limited Cl- Salt Solubility (Ksp)	Absorption was not found to be influenced by salt precipitation or dissolution	Minimal	N/A
pH solubility resulting in precipitation of free form	Rapid precipitation of a free form could result in poor absorption, depending on kinetics of precipitation	Potential Risk	1) *In vitro* experimentation to estimate precipitation kinetics 2) Clinical study to estimate the *in vivo* precipitation
pH solubility limiting dissolution	pH solubility was shown to limit dissolution of the free base API in fed state	Potential Risk – with high stomach pH (fed, PPI)	Evaluate food effect using two different formulations - with and without solubilization technique - to mitigate risk of potential negative food effect
Solubility Limited Dissolution	Solubility of free form was found to limit fraction absorbed Amount absorbed is sensitive to free fraction of permeating species in solution	Potential Risk	Investigation of nanoparticle formulation or other formulation solubilization techniques for increase of solubility

gCOAS Summary

- Successfully developed a bottoms up approach for simulation of oral absorption incorporating basic physics, chemistry and physiology
- gCOAS is a powerful tool for Formulation Scientists
  - Diagnostic tool for identifying risk factors contributing to poor or incomplete absorption
    - Enables collaboration with Medicinal Chemists, Drug Metabolism & Pharmcokinetists, Clinical Pharmacologists and Clinical Researchers to efficiently deliver a new medicine to patients!
  - Assessment of risk mitigation strategies
  - Guidance for experimentation and clinical study design – increased efficiency!

Future Opportunities and Plans for gCOAS

- Incorporation of physics of solubilization technologies for improving oral bioavailability of insoluble drugs
- Improvement of permeation, including determination of ionized species permeation via transcellular diffusion with electrical potential.
- Creation of libraries of (a) physiology and (b) drug properties to enable sharing of data and for enhancing knowledge management
- Integration into Systems Based Pharmaceutics (SbP) Framework
- Incorporation of parameter estimation and global sensitivity analysis

Thank you for your Attention

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