A Predictive Oral Absorption Tool for Formulators: A New and Key Element for Realization of the Systems-based Pharmaceutics Approach

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Pfizer
WORLDWIDE RESEARCH & DEVELOPMENT
PharmaTherapeutics Pharmaceutical Sciences

Acknowledgement

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- PSE – excellence in partnership
- Drug Product Design Department (Pfizer) – believing that we are heading in the right direction
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- Kazuko Sagawa (Pfizer, USA) – unparalleled support & effort
- Literature – insights as well as misrepresentation of modeling (fitting) by researchers near and far

Contextual Framework of Modeling in Biopharmaceutics

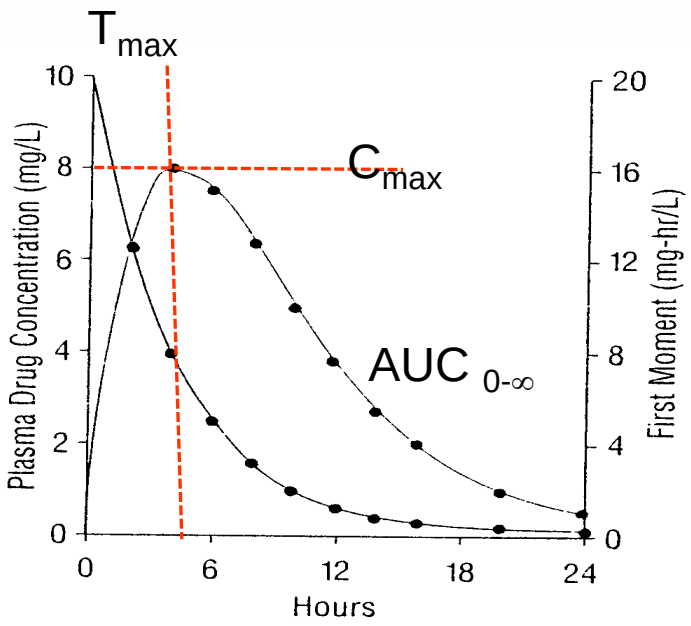
- Progressively Advance Computational Tools along with Unprecedented Partnerships to Accomplish
  - Predictive Oral Absorption: Identify Risk Factors and Overcome Liabilities through Superior Molecular Design and Formulation Composition
  - Predictive Control of PK: Achieve Desired PK-PD through Superior Drug Product Design
- Serve the Patient's Needs & Bring Valuable Differentiated Drug Products to the Market

Outline

1. A few definitions and fundamental concepts
2. Framework for development of gCOAS
3. Incorporation of physiology and physics into gCOAS
4. Illustrative example of gCOAS simulation
5. Future plans for gCOAS and beyond
6. Conclusions

Biopharmaceutics: Definition & Concepts

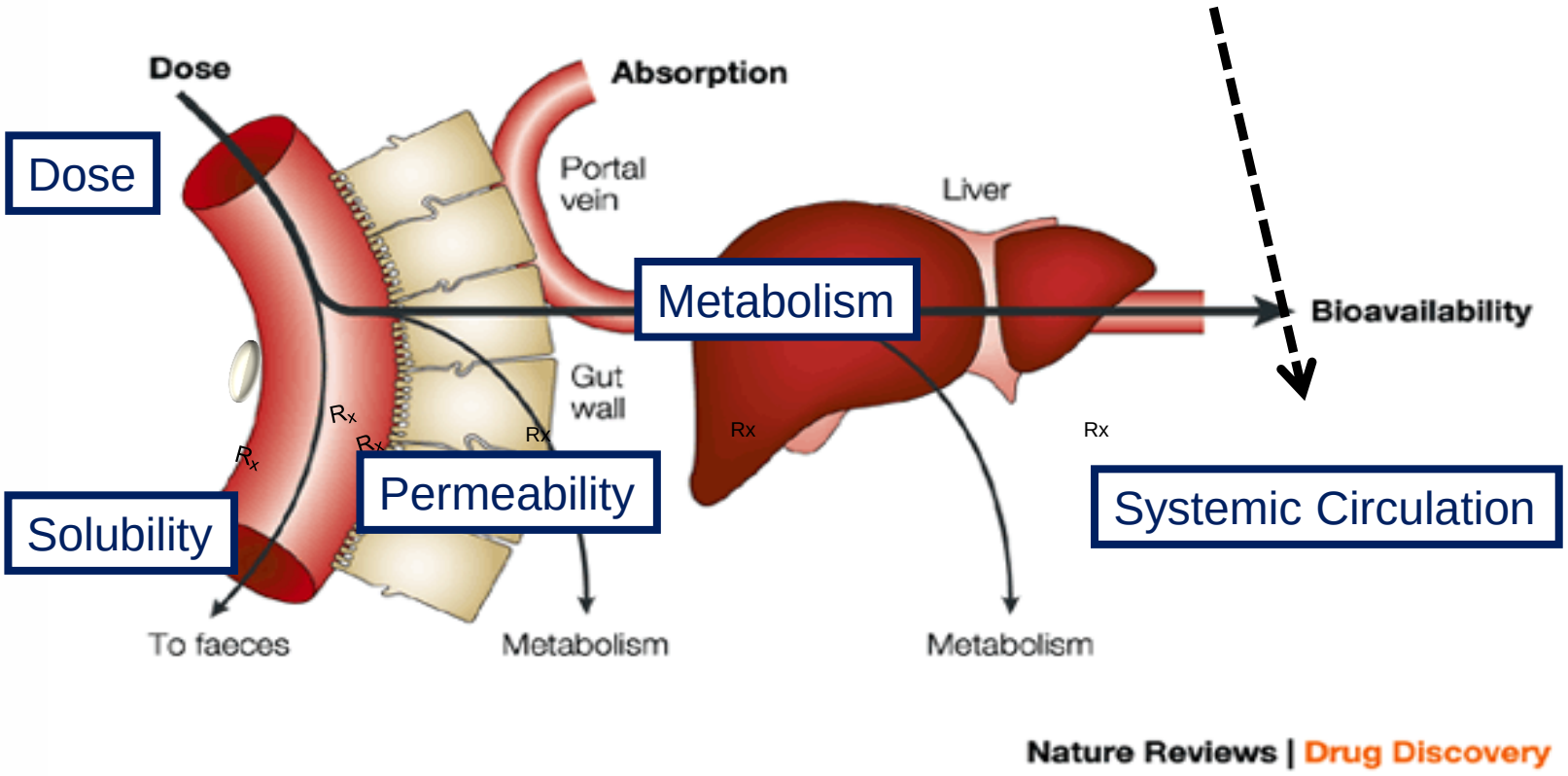
- Study of the physical and chemical properties of a drug and its dosage form as related to the onset, duration and intensity of its action



- onset, intensity and duration of action

Oral Bioavailability

- Bioavailability: the extent to which the dose reaches systemic circulation



Regulatory definition of Bioavailability (BA) and Bioequivalence (BE) - Abbreviated

- ***Bioavailability*** is defined in § 320.1 as: the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
  - For drug products that are not intended to be absorbed into the bloodstream, bioavailability reflects the rate and extent to which the active ingredient or active moiety becomes available at the site of action
- ***Bioequivalence*** is defined in § 320.1 as: the absence of a significant difference in the rate and extent when administered at the same molar dose under similar conditions

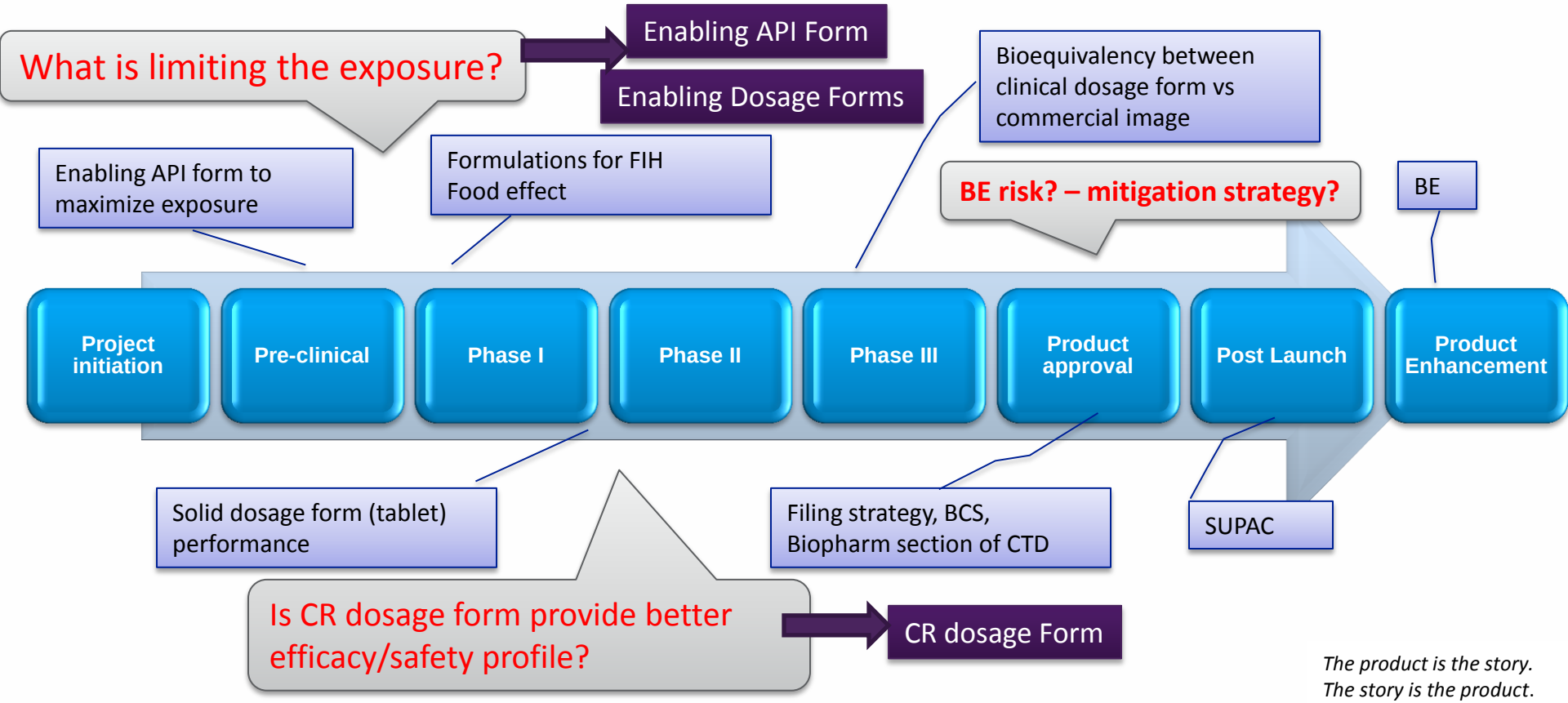
- **Two dosage forms are bioequivalent (BE) when the 90% confidence interval of the ratio (Test/Reference) of Cmax and AUC is within the range of 80.0 – 125.0% (BE limits)**

Bioavailability ≠ Bioequivalence

- Bioequivalence can be demonstrated for any two similar products irrespective of their absolute oral bioavailability
- Bioequivalent dosage forms have same bioavailability
- Two formulations having same bioavailability need not be bioequivalent
  - Bioequivalence requires both Cmax and AUC similarity
  - Bioavailability is an assessment of fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug
- Biopharmaceutics deals with both bioavailability and bioequivalence (degree of regulatory elements beyond science!)

Biopharmaceutics Modeling is a part of Biopharmaceutics Risk Assessment

- Provide an overview of a simple, integrated, science based, milestone as well as drug and drug product property change driven biopharmaceutics risk assessment for the portfolio



The product is the story.
The story is the product.

Oral Dosage Form Performance

Strategies to Address Low Drug Solubility in Discovery and Development

Hywel D. Williams, Natalie L. Trevaskis, Susan A. Charman, Ravi M. Shanker, William N. Charman, Colin W. Pouton, and Christopher J. H. Porter

http://dx.doi.org/10.1124/pr.112.005660
Pharmacol Rev 65:315–499, January 2013

Pharmacokinetic Measurement

Pharmacodynamics Measurement

Absorption

Distribution

Excretion

Dosage Form

Drug in Solution

Gut Wall

Blood/ Plasma

Site of Action

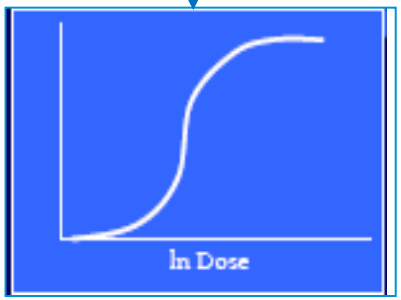
Therapeutic Effect

Dissolution

Permeability

Metabolism

Solubility, Particle size, ionization, bile-salt micelles etc



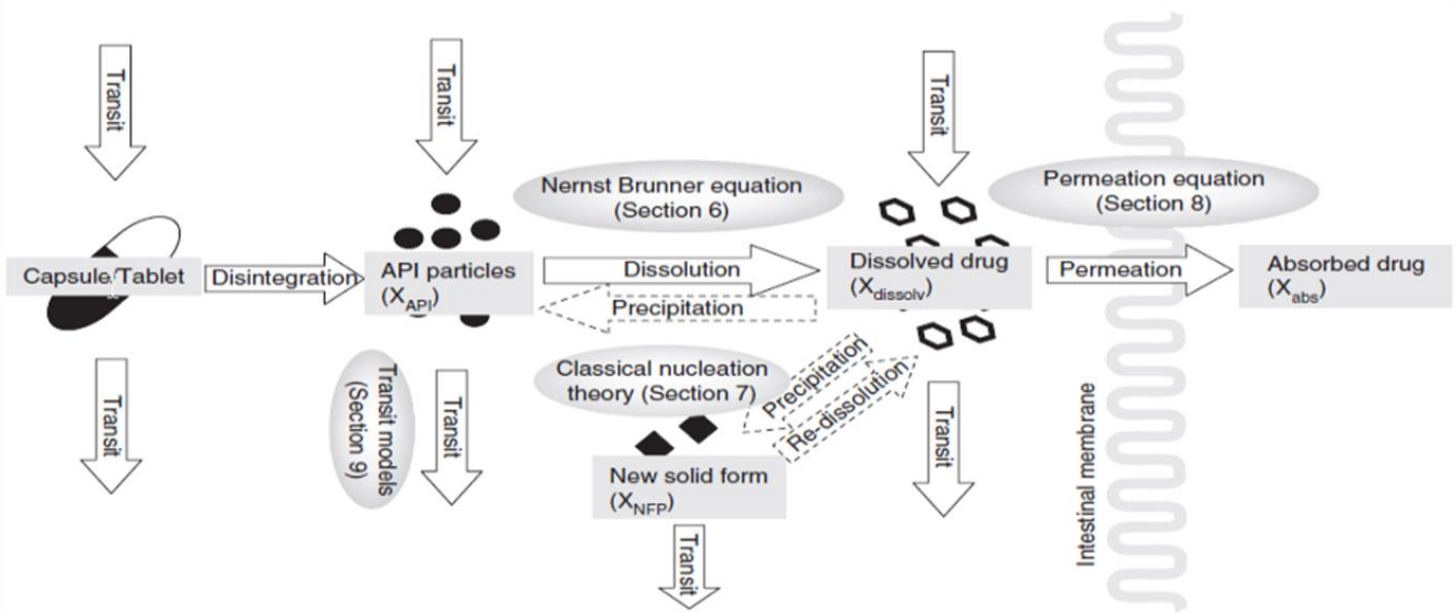
Focus for developing the Pfizer-PSE simulation tool (gCOAS) is ORAL ABSORPTION and not PK prediction.

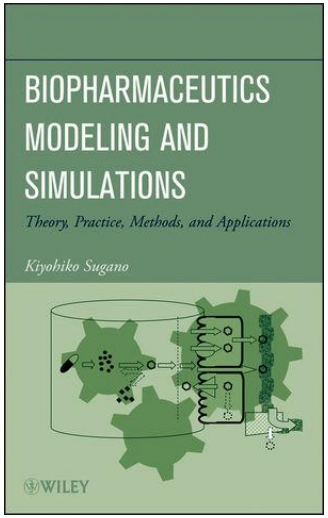
gCOAS Framework
(Computational Oral Absorption Simulation)

BioPfarm-X-treme ver.2.1 *

- Inspired by Sugano framework

K. Sugano, *Expert Opin. Drug Metab. Toxicol.* (2009) **5**(3), pp. 259-293





- Framework populated with models from various sources
  - typically no consensus regarding the right/best model for a phenomenon
- Open model architecture allows users to add/modify models for phenomena

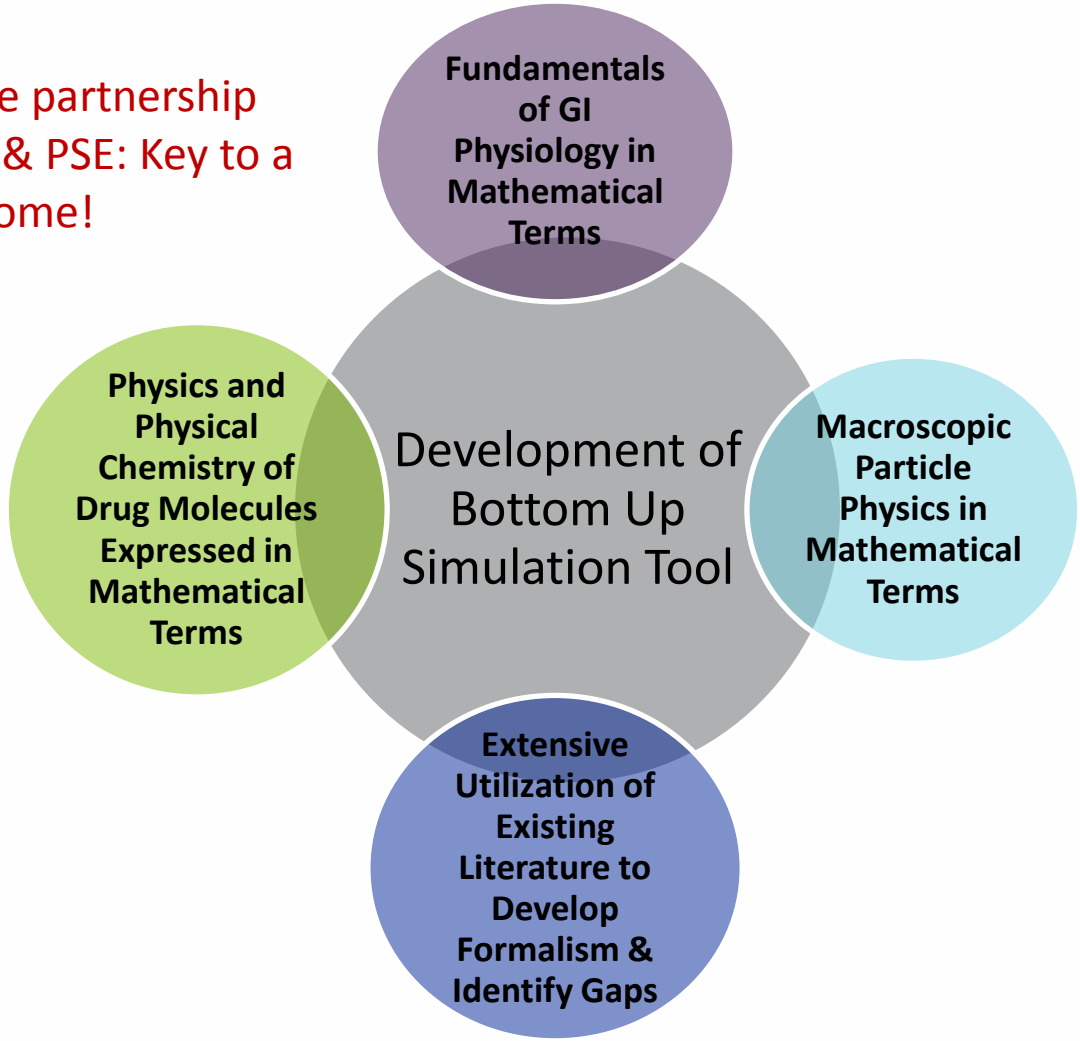
* An Excel program for oral absorption
- Unwieldy, unmanageable and unstable!

gCOAS: Created As Bottom Up Approach

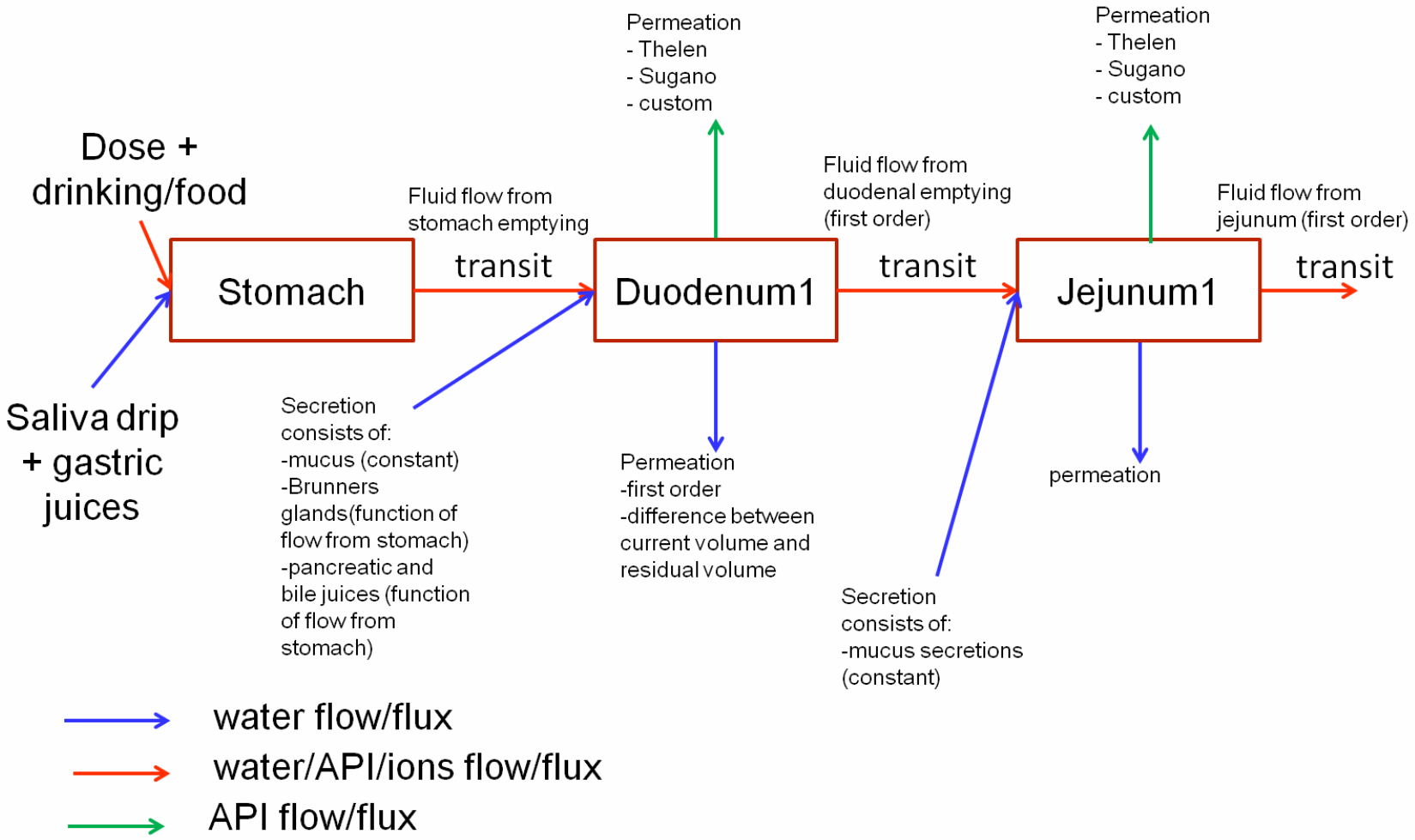
- **gCOAS model has several advanced features for simulating oral absorption. Features include;**
  1. **Mass and charge balances** of drug species (ionic, non-ionic and micellar) and physiological ions in solution in the gastrointestinal (GI) tract
  2. Drug dissolution is modeled incorporating **surface 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. **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
  4. **Nucleation and crystal growth kinetics** include calculating the supersaturation with respect to the relevant species forming the solid phase
  5. The GI tract is modeled based on anatomical segments including **fluid movement kinetics**.

gCOAS: Creation of the bottom up framework

Strong and close partnership between Pfizer & PSE: Key to a successful outcome!



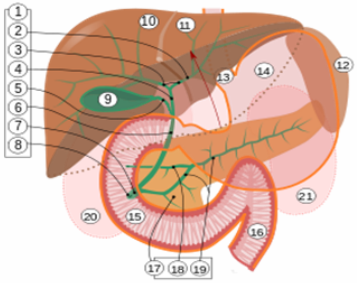
GI Transit Anatomical Segments (GITAS) Model



Physiological Dimensions

	Stomach	Duodenum	Jejunum		Ileum			Cecum (http://www.theodora.com/anatomy/the_large_intestine.html)
			J1	J2	I1	I2	I3	
Radius (cm)*		1.7	1.6	1.5	1.4	1.3	1.2	3.125
Length (cm)**		21 (18-26)	52.5	52.5	52	52	52	7.5
Surface Area (smooth tube) (cm^2)		242	528	495	408	368	327	59

*Interpolated from Thelen 2012 **Taken from Sugano book, pp. 161



1. D1: The first (superior) part begins as a continuation of the duodenal end of the pylorus. From here it passes laterally (right), superiorly and posteriorly, for approximately 5 cm, before making a sharp curve inferiorly into the superior duodenal flexure (the end of the superior part).
2. The second (descending) part of the duodenum begins at the superior duodenal flexure. It passes inferiorly to the lower border of vertebral body L3, before making a sharp turn medially into the inferior duodenal flexure (the end of the descending part).
3. The third (inferior/horizontal) part of the duodenum begins at the inferior duodenal flexure and passes transversely to the left, crossing the right ureter, right testicular/ovarian vessels, inferior vena cava, abdominal aorta, superior mesenteric artery and the vertebral column.
4. The fourth (ascending) part passes superiorly, either anterior to, or to the left of, the aorta, until it reaches the inferior border of the body of the pancreas. Then, it curves anteriorly and terminates at the duodenojejunal flexure where it joins the jejunum. The duodenojejunal flexure is surrounded by a peritoneal fold containing muscle fibres: the ligament of Treitz.

Intestinal Volumes

	Duodenum	Jejunum		Ileum			Cecum (http://www.theodora.com/anatomy/the_large_intestine.html)
		J1	J2	I1	I2	I3	
Volume (fully distended) (cm^3)	179	396	347	298	255	216	22
Calculated Fluid Volume[1] (cm^3)	11.1	24.6	21.5	18.5	15.8	13.4	5

1. Fluid volume calculated based on SI(not including Cecum) total fluid volume of 105mL. Fluid volume then distributed as percentage of total smooth tube volume calculated from physiological dimensions based on cut cone GITAS.

Stomach Emptying and Small Intestine Transit

- First Order Emptying
  - $V = V_{init} + \phi_{v,in} \cdot t - \phi_{v,out} \cdot t$
  - $k = -\frac{\ln(\frac{V_{min}}{V_{init}})}{t_{final}}$
    - V_{min} = residual volume (from physiology/custom)
    - $V_{init} = V_{dose} + V_{min}$
    - V_{dose} comes from dose model
    - t_{final} = emptying time (from physiology/custom)
    - $\phi_{v,in}$ = volume flow of secretions
    - $\phi_{v,out}$ = volume flow of fluid out of segment
  - $\frac{dV}{dt} = -kV + \phi_{v,in}$

- Small intestine
  - Duodenum, Jejunum, Ileum
    - Will make easily adjustable number of GITAS
    - Residence times same for fed and fasted states (~3.5hrs)
  - Water permeation in each GITAS will be defined as:
    - Percentage of time averaged total permeation rate for small intestines
    - Permeation constant, k_p
  - Water can secrete in all GITAS
    - Water secretion in first intestinal GITAS (duodenum) influenced by stomach emptying
    - Subsequent compartments secretions consist of mucus
  - Bile and pancreatic juices secrete into first intestinal GITAS
    - Desire pulsed secretion
    - Bile dies in Ileum GITAS

User can choose transit volumes in intestine
- Varying volume option
- Constant volume option

Drug Mass and Charge Balance

gCOAS mass and charge balances of drug species (ionic, non-ionic and micellar) and physiological ions in solution in the gastrointestinal (GI) tract

Drug [BHX]

Illustrative Example: Salt Form of Basic Drug

$$K_{sp} = [BH^+][X^-]$$

$$[BH^+] = [B] + [H^+]$$

Kinetically up to three solid phases may coexist
e.g. For basic drug: **[BHX], [BH⁺], [B]**
At any point in time, one phase may be dissolving whilst another may be precipitating simultaneously

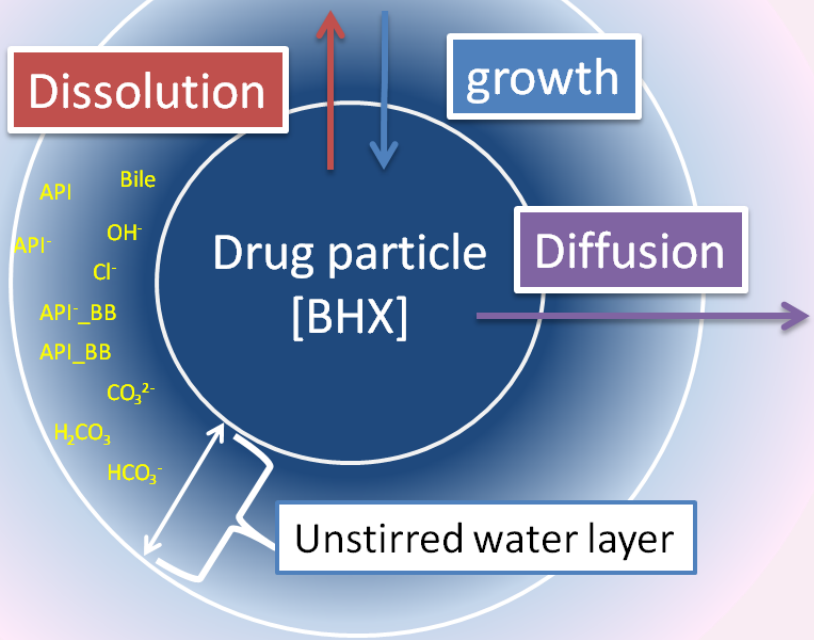
Counter ion effect
With physiological ions

physiological ions in GI tract

Cl^-, H^+, $HCO3^-$, $CO3^{2-}$, OH^-, Na^+, Bile

Only unionized form [**B**] will permeate (absorbed)

Particle Dissolution



Species in liquid phase:

API; API^-; API_BB; API^-_BB; Bile; H_2O; H^+; OH^-; H_2CO_3; HCO_3^-; CO_3^{2-}; Na^+; Cl^-

Liquid bulk

BHX, BH^{+-}, B,

Bile, H_2O, H^+, OH^-,

H_2CO_3,

HCO_3^-, CO_3^{2-}, Na^+,

Cl^-

Physiological ions and bile in the GI fluid

Solid Liquid Interface to Bulk Solution

- The phenomena occurring at the solid-liquid interface are linked to the bulk:
  - The flux of diffusion of each species $\emptyset''_{diff}$ is part of the mass balance to the bulk of the liquid phase:

Flux of diffusion

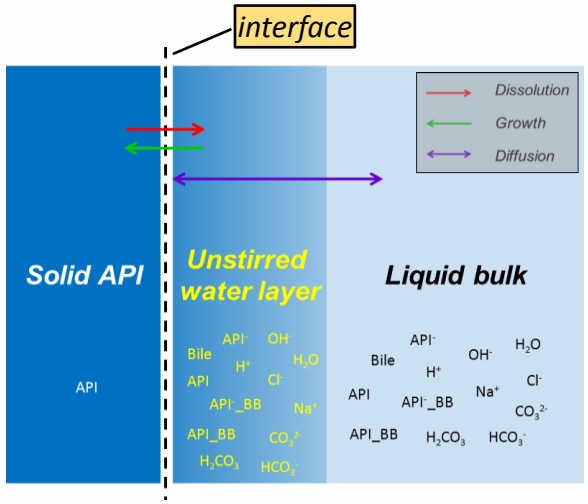
$$\frac{\partial(C^b.V)}{\partial t} = \emptyset'_{in} - \emptyset'_{out} + \sum_{j}^{NSP}\left(\emptyset''_{diff,j}\cdot SA_j\right) + \sum_{r}^{NR}(\emptyset'_{reac,r}) - \sum_{j}^{NSP}\left(\emptyset'_{birth,j}\right) - \emptyset'_{perm}$$

Variable	Units	Description
V	m^3	Fluid volume
C^b	mol/m^3	Molar concentration in the liquid bulk
$\emptyset'_{in}$	mol/s	Inlet molar flowrate
$\emptyset'_{out}$	mol/s	Outlet molar flowrate
SA_j	-	Surface area of solid phase j
$\emptyset'_{reac,r}$	mol/s	Term that accounts for liquid bulk reactions
$\emptyset'_{birth,j}$	mol/s	Term that accounts for birth of particles
$\emptyset'_{perm}$	mol/s	Term that accounts for absorption

Diffusion

- The flux of diffusion of species entering/leaving each solid-liquid interface is defined as:

$$\phi''_{diff} = \frac{D}{h_{UWL}} \cdot \left(C^s - C^b\right)$$



Variable	Units	Description
ϕ''_{diff}	mol/m^2.s	Flux entering/leaving interface due to diffusion
D	m^2/s	Diffusion coefficient
h_{UWL}	m	Thickness of unstirred water layer (UWL)
C^s	mol/m^3	Molar concentration at the interface
C^b	mol/m^3	Molar concentration at the liquid bulk

Particle Size Distribution & Nucleation

- **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

$$\frac{n_j(L)V}{t} = -V\frac{n_j(L)G_j(L)}{L} + f_{V,in}n_{j,in}(L) - f_{V,out}n_{j,out}(L)$$

- **Nucleation**

  Rapid increase in the rate of nucleation after a critical level of supersaturation is exceeded in solution for the species forming the solid phase

  Classical nucleation $J_{prim} = \ln A_0\left(\frac{-16\pi(\alpha\sigma)^3 v^2{}_0}{3\kappa^3 T^3(\ln S)^2}\right)$

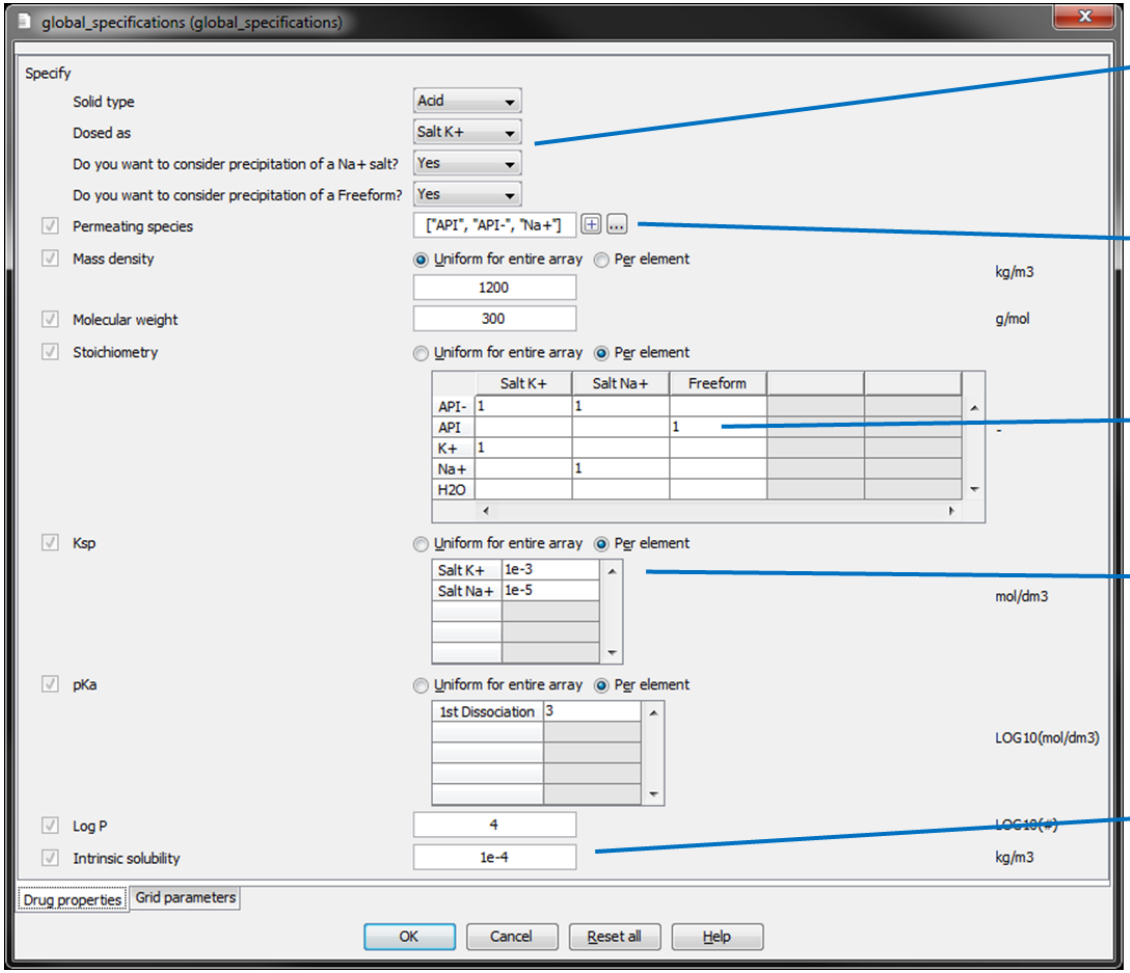
  Power law kinetics $J_{prim} = \ln k_n\left(\frac{\Delta C}{\rho_c}\right)^n \exp\left(\frac{-E_{A,n}}{RT}\right)$

  Custom kinetics (user defined option)

  E.g. using probability distribution functions of induction time

$$P(t) = 1 - \exp(jV(t - t_g))$$

Input to gCOAS: Drug Properties



Drug dosed in one form, but can precipitate as other forms

User can specify which species permeate, e.g. API in neutral form only

Stoichiometry of solid phases with respect to liquid phase species

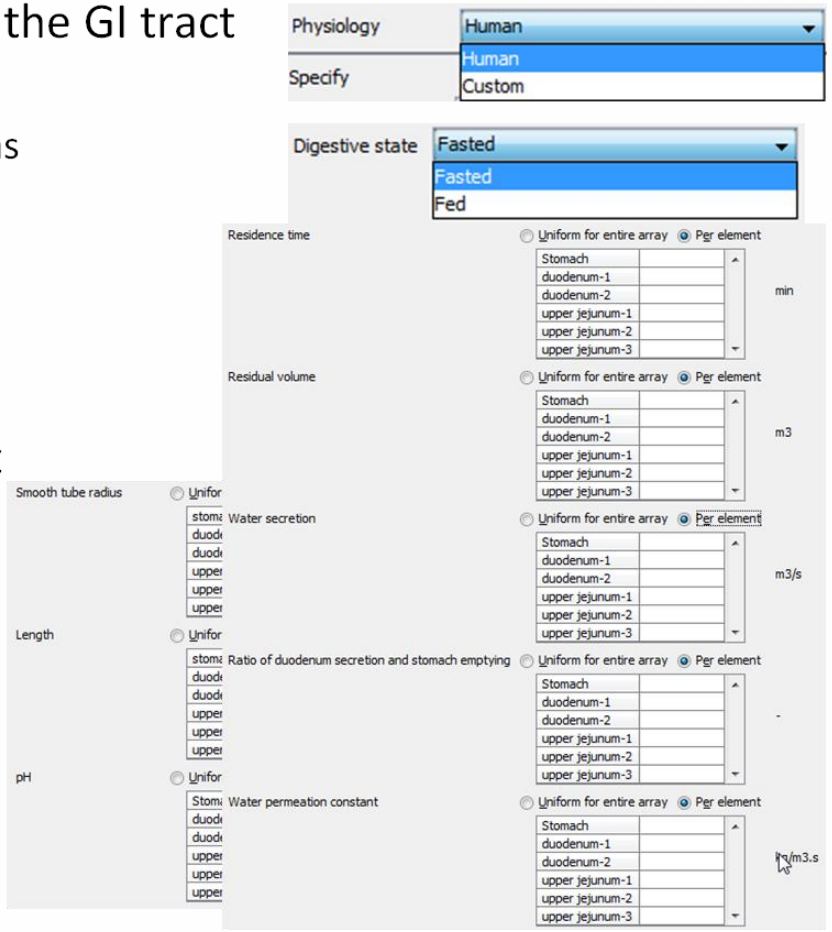
Solubility product for each salt phase

Intrinsic solubility for the freeform

Input to gCOAS: GI Tract and Physiology

- Built-in specifications for
  - physiology and segmentation of the GI tract
    - currently 'only' human
    - can be extended to other organisms
  - digestive state: fed or fasted

- Custom option allows for
  - any segmentation of the GI tract
  - complete freedom in specifying segment radii, lengths, residual volumes, pH values, bile concentration, etc.



gCOAS Developer 1.0.0 (dev)

File Edit View Activities Tools Window Help

3 library projects hidden
PSD effect width of PSD
Models
PSD_effect
Processes
Acetaminophen_Results
Original Entities
Trajectories
Execution Output
PSD_effect_20130415_
Original Entities
Trajectories
Execution Output

Projects

Execution Output (Acetaminophen_Results)

Time 10,800

Output | Topology: Flowsheet | Stream tables: Flowsheet | Properties

Execution Output (PSD_effect_20130415_222359)

Time 30,760

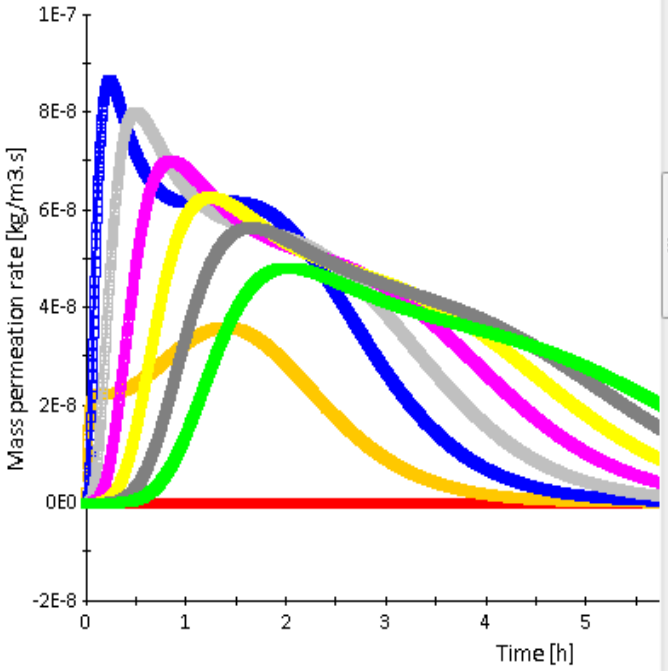
Output | Topology: Flowsheet | Stream tables: Flowsheet | Properties

PSD_effect_20130415_222359:Flowsheet.GI_tract001

Time 30,760

Select report to display: Dissolution and absorption (basic)

3. Mass rate of permeation in segment (API neutral equivalents)



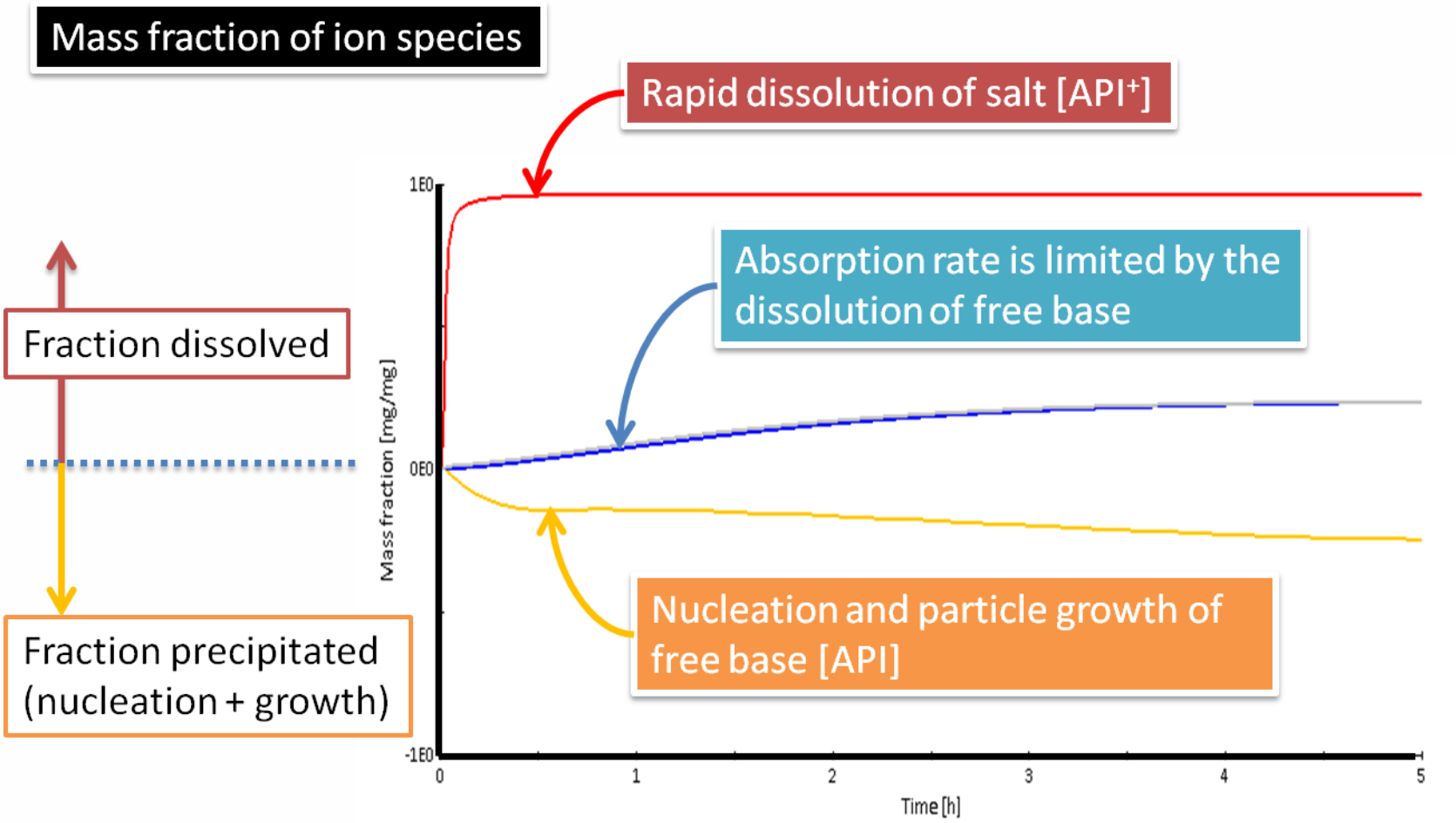
4. Cumulative fraction dissolved in segment (API neutral equivalents)

Precipitation | Initial conditions | Stream tables | Reports | Properties
Physiology | Transit | Permeation

84.6 / 91

Illustrative Results:

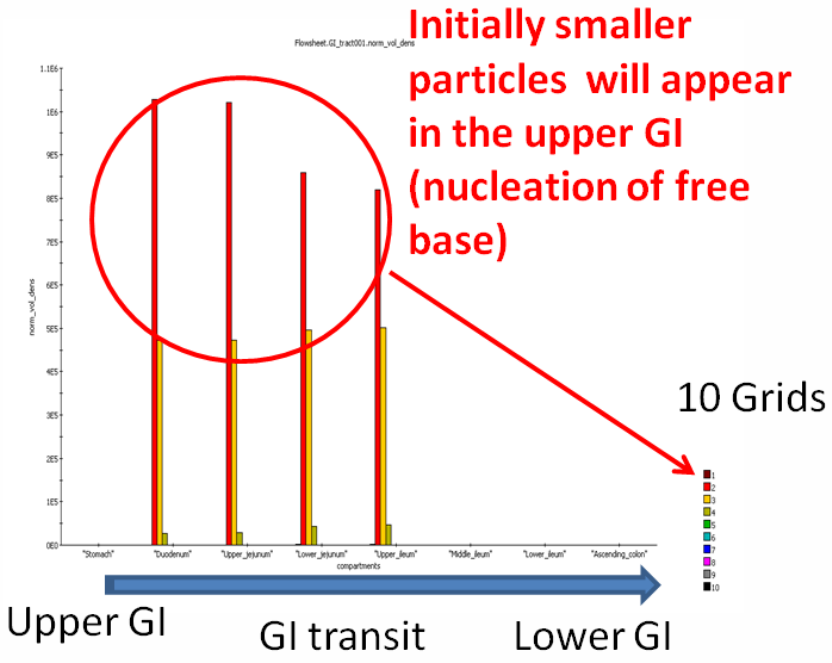
Administered as salt of a basic drug [API^+] [X^-]



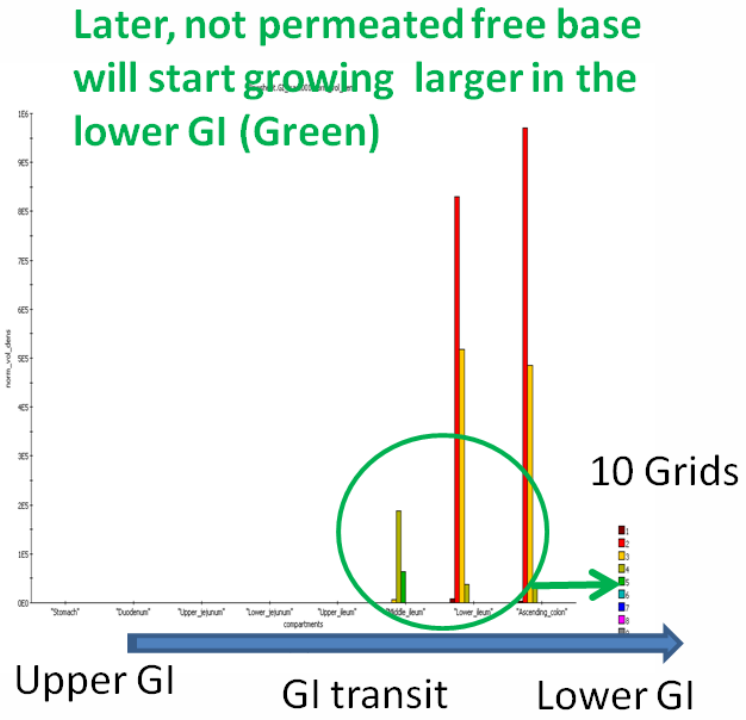
Simultaneous monitoring and visualization of multiple solid and solution species in the GI tract

Monitoring Particle Size Changes in GI Tract

15 min post dose



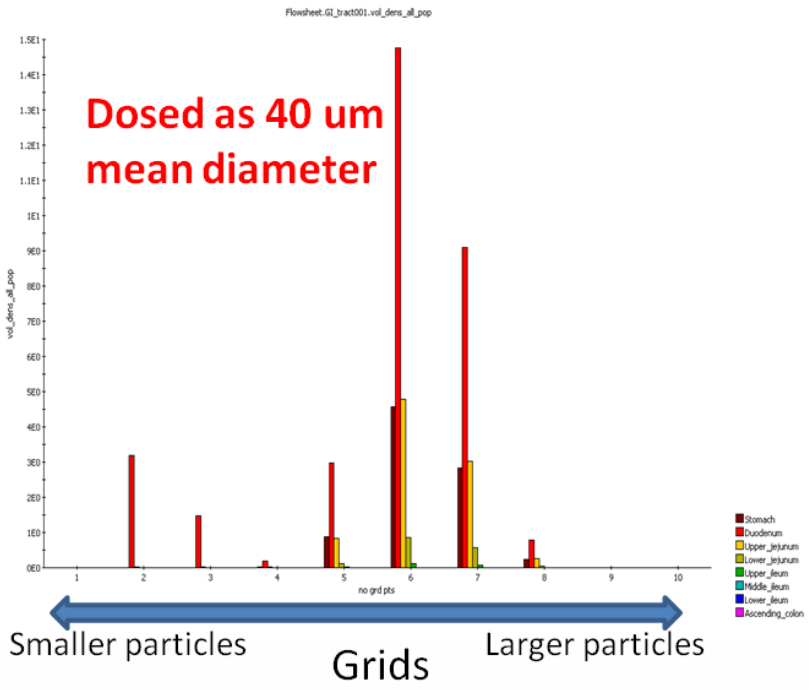
3 hr post dose



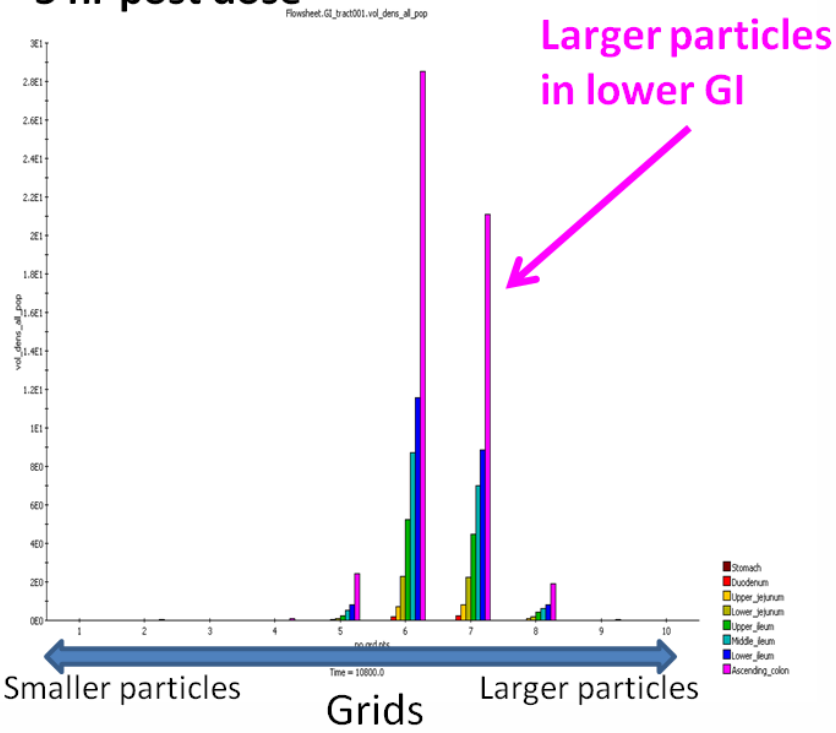
Ability to track particle size changes (dissolution and crystal growth) in all segments of GI tract

Monitoring Particle Size Changes when Administered as Insoluble Free Base

15 min post dose



3 hr post dose



Particle size changes can be monitored throughout the simulation period

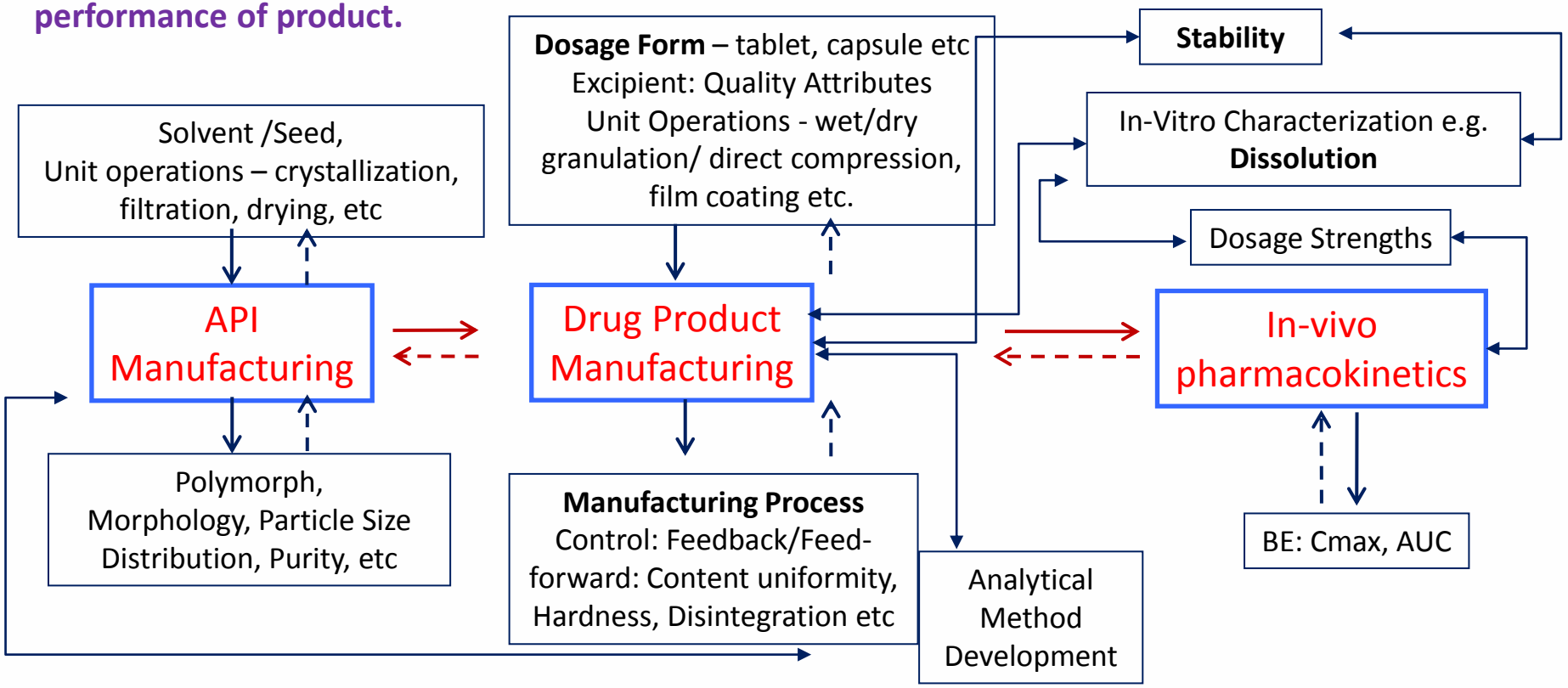
Ability to demonstrate root cause for poor or incomplete absorption: particle size and particle growth kinetics combined with low fluid volume in the GI tract. Risk Mitigation – SOLUBILIZATION and not Particle Size Reduction!

Future opportunities and plans for gCOAS

- Discussions are underway to incorporate enhancements to deliver Version 2.0
  - Proposed features include
    - Fluid dynamics with standard feeding paradigm (breakfast, lunch and dinner)
    - Permeability correction factor for active transport (including efflux)
    - Ionic equilibria of zwitterions
    - Probability of nucleation
- Future plans envisioned to incorporate physics of solubilization technologies for improving oral bioavailability of insoluble drugs

Systems based Pharmaceutics (SbP) – A Conceptual Framework in Partnership with PSE : Launched in 2014

Objective: To create an integrated and inter-connected modeling and simulation framework based on existing computational models that would provide unprecedented capability of considering the complete train of effects from synthetic crystallization to oral absorption in the design of medicines to enable assessment of local perturbations of attributes on final quality & performance of product.



Ongoing Modeling Efforts in Biopharmaceutics at Pfizer

Commercial PK Simulation Software
- Gastroplus
- Simcyp
- Pharsight/ Phoenix
  - WinNonlin
  - IVIVC Toolkit

Custom Developed Simulation Software – Oral Absorption
- gCOAS – PSE

Integrated Simulations

Consortium Based Simulation Software Under Development
- Systems Based Pharmaceutics
  - PSE
- **TSB** (Technology Strategy Board – UK): Digital Design
  - AZ, GSK, Britest and PSE
- Simcyp PBPK (physiological based PK)
  - Pharma companies, Univ. of Manchester
- **IMI** (Innovative Medicines Initiative_EU) OrBiTo
  - 5 year project (9 million euros)
  - Academics, research organizations, industry, SME's

Molecular Properties

Research Based Simulation Tool Under Development
- SAFT-gamma (Imperial College)

PSE → gSAFT (in development)

Conclusions

- Successfully developed a bottoms approach for simulation of oral absorption and delivered Version 1.0 of gCOAS
- gCOAS is a powerful tool for the Formulation Scientist
  - Diagnostic tool for identifying risk factors contributing to poor or incomplete absorption
  - Assessment of risk mitigation strategies including solubilization
  - Guidance for experimentation – increased efficiency!
- gCOAS an emerging tool for the Medicinal Chemist
  - Quantitatively compare physicochemical factors contributing to oral absorption
  - Improve design of molecules to overcome physicochemical barriers or partner with Pharm Sci for coupling with drug delivery technologies
- Initiated Systems Based Pharmaceutics
- Identified opportunities to enhance capabilities of gCOAS
- Looking forward to increased collaborations within and outside of Pfizer for improving gCOAS and advancing Systems Based Pharmaceutics

Biopharmaceutics: A Conundrum Between Thermodynamics & Kinetics ?

Nature

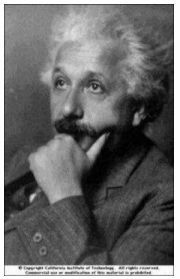
Thermodynamics
(independent of pathway)

Kinetics
(it is the pathway!)

Initial State

Final State

Metastable states



- 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

Thank you for your Attention

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