

APM 2013

The Advanced Process Modelling Forum

June 5–6, 2013, New York



Oral absorption modelling for targeted drug product design

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- Background and motivation
- Desired features of an Oral Absorption modelling tool
- Preview of gCOAS, PSE's Oral Absorption modelling tool
- Validation of an Oral Absorption model – need for a toolset
- gCOAS roadmap

Background and motivation

- SbP is a holistic, model-based approach to the development and optimisation of drug manufacture and drug delivery systems



- more about SbP in the last talk of today
- A holistic approach is required to eliminate the silo mentality existing in many companies and hence
 - increase R&D efficiency: reduce iterations between and within stages
 - increase effectiveness: move from local optima towards global optimum

- PSE has an extensive track record in developing modelling tools for a wide range of manufacturing processes ...



- ... but not in modelling biological systems
- Explored options for interfacing to existing tools for the modelling of drug delivery systems
 - would work for simulations: given a certain PSD, dose amount, etc. what is the rate of absorption?
 - but the goal of SbP is a holistic, optimisation-based approach where one can specify the desired absorption behaviour, constraints on CU and FFC, and have the optimiser determine the optimal PSD and dose of the drug

- For this reason and several other reasons, PSE started the development of a gPROMS-based oral absorption modelling tool with financial and scientific support from Pfizer
- In summary, key reasons to develop a gPROMS-based OA tool
 - optimisation capabilities: reduce trial-and-error approaches
 - efficient solvers allow explicit accounting for the evolving PSD of several phases, i.e. freeform and salt(s)
 - custom modelling capabilities: domain experts can implement own models for transit, permeation, dissolution, etc.
 - ability to integrate with drug manufacture models (gSOLIDS and gCRYSTAL) using the same platform

Desired features of an Oral Absorption modelling tool (user requirements)

- Sufficiently predictive biopharm assessment tool that allows targeted design of
 - drug molecules
 - permeability
 - solubility of various solid forms
 - drug products (dosage form)
 - excipients, e.g. nucleation inhibitors, solubilisation agents, ...
 - PSD
 - dose
- Library of correlations for phenomena
 - dissolution, transit, permeation, nucleation, etc.
- Open framework that allows domain experts to add/modify correlations without vendor involvement
- Integration with manufacturing models

- ... Physiology parameters

- patient-to-patient variability

- ... Uncertainty in physical model parameters

- dissolution kinetics
- permeation kinetics
- nucleation and growth kinetics
- pharmacokinetics

- ... Formulation parameters

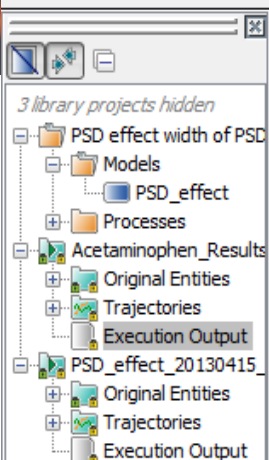
- particle size
- dose
- dosing times

subject to uncertainty arising from categories on the left

A gPROMS-based Computational Oral Absorption Simulation framework

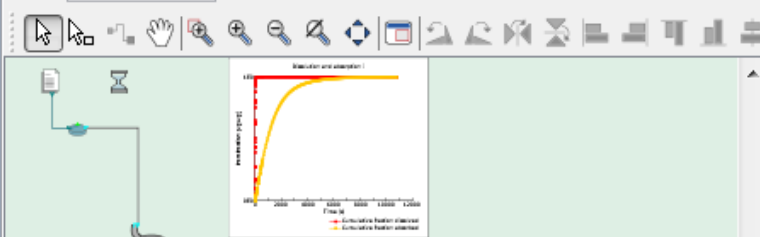
A gPROMS-based Computational Oral Absorption Simulation framework





Execution Output (Acetaminophen_Results)

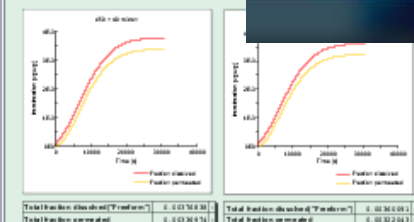
Time 10,800



Output Topology: Flowsheet

Execution Output (PSD_)

Time 30,760



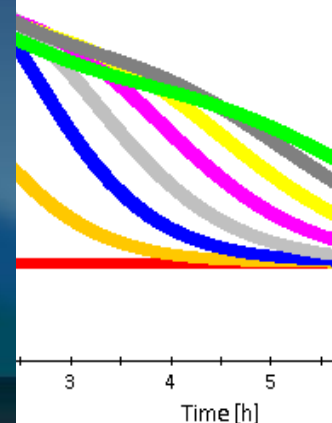
Output Topology: Flowsheet Stream tables: Flowsheet Properties

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)

 $1E-7$ 

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

Precipitation Initial conditions Stream tables Reports Properties
Physiology Transit Permeation

Annotations



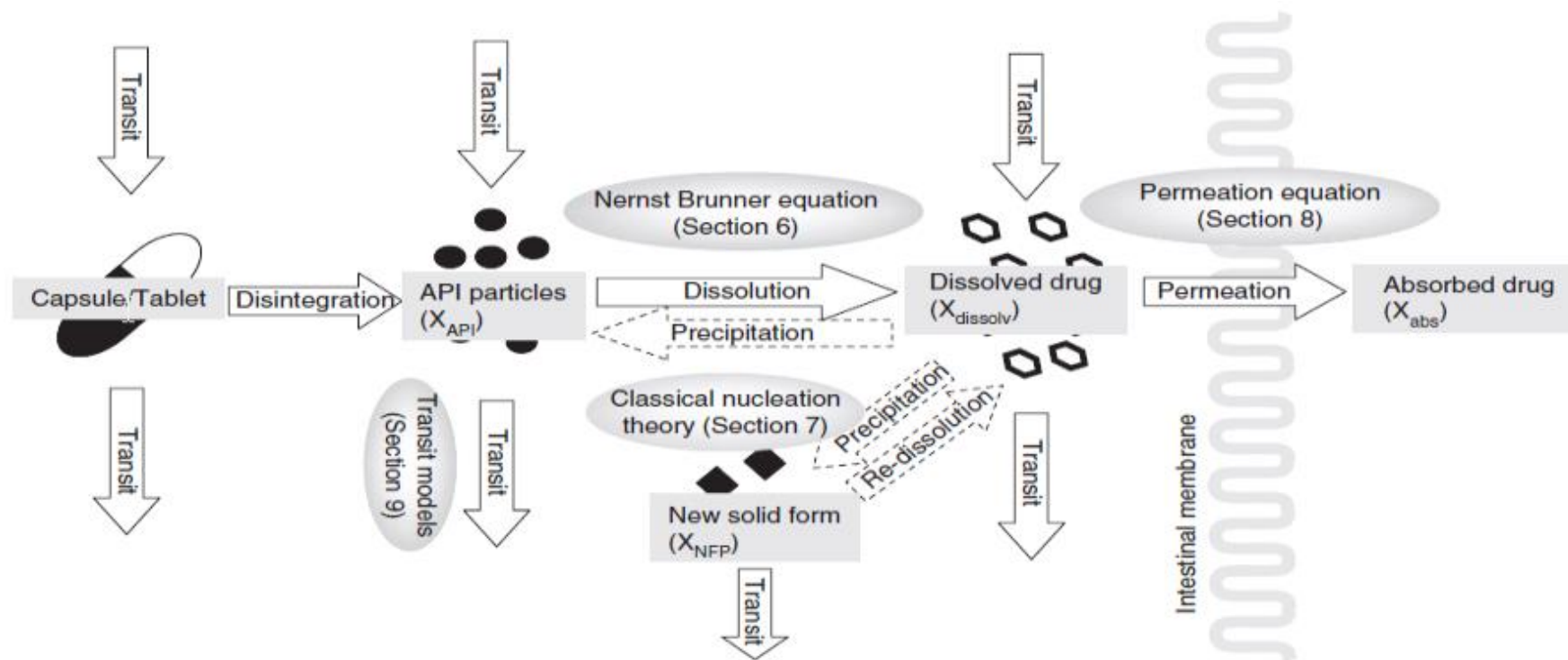
gCOAS M...



Palette

- 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

Drug properties

global_specifications (global_specifications)

Specify

Solid type: Acid

Dosed as: Salt K+

Do you want to consider precipitation of a Na+ salt? Yes

Do you want to consider precipitation of a Freeform? Yes

☒ Permeating species: ["API", "API-", "Na+"]

☒ Mass density: 1200 kg/m3

☒ Molecular weight: 300 g/mol

☒ Stoichiometry

	Salt K+	Salt Na+	Freeform
API-	1	1	
API			1
K+	1		
Na+		1	
H2O			

☒ Ksp

☒ pKa

☒ Log P: 4

☒ Intrinsic solubility: 1e-4 kg/m3

Drug properties | Grid parameters

OK Cancel Reset all Help

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

- Can handle any number of solid phases
 - typically up to three phases may (co-)exist
 - e.g. for an acid drug: non-sodium salt, sodium salt and freeform
 - at any point in time, one phase may be dissolving whilst another is precipitating
- Solid phases are characterised by their solubility in the GI fluid and their Particle Size Distribution (PSD)
- Evolution of the PSD of the various phases is described using a population balance framework

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

same framework used in other PSE products

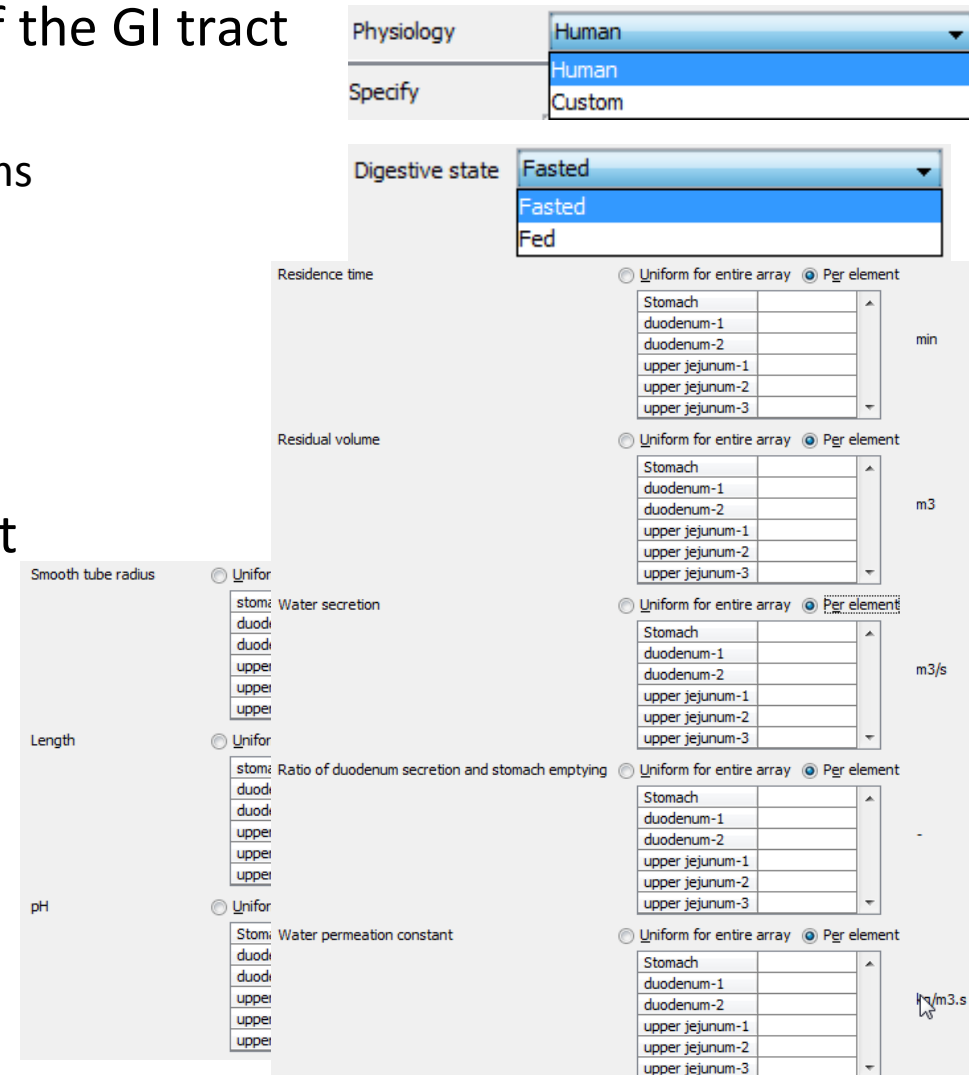


■ Built-in specifications for

- 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.



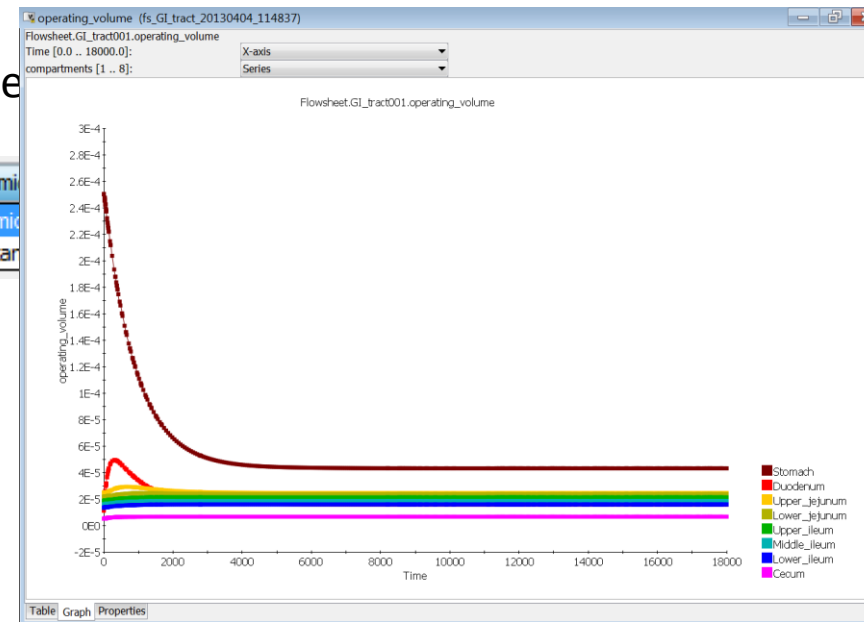
The screenshot displays a software interface for configuring GI tract parameters. It includes dropdown menus for 'Physiology' (set to Human), 'Specify' (set to Human), and 'Digestive state' (set to Fasted). Below these are sections for 'Residence time' and 'Residual volume', each with a radio button for 'Uniform for entire array' and a table for 'Per element' settings across various GI segments (Stomach, duodenum-1, duodenum-2, upper jejunum-1, upper jejunum-2, upper jejunum-3). The 'Per element' tables include columns for 'min' and 'm3/s'. Other parameters include 'Smooth tube radius', 'Length', 'pH', 'Water secretion', 'Ratio of duodenum secretion and stomach emptying', and 'Water permeation constant', each with a radio button for 'Uniform' and a table for 'Per element' settings.

Parameter	Setting	Segment	min	m3/s
Residence time	<input type="radio"/> Uniform for entire array <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Residual volume	<input type="radio"/> Uniform for entire array <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Smooth tube radius	<input type="radio"/> Uniform <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Length	<input type="radio"/> Uniform <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
pH	<input type="radio"/> Uniform <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Water secretion	<input type="radio"/> Uniform <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Ratio of duodenum secretion and stomach emptying	<input type="radio"/> Uniform for entire array <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		
Water permeation constant	<input type="radio"/> Uniform for entire array <input checked="" type="radio"/> Per element	Stomach		
		duodenum-1		
		duodenum-2		
		upper jejunum-1		
		upper jejunum-2		
		upper jejunum-3		

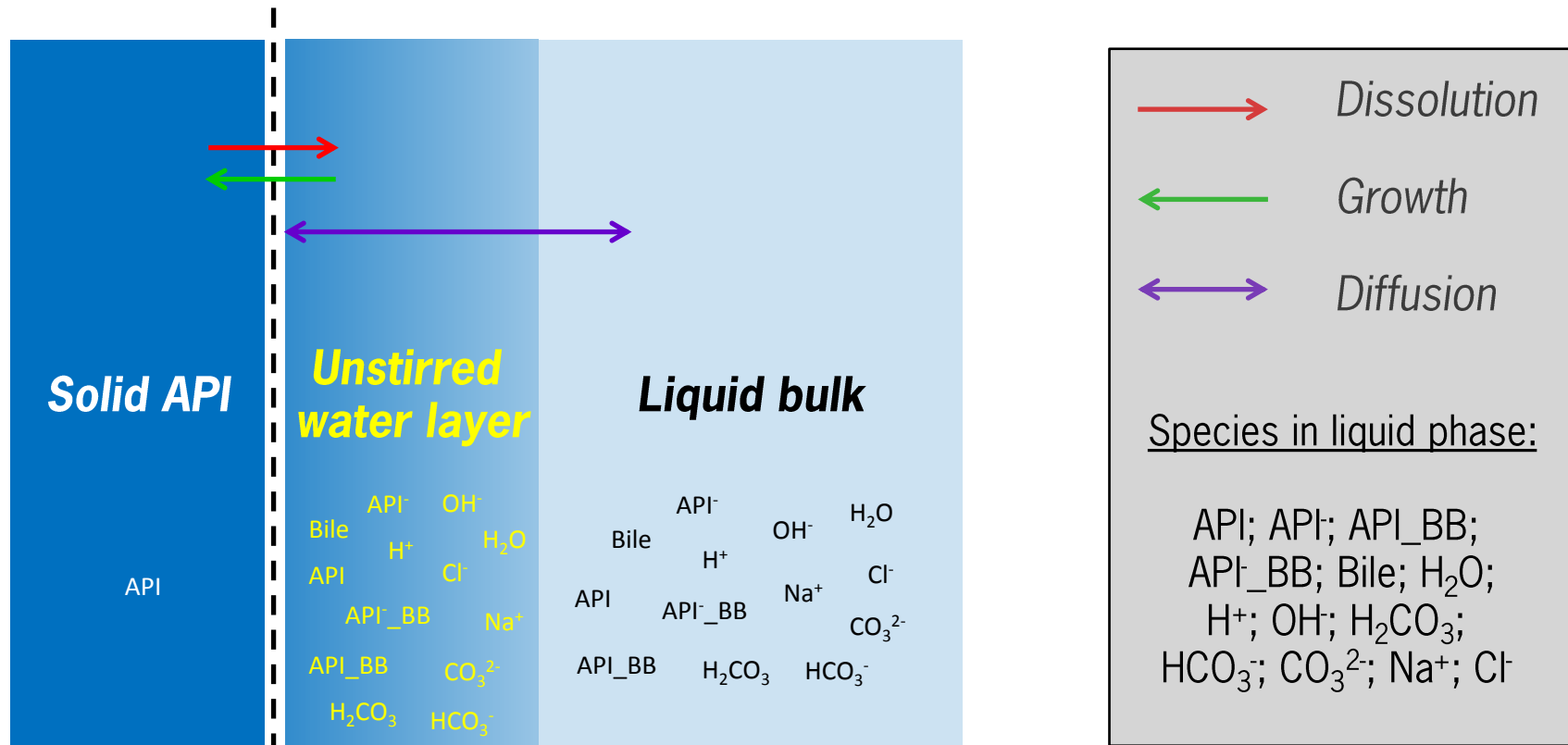
- Not only of the API in its various forms
 - dissociated, undissociated, bile bound
- But also of water, buffers and bile
- What happens to the volume of the GI tract segments when you take a tablet with a glass of water?
 - nothing, i.e. constant volumes; or
 - varying volumes
 - variations depend on intake of fluid, water permeation
 - both options implemented
- Need to investigate impact of normally neglected variations in chyme volume on absorption

Fluid transit

Dynamic
Dynamic
Constant

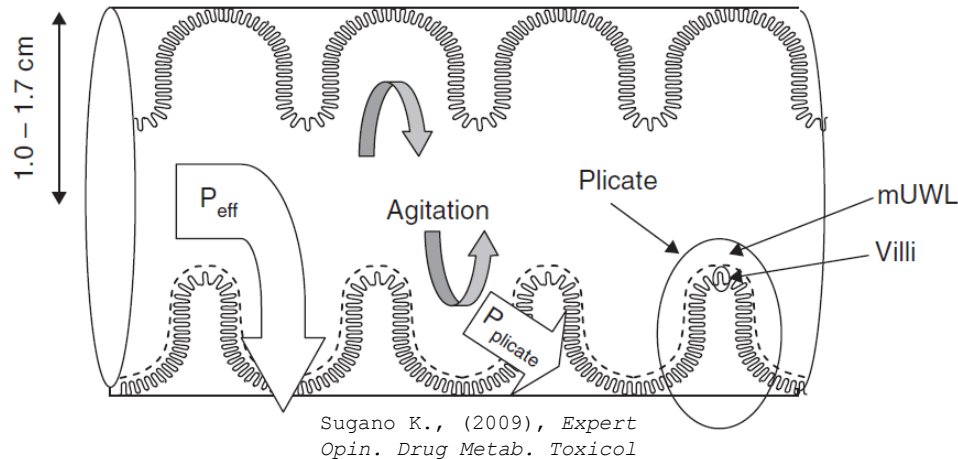


■ Detailed description of UWL and chemical equilibria



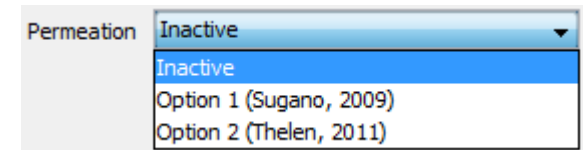
At the solid-liquid interface:

$$0 = \{\text{dissolution}\} + \{\text{reaction}\} + \{\text{diffusion}\}$$



■ The GI_tract model allows four options for the calculation of effective permeability:

- Inactive
- Option 1 (Sugano, 2009)
- Option 2 (Thelen, 2011)
- Experimental



Sugano K., (2009), *Expert Opin. Drug Metab. Toxicol.*, 5 (3)

Thelen K., Coboeken, K., Willmann, S., Burghaus, R., Dressman, J., Lippert, J. (2011), *J. Pharm. Sci.*, 100 (12)

- Nucleate after being supersaturated for a given amount of time

- Classical nucleation

- $J_{prim} = \ln A_0 \left(\frac{-16\pi(\alpha\sigma)^3 v_0^2}{3k^3 T^3 \ln S^2} \right)$

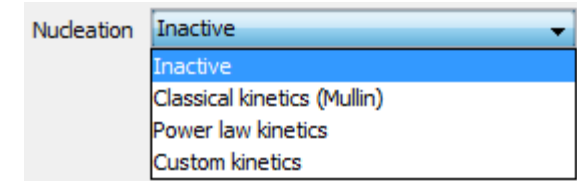
- Power law kinetics

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

- Custom kinetics

- Allows a domain expert to add a nucleation model
 - E.g., using probability distribution functions of induction time

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



Nice framework, but where do values for the numerous parameters come from?

Validation of an Oral Absorption model

A supporting modelling tool set for processing experimental data



- **Intrinsic solubility or K_{sp} :** solubility experiments
- **pK_a values:** measure dissociation constants using solution-based NMR, ...
- **Disintegration & dissolution parameters:** in-vitro experiments (e.g. USP-2)
- **Nucleation & growth parameters:** in-vitro experiments
- **Effective permeability**
 - LOC-I-GUT experiments → effective permeability directly
 - Oral solution experiments (dissolved API): need to subtract PK effect
 - cell-based (e.g. CaCo-2) experiments → apparent permeability → use LVM model to determine effective permeability
 - Cancer cells of the Colon
 - LVM model to be developed using systems for which loc gut and CaCo-2 data is available
- **Human PK parameters**
 - human IV experiments
 - correlate to PK parameters from other sources (e.g. animal IV data)
- **Fine tune physiology / transit:** Clinical data, $C_p(t)$

gCOAS roadmap

gCOAS v1 (July 2013)

gCOAS v2 (Dec 2013)

- Pharmacokinetics
- Multiple dose (of one API) under feeding regime
- Zwitter ions
- Inclusion of solubilisation technologies

gCOAS v3+

- Controlled release formulations
- Effect of other surfactants
- Longer residence times for colloids and nanoparticles
- Co-crystals

gCOAS v2 (Dec 2013)

- USP-2 model
- ASD model
- Solubility model

gCOAS v3+

- LOC-I-GUT model
- IV model

Thank you!



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