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The Advanced Process Modelling Forum

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Oral absorption modelling for targeted drug product design

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Overview

- 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

Systems-based Pharmaceutics (SbP)

- 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

An oral absorption modelling tool for SbP

- 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

gPROMS-based Oral Absorption modelling tool

- 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)

Initial list

- 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

Sensitivity analyses with respect to …

- … 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

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A gPROMS-based Computational Oral Absorption Simulation framework

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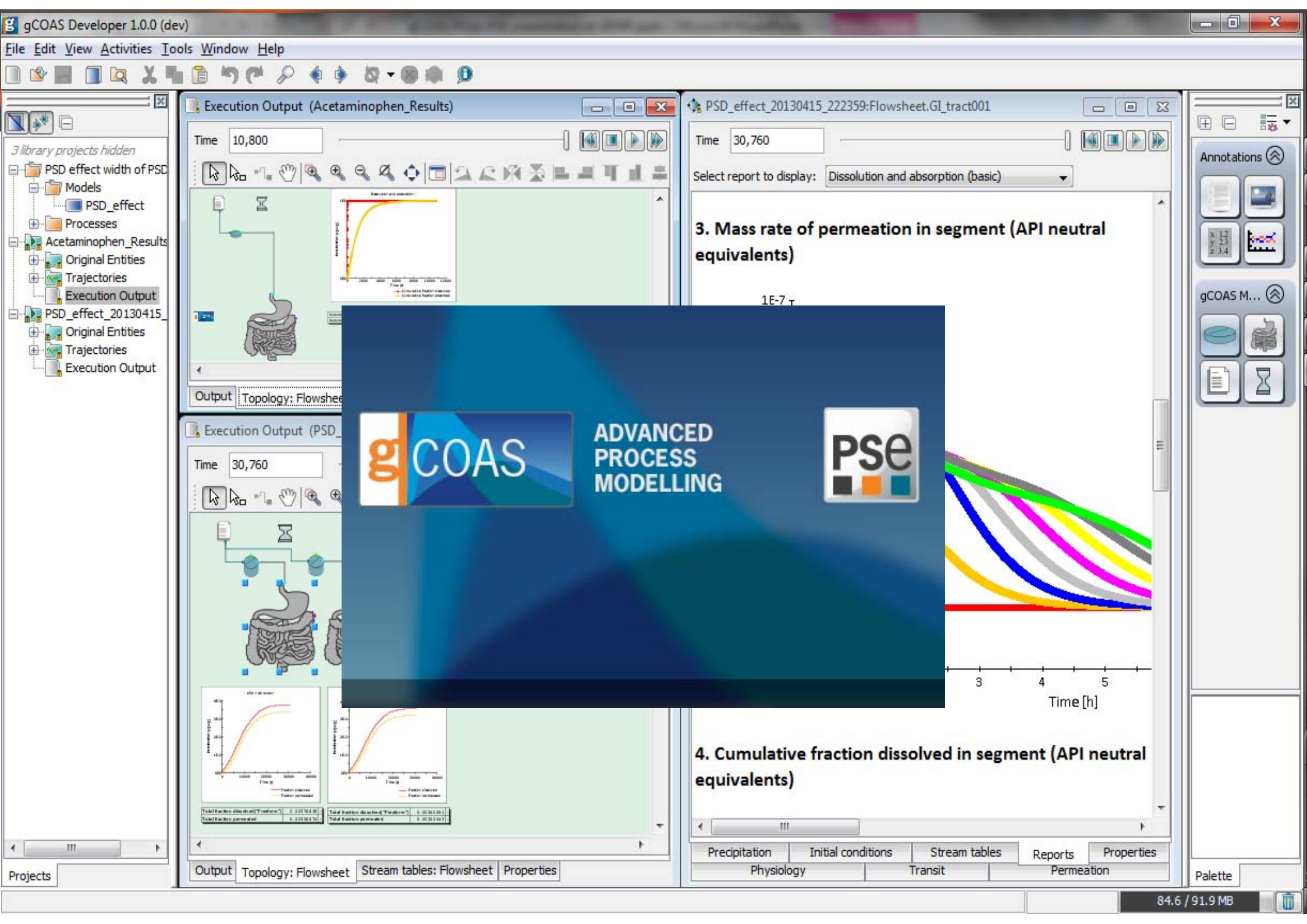
gCOAS Developer 1.0.0 (dev)
File Edit View Activities Tools Window Help
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Acetaminophen_Results
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Execution Output (PSD_
Time 30,760
Output
Topology: Flowsheet
Stream tables: Flowsheet
Properties
gCOAS
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PSE
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
3
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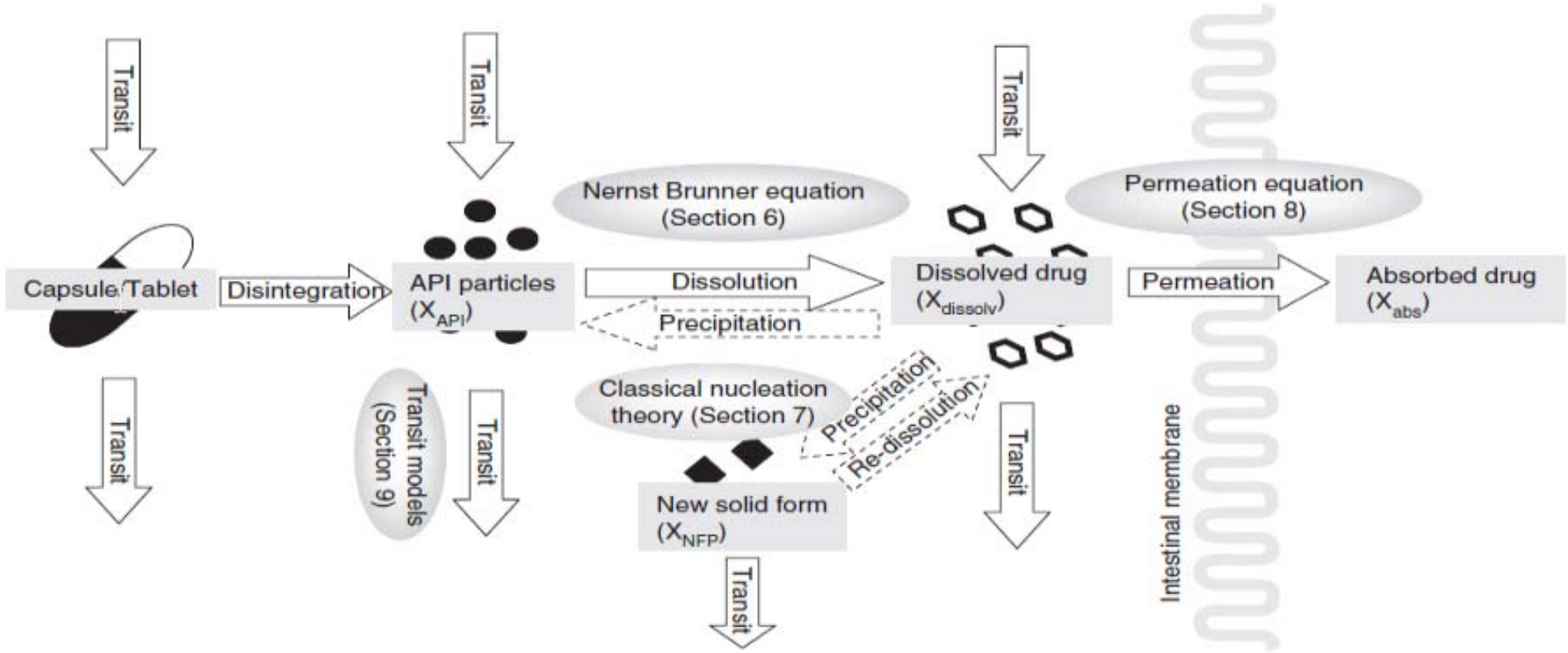
Time [h]
4. Cumulative fraction dissolved in segment (API neutral equivalents)
Precipitation
Initial conditions
Stream tables
Reports
Properties
Physiology
Transit
Permeation
Annotations
gCOAS M...
Palette
84.6 / 91.9 MB

gCOAS model framework

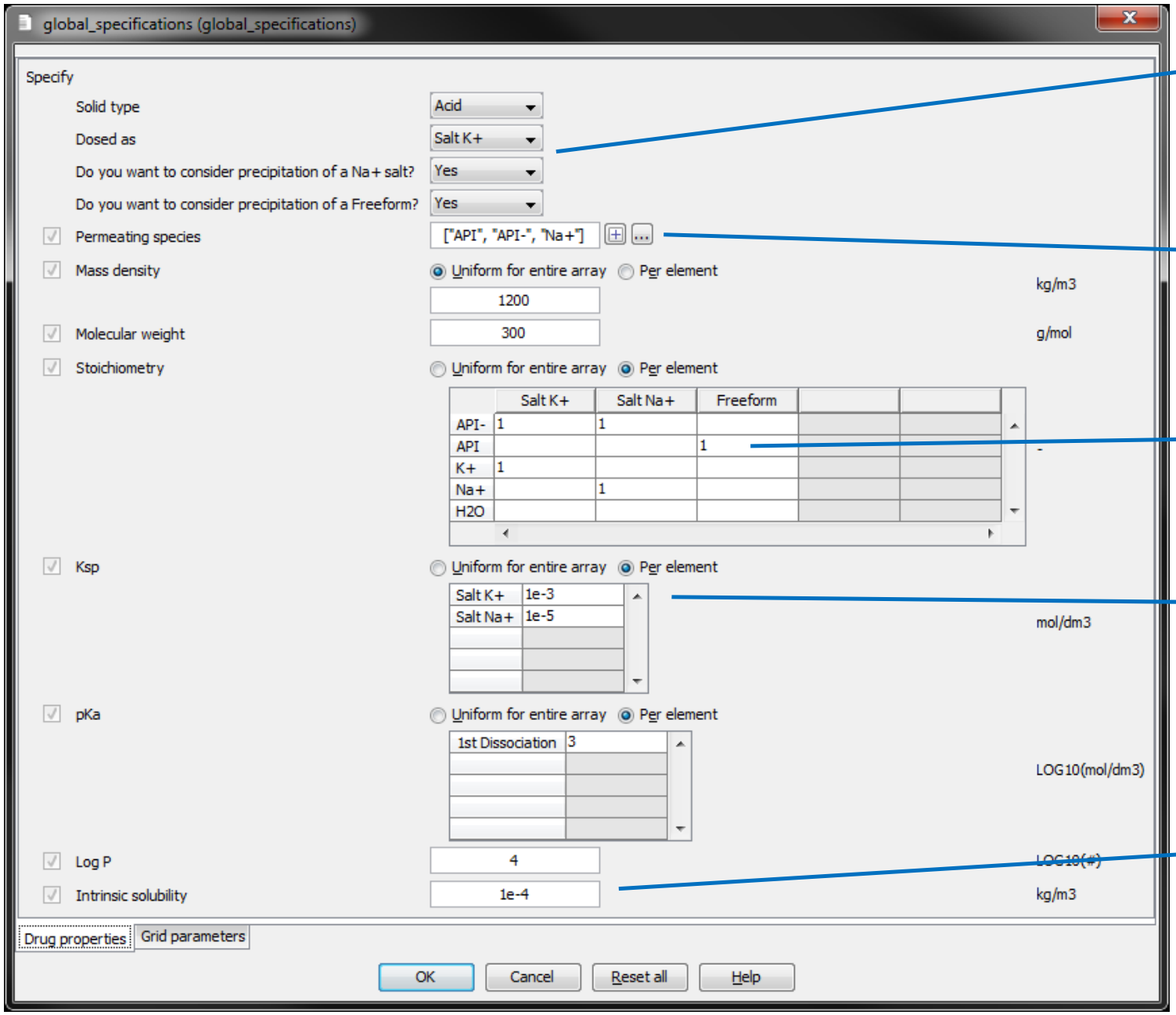
- Inspired by Sugano framework

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



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

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Solid phases

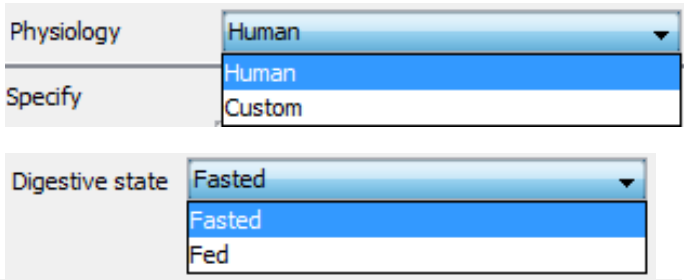
- Can handle any number of solid phases
  - typically up to three phases may (co-)exist
    - e.g. for an acid drug: non-sodium salt, sodium salt and freeform
  - at any point in time, one phase may be dissolving whilst another is precipitating
- Solid phases are characterised by their solubility in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

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

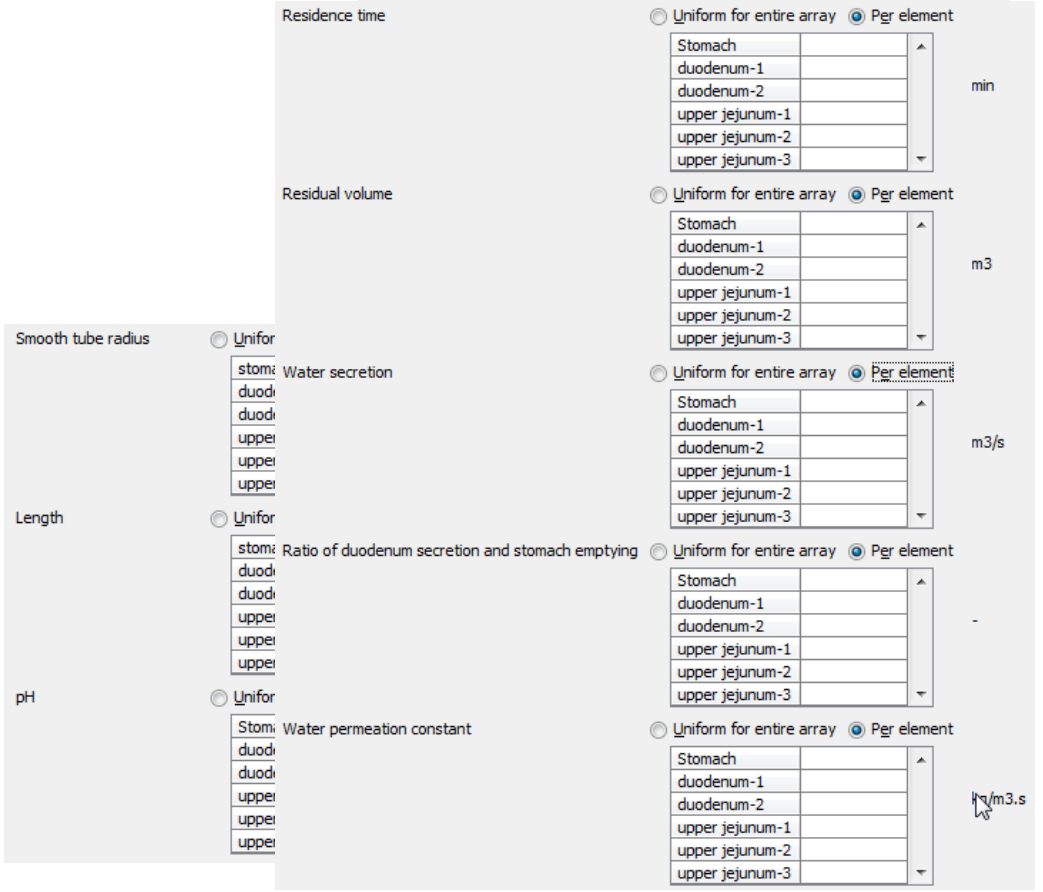
same framework used in other PSE products gCRYSTAL gSOLIDS

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

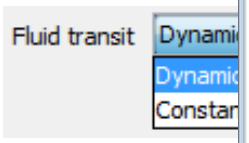


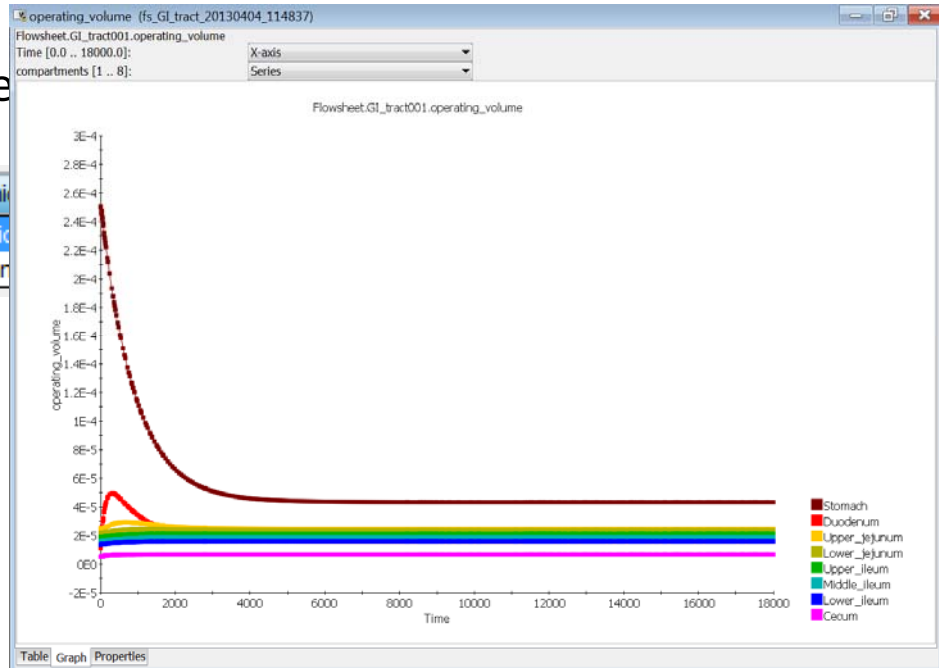
- Custom option allows for
  - any segmentation of the GI tract
  - complete freedom in specifying segment radii, lengths, residual volumes, pH values, bile concentration, etc.



Transit

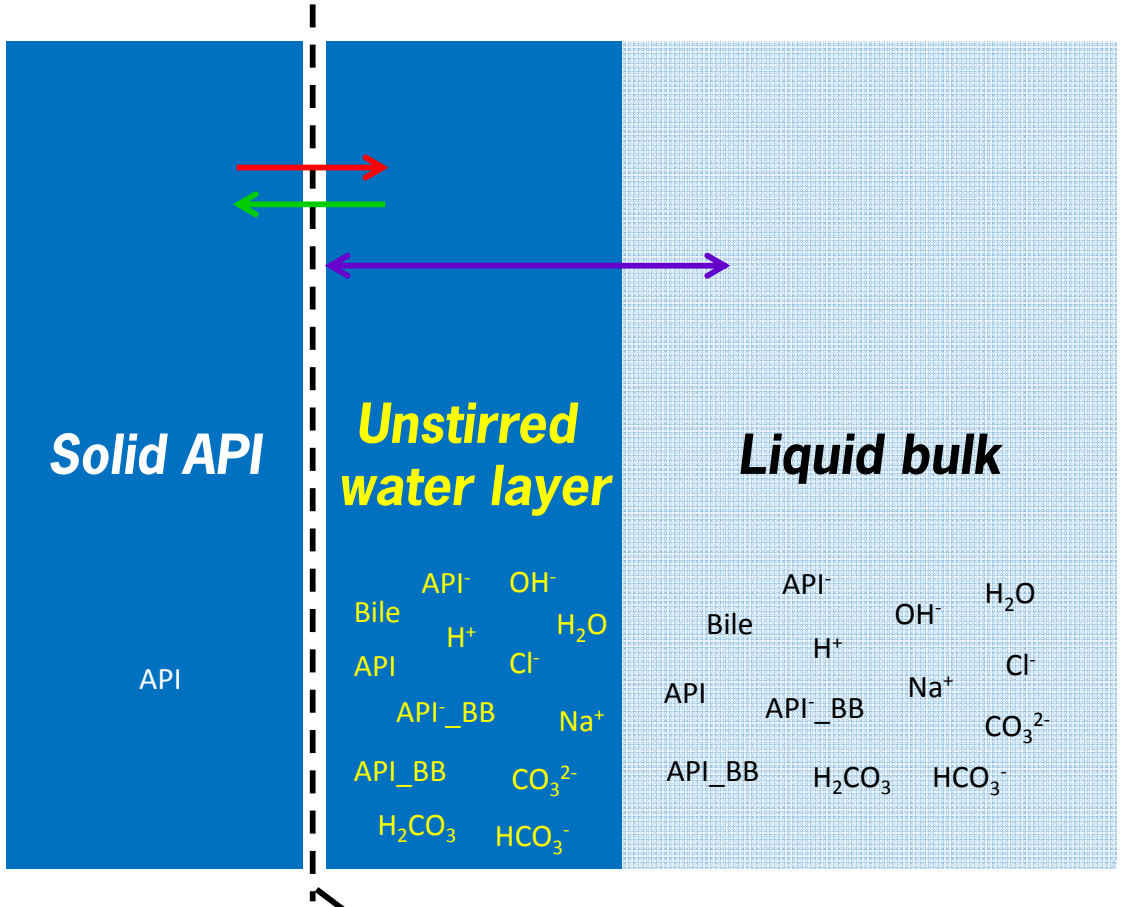
- Not only of the API in its various forms
  - dissociated, undissociated, bile bound
- But also of water, buffers and bile
- What happens to the volume of the GI tract segments when you take a tablet with a glass of water?
  - nothing, i.e. constant volumes; or
  - varying volumes
    - variations depend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

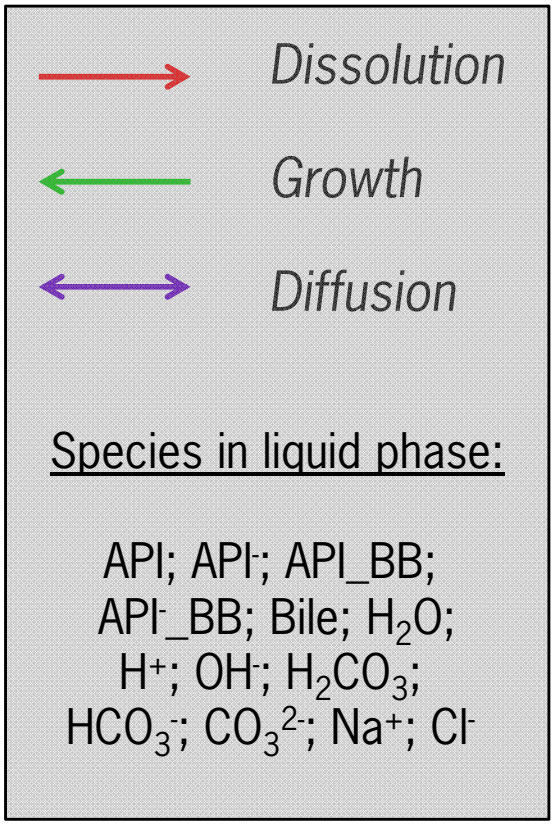




Dissolution (and growth)

- Detailed description of UWL and chemical equilibria

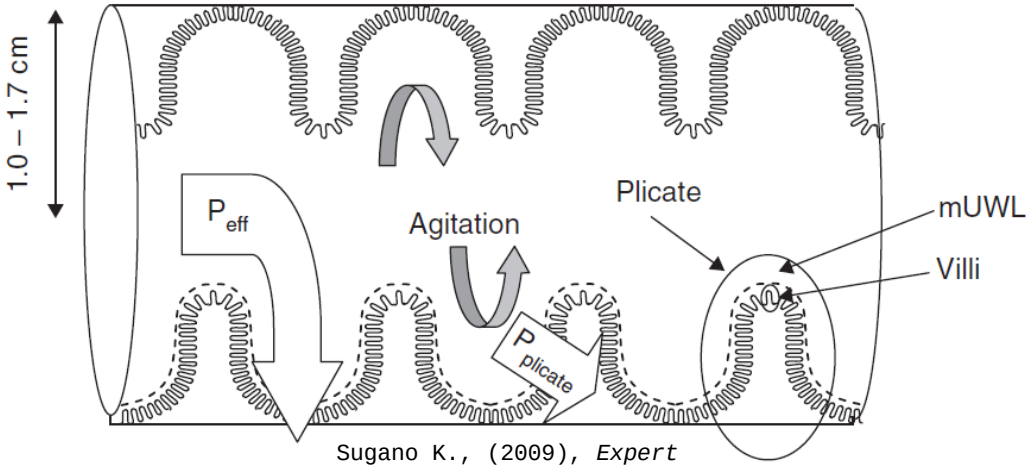




At the solid-liquid interface:

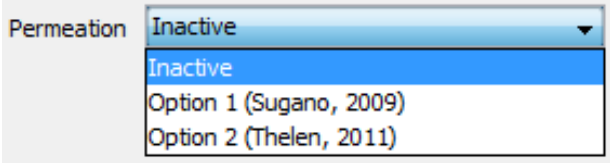
0 = {dissolution} + {reaction} + {diffusion}

Permeation through the intestine wall



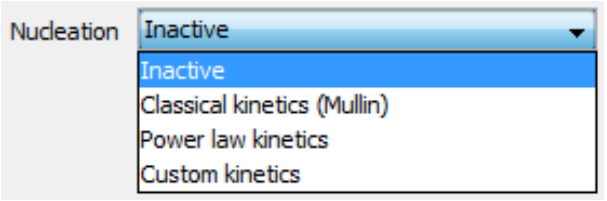
Sugano K., (2009), *Expert Opin. Drug Metab. Toxicol*

- 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)

Nucleation



- Nucleate after being supersaturated for a given amount of time
- Classical nucleation
  - $\left(\frac{(\quad)}{\qquad}\right)$
- Power law kinetics
  - $\left(-\right)$ $\frac{}{\qquad}$
- Custom kinetics
  - Allows a domain expert to add a nucleation model
  - E.g., using probability distribution functions of induction time

( ) ( )

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

Validation of an Oral Absorption model

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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
    - **Ca**ncer cells of the **Co**lon
    - 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

Oral absorption model roadmap

gCOAS v1 (June 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

Oral absorption modelling tool set roadmap

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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molar_flux_diss (PSD_effect_20130415_222359)

Flowsheet.GI_tract001.zone("Duodenum").kinC.growth_diss_UWL.molar_flux_diss

Time [0.0 .. 30760.0]: Rows

solid_phases [1 .. 1]: Fixed at 1 = "Freeform"

no_grd_pts [1 .. 10]: Fixed at 1 = 1

Time	
2340.0	9.036646E-8
2350.0	9.040349E-8
2360.0	9.04431E-8
2370.0	9.048528E-8
2380.0	9.053E-8

Table | Graph | Properties

molar_flux_diff (PSD_effect_20130415_222359)

Flowsheet.GI_tract001.zone("Duodenum").kinC.growth_diss_UWL.molar_flux_diff

Time [0.0 .. 30760.0]: Rows

solid_phases [1 .. 1]: Fixed at 1 = "Freeform"

no_grd_pts [1 .. 10]: Fixed at 1 = 1

species_liq [1 .. 11]: Columns

	species liq										
Time	"H2CO3"	"H2O"	"API"	"Bile"	"H+"	"HCO3-"	"CO3--"	"OH-"	"Na+"	"Cl-"	"API_BB"
2340.0	-2.315156E-21	0.0	8.886929E-8	0.0	2.315134E-21	2.315155E-21	8.212093E-29	9.053543E-31	0.0	0.0	1.497173E-9
2350.0	1.534533E-20	0.0	8.890627E-8	0.0	-1.534534E-20	-1.534533E-20	-3.168144E-29	1.316534E-30	0.0	0.0	1.497222E-9
2360.0	7.665642E-21	0.0	8.894583E-8	0.0	-7.665639E-21	-7.665642E-21	1.019622E-29	2.119888E-31	0.0	0.0	1.497275E-9
2370.0	-5.66656E-21	0.0	8.898795E-8	0.0	5.666561E-21	5.66656E-21	2.090752E-29	1.729707E-31	0.0	0.0	1.49733E-9
2380.0	2.265565E-20	0.0	8.903261E-8	0.0	-2.265565E-20	-2.265565E-20	-1.265235E-28	-4.051268E-31	0.0	0.0	1.497389E-9

Table | Graph | Properties

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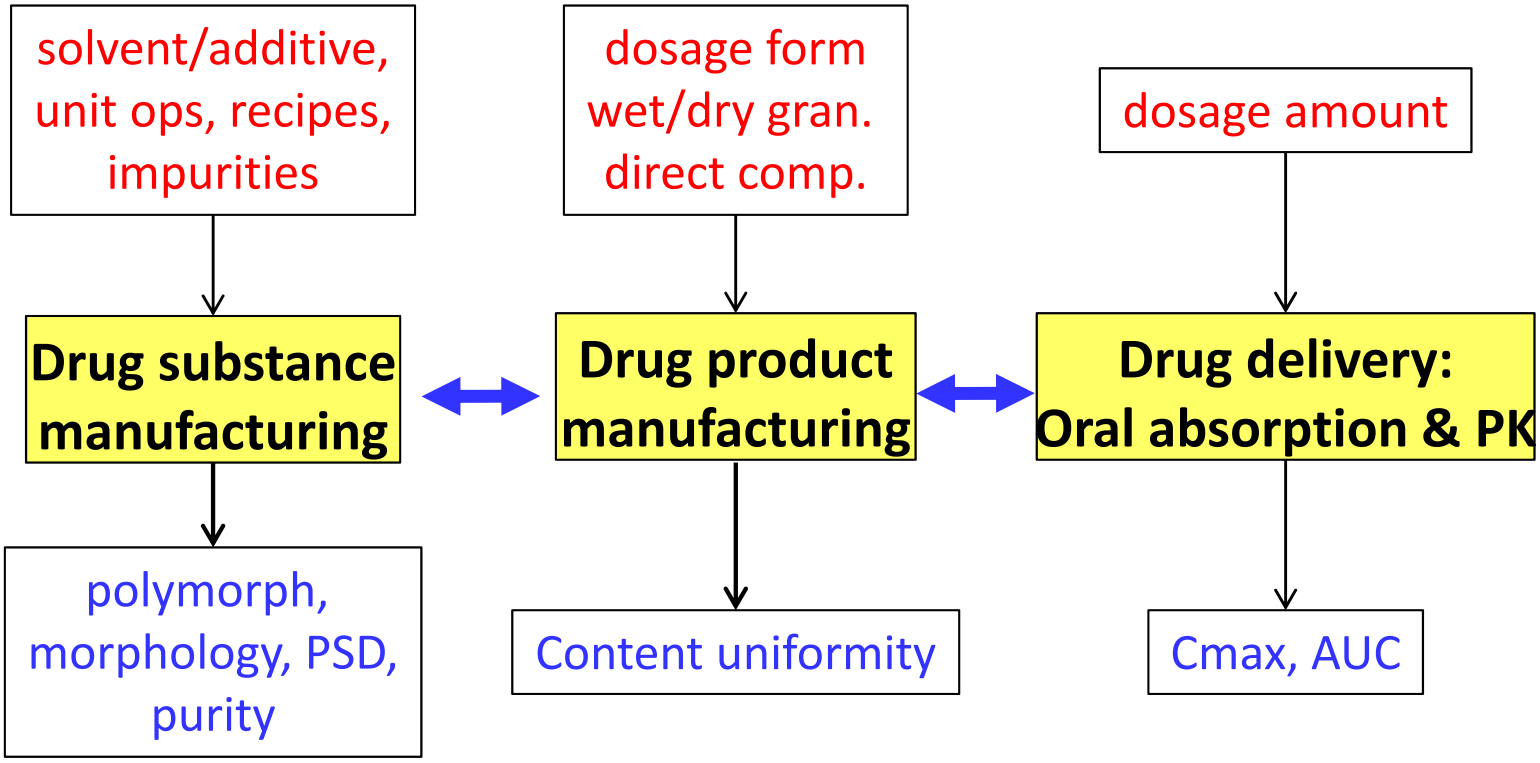
Background and motivation

- Systems-Based Pharmaceutics is a holistic approach to the development and optimization of drug manufacture and drug delivery systems



Model Builder gCRYSTAL gSOLIDS

Features of v1 (release in June 2013)

- User defined segmentation of GI tract and physiological parameters
  - Nucleation
    - we have kinetics; use concentration of correct species; which one actually precipitates
  - Growth kinetics
    - not simply the inverse of dissolution kinetics: taking into account surface integration
  - Species specific permeation
    - use concentration of correct species
  - Explicit dynamic handling of ionic and colloid equilibria in bulk, UWL of each solid phase and UWL of membrane → partitioning of drug species allows calculation of correct driving force for precipitation and permeation
  - Impact of PSD on dissolution and fraction dose absorbed using a population balance approach
- Transit models: options 1-3 / feeding regime
- Fluid secretion and reabsorption across the anatomical segments of the GI tract
- Expert version allows custom kinetic and transit models to be included
- Integration with drug substance and drug product manufacturing models (SbP)
- Built on the powerful gPROMS platform

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Looking ahead (v2+) – In-vitro dissolution and tablet disintegration

Tablet Disintegration

(simple fitting approach as opposed to mechanistic model, which will be done later)

- Simple 0 order or 1st order decay for IR tablets
- First order erosion model for IR based on evolving SA

In-Vitro Dissolution

- Reverse gCRYSTAL - adding different dissolution rate expressions
- Hintz / Kevin Johnson dissolution model

In-Vitro Dissolution (cont'd)

- Extension to consider "fixed" compartments from a CFD model of the USP apparatus

Bio-relevant In-Vitro Dissolution (accounting for pH, lipids, colloids/micelles effects)

- Taking elements from Sugano paper