

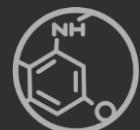


ADVANCED PROCESS MODELLING FORUM

22–23 APRIL 2015

Integrated mechanistic modelling for design and optimisation of formulated products and their manufacturing processes

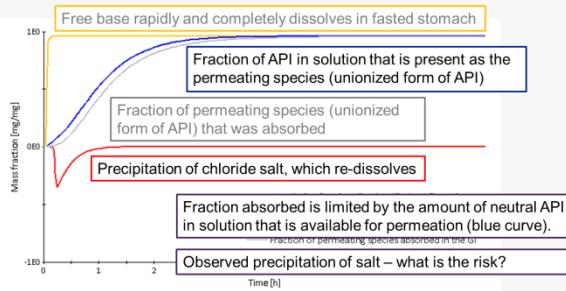
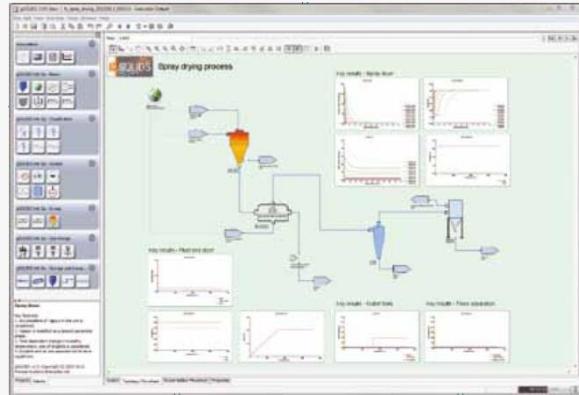
Frances Pereira
Head of Product Development
Life Sciences, Food, Consumer Goods and Specialty & Agrochemicals



Typical formulated product applications

In the Life sciences, food, consumer good, specialty and agrochemicals industries

Integrated design of spray dryer and fluid bed dryer system



Risk assessment for Oral Solid Dosage forms [Pfizer]

Optimisation of the batch recipe for pharma-grade lactose to reduce cycle time by 44% [FrieslandCampina]



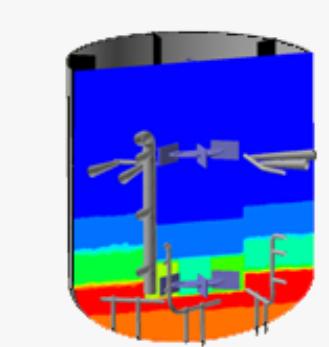
Optimisation of a pharmaceutical reactor to minimise impurity production [GSK]



Optimising a pill coating process [Pfizer]

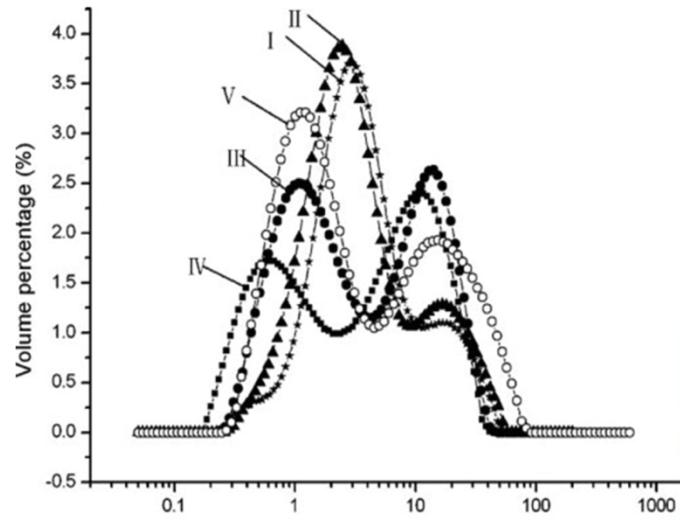


Scale-up of milling [P&G]



Crystalliser scale-up for a new process

PSE tools that support decision making in the design of formulated products and their manufacturing processes



The figure displays three screenshots of Process Systems Enterprise (PSE) software interfaces:

- gCRYSTAL**: Shows a process flow diagram for a continuous cooling stage. It includes various unit operations like tanks, heat exchangers, and pumps, along with real-time data plots for temperature (TC) and liquid level (LC).
- gSOLIDS**: Shows a spray drying process. The interface includes a schematic of the equipment (feed, atomizer, cyclone, and collection), key results for the spray dryer, fluid bed dryer, outlet flows, and fines separation, and corresponding data plots.
- gCOAS**: Shows a pharmacokinetic model for Ketoprofen. It includes a schematic of the drug absorption and metabolism pathway through the stomach and intestine, a graph of the mass fraction over time, and a legend for the cumulative fraction dissolved, fraction permeating species dissolved in GI, and fraction permeating species absorbed in GI.

Product timelines and adoption



1.0

2.0

3.0

4.0

4.1

4.2



1.0

2.0

3.0

3.1

4.0

4.1



1.0

1.2

2011

2012

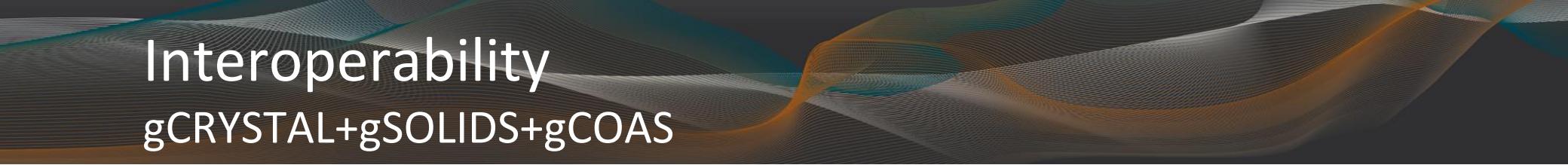
2013

2014

2015



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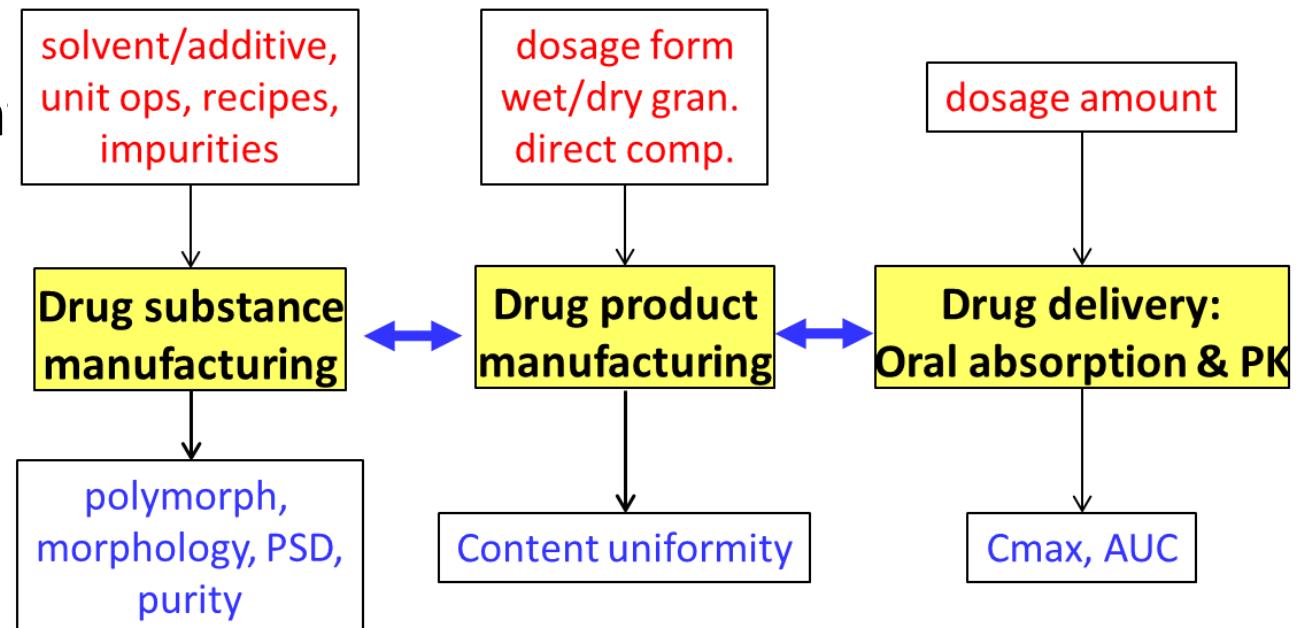


Interoperability

gCRYSTAL+gSOLIDs+gCOAS

- PSE customers increasingly using multiple products
- Enable holistic view, e.g. Systems-based Pharmaceutics

- Consistency in con



- PSE customers increasingly using multiple products
- Enable holistic view, e.g. Systems-based Pharmaceutics
- Consistency in content, look and feel and terminology

Interoperability illustrated

gPROMS ModelBuilder 4.1.0 (beta2)

File Edit View Activities Tools Window Help

Execution Output (Fenofibrate_Interoperability_Case_Study_Scenario1)

Time 86,400

Crystallisation

gCRYSTAL

Level_controller001

TC

Feed Pump

vessel

Product_Pump

liquid_composition_sensor A

PSD_sensor

ideal_classifie

Micronisation

global_specification

Simulation_duration

D10 0.657098 mu
D50 1.88289 mu
D90 4.81965 mu

Drug product manufacture

gSOLIDS

solvent/additive, unit ops, recipes, impurities

Drug substance manufacturing

Drug product manufacturing

Content uniformity

dosage form wet/dry gran. direct comp.

dosage amount

Drug delivery: Oral absorption & PK

Cmax, AUC

Mass fraction dose absorbed in GI tract (-)

Extensive micronisation

Limited micronisation

No micronisation

Time (s)

Mass dosed 145.000-

Oral absorption

gCOAS

on the fraction absorbed

Output Topology: Flowsheet Stream tables: Flowsheet Reports: Flowsheet Properties

A single modelling framework



Integrated mechanistic modelling for design and optimisation of formulated products and their manufacturing processes





The challenges of interoperability

Challenges? What challenges?

All three products are built on the same gPROMS Platform

BUT...

- Material streams carry very different physical properties information
- Multiple versions of similar models

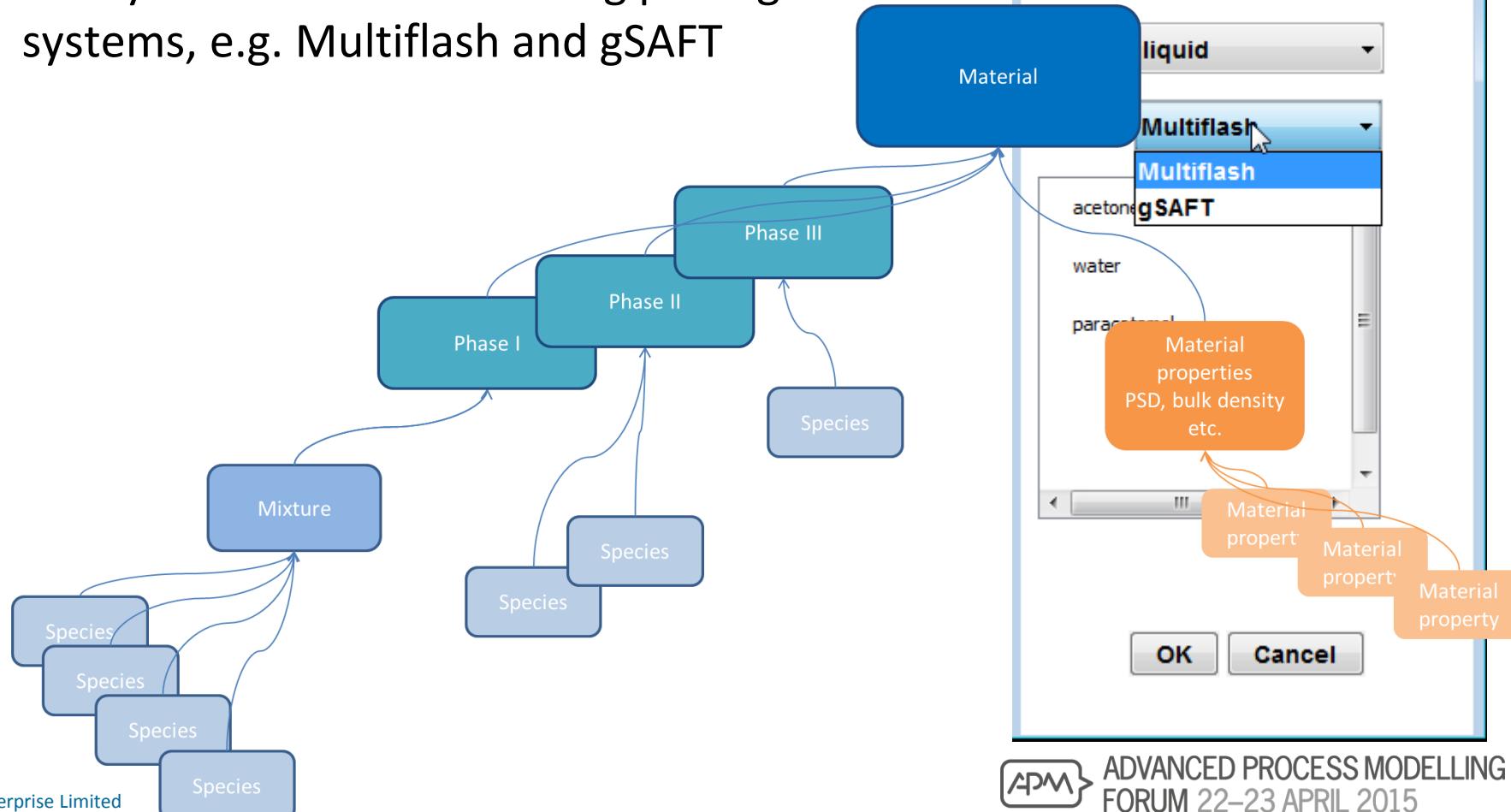


The gPROMS platform
Equation-oriented modelling & solution engine

A unified description of materials & their behaviour

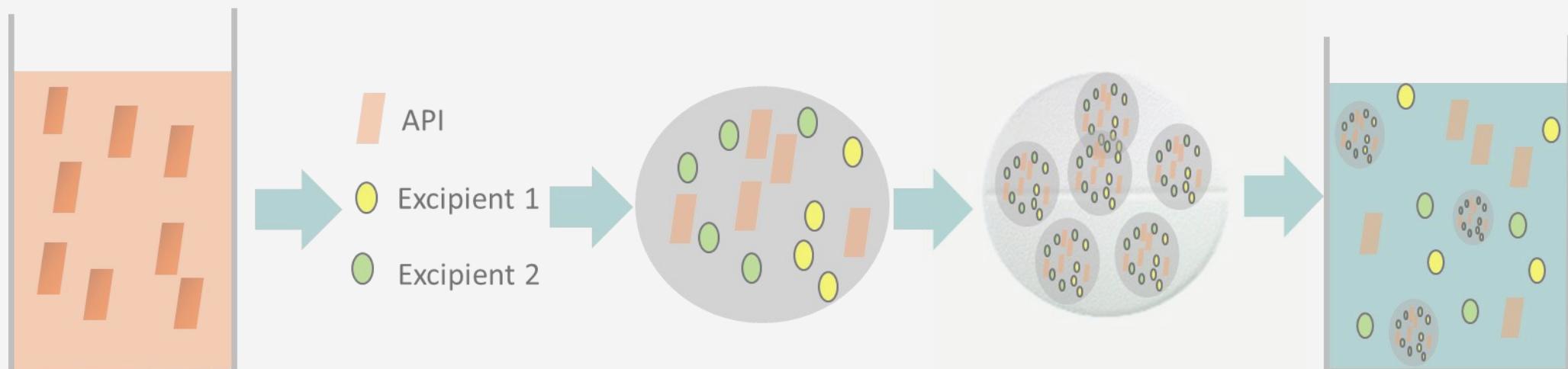
■ Suitable for complex materials (*and simple ones too*)

- representation of material in terms of species, mixture, phases
- ability to make use of existing packages for fluid systems, e.g. Multiflash and gSAFT



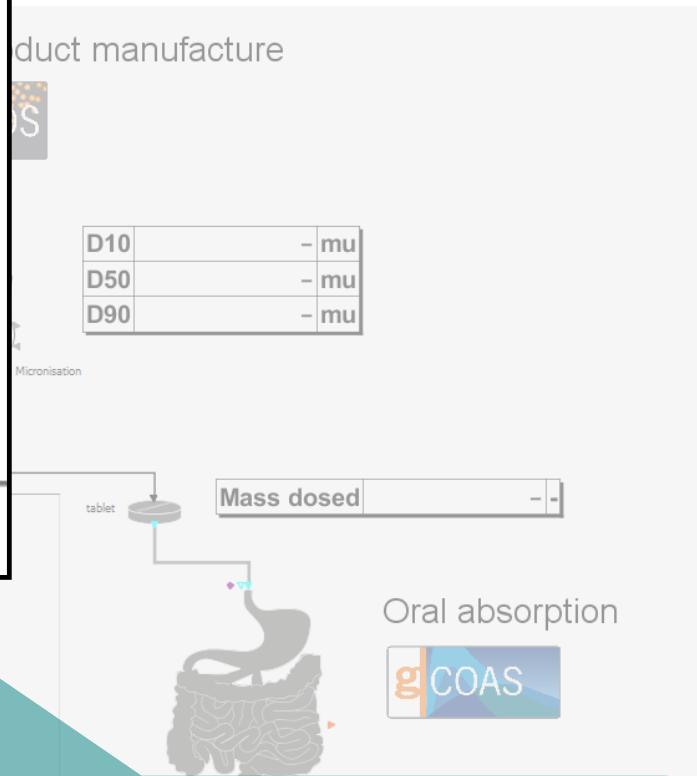
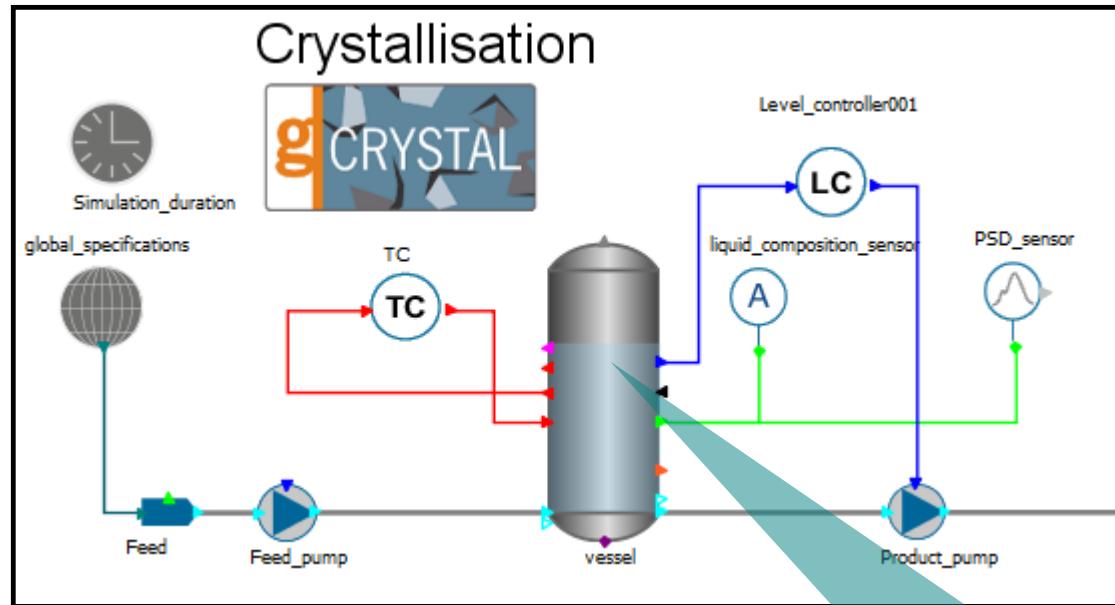
A unified material connection

- Development of an architecture to describe,
 - evolution of distributed phases
 - existence of composite phases



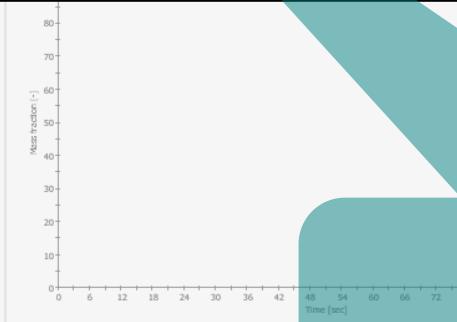
Property package and phase structure to handle the following complex phenomena

Crystallisation



Complex phase behaviour:
Multiple precipitating / dissolving
Liquid-liquid immiscibility
Vapour-liquid equilibrium
Ionic speciation and equilibria

The impact of changes in the crystallization and milling operations on the fraction absorbed



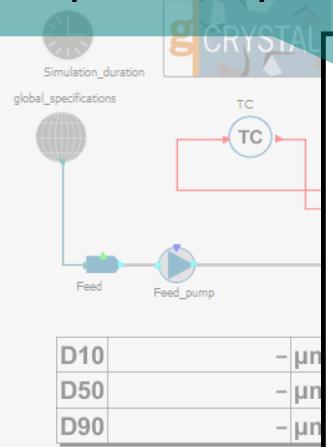
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Property package and phase structure to handle the following complex phenomena

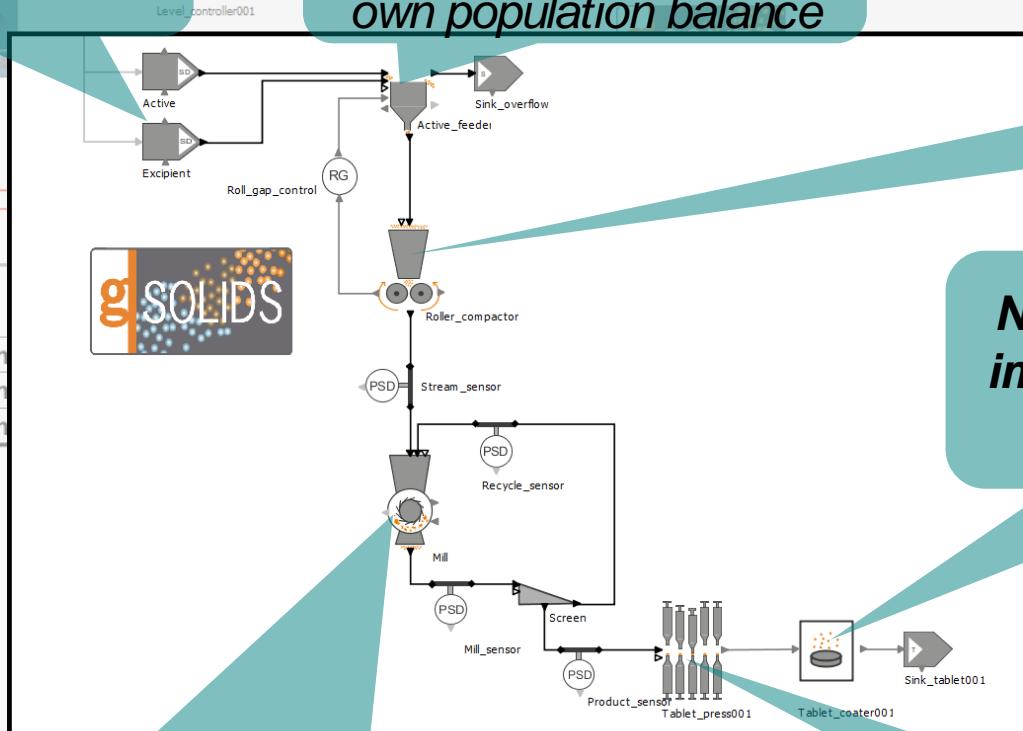
Solids processing



Multiple species per solid phase



Multiple solid phases, each described by its own population balance



Primary particles combined into granules

Nested phase structure impacts disintegration / dissolution behaviour

Granules and roll compaction bypass are being milled. Preserve relevant properties of nested phases

The impact of changes in the crystallization and milling operations on the final tablet properties

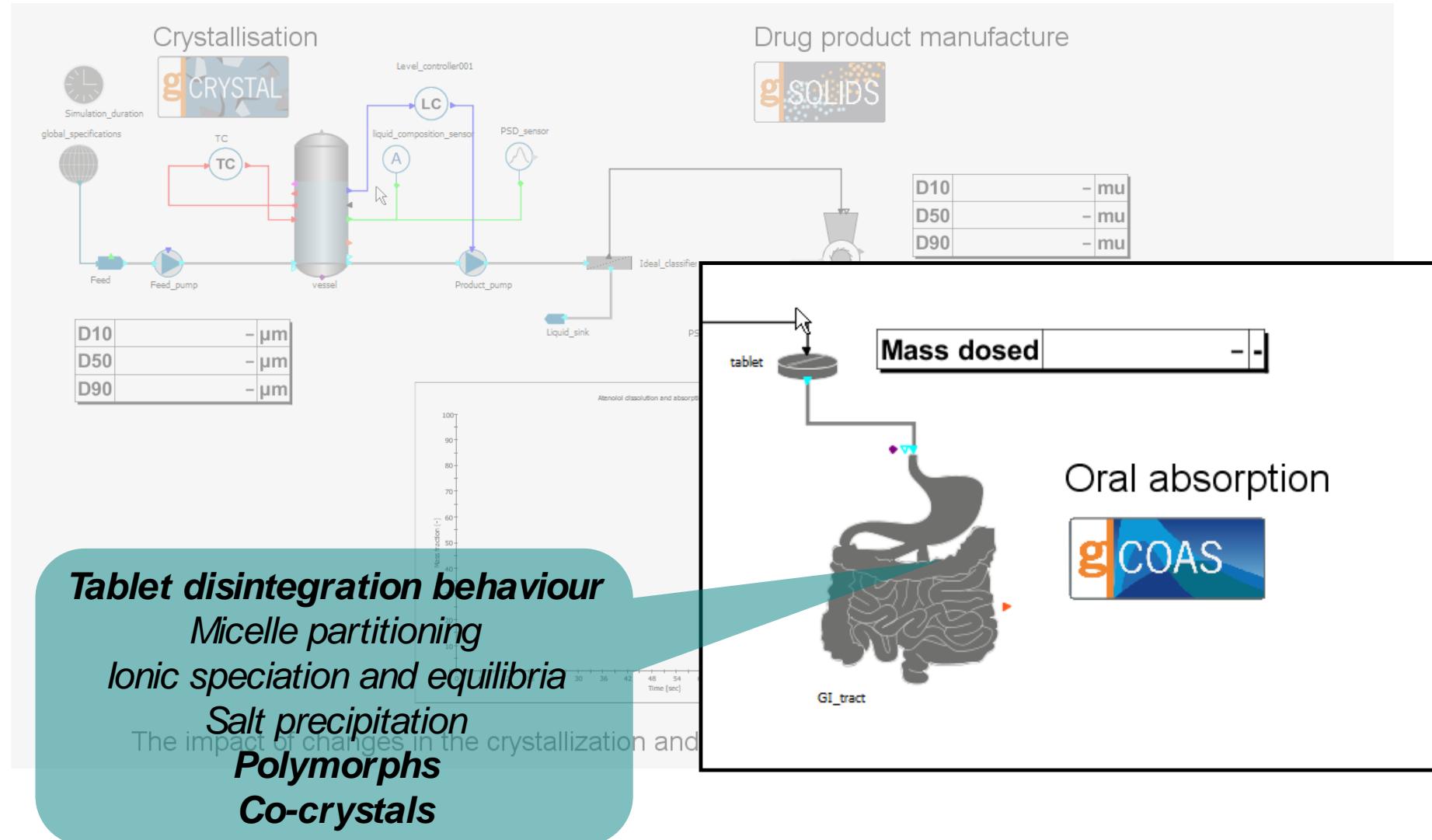
Granules combined into tablets. Preserve relevant properties of granules

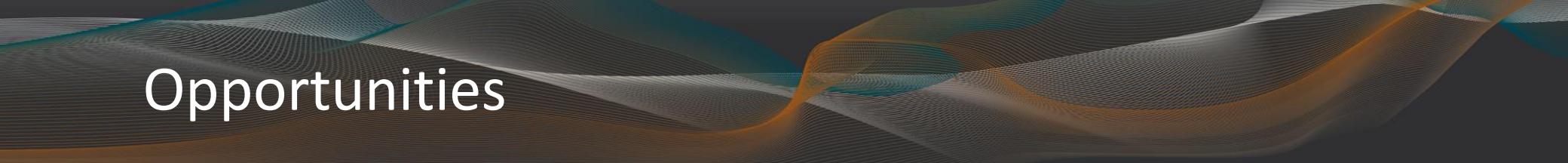


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Property package and phase structure to handle the following complex phenomena

Oral absorption





Opportunities

Increasing usability

The new physical property infrastructure has enabled more general database feature



■ Flexible database structure compatible with

- PSE provided databases
- 3rd party databases
- corporate databases, etc.

Materials



Dosage forms



Equipment



Physiology



■ Significant increase in usability

- single repository for validated data
- less looking up of data
- fewer transcription errors



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Significant increase in usability Material database

Pre-database

source_sieve_data (Source_solid_distributed)

Is the flowrate controlled?	No
PSD specification	Specified from sieve analysis
Density specifications	Specify bulk density and intra-particle void
Sieves specified in	Descending order
Flowrate specified as	Mass

Specify

Single solid phase leaving source: Coffee

Mass flowrate: 1 kg/s

Mass fraction: Uniform for entire array (radio button selected) 1 kg/kg

Temperature: 298.15 K

No. of sieves: 4

Sieve analysis data: Uniform for entire array (radio button selected) Per element

Sieve analysis results:

No. of sieves	Screen size ...	Weight on s...
1	1000	0.2
2	800	0.2
3	600	0.2
4	400	0.2
5		

Weight on pan: 0.2 kg

Bulk density: 600 kg/m³

Intra-particle void: 0 m³/m³

OK Cancel Reset all Help

Using database

solid_source_1 (Source_only_solid_distributed_gWIZ)

Conditions	Specify
<input checked="" type="checkbox"/> Material: Fast Flo Lactose	
<input checked="" type="checkbox"/> Material grade: 315 NF Lactose	
<input checked="" type="checkbox"/> PSD D25: 23.69 Micron	
<input checked="" type="checkbox"/> PSD D50: 27.146 Micron	
<input checked="" type="checkbox"/> PSD D75: 31.651 Micron	
<input checked="" type="checkbox"/> Bulk density: 280.0 kg/m ³	

OK Cancel Reset all

- Material list filtered by species available
- User now only needs to specify values for flowrate and temperature
- Custom material still a possibility: pre-database functionality

Significant increase in usability Equipment database



Pre-database

Roller_compactor (Roller_compactor_gWIZ)

Specify

Equipment	User input
Material properties	Roll force per width
Ribbon properties	

Equipment

Roll diameter	1	m
Roll width	1	m
Maximum roll gap	0.01	m
Minimum roll gap with closest distance between rolls	0.00001	m

Operating conditions

Roller speed	10	rpm
Angular position at which feed pressure is applied	50	degree
Thermal energy addition during compaction	0	J/s
Feed material bypass fraction	0.0	Per element
Applied roll force per width of roll	10	kN/cm

OK Cancel Reset all Help

Using database

Roller_compactor (Roller_compactor)

Modelling approach Reynolds et al, 2010

Specify

Equipment	From database
Material properties	Roll force per width
Ribbon properties	

Equipment

Manufacturer	Alexanderwerk	
Roller compactor	Alexanderwerk WP 120	
Roll diameter	0.12	m
Roll width	0.04	m
Maximum roll gap	0.005	m

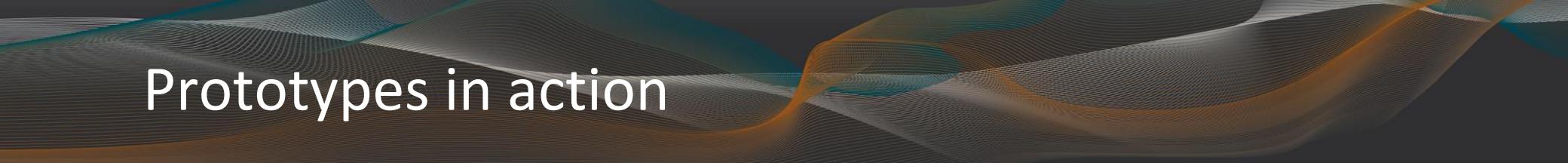
Operating conditions

Roller speed	20	rpm
Angular position at which feed pressure is applied	The specified value (20) is greater than the stipulated range.	
Thermal energy addition during compaction	0	J/s
Applied roll force per width of roll	10	kN/cm

OK Cancel Reset all Help

- User now only specifies operating conditions, which are verified against bounds also provided by the database
- Custom equipment still a possibility: pre-database functionality





Prototypes in action

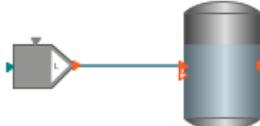
Configure this flowsheet

Crystallisation, granulation and tablet compaction



Liquid source

Active phases - -



Solid source 1

Active phases - -

Solid source 2

Active phases - -



Crystalliser

Crystalliser D₅₀ - μ

Active phases - -

Blender

Active phases - -

Roller compactor

Granule porosity - m³/m³

Active phases - -

Phase hierarchy - -

Mill

Tablet press

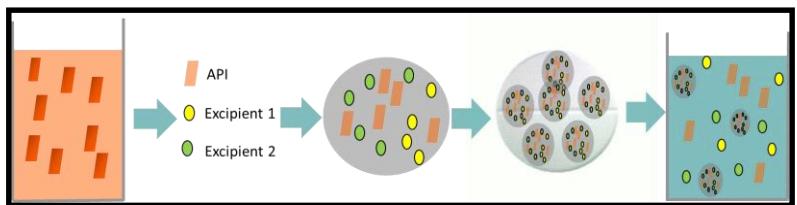
Tablet porosity - m³/m³

Active phases - -

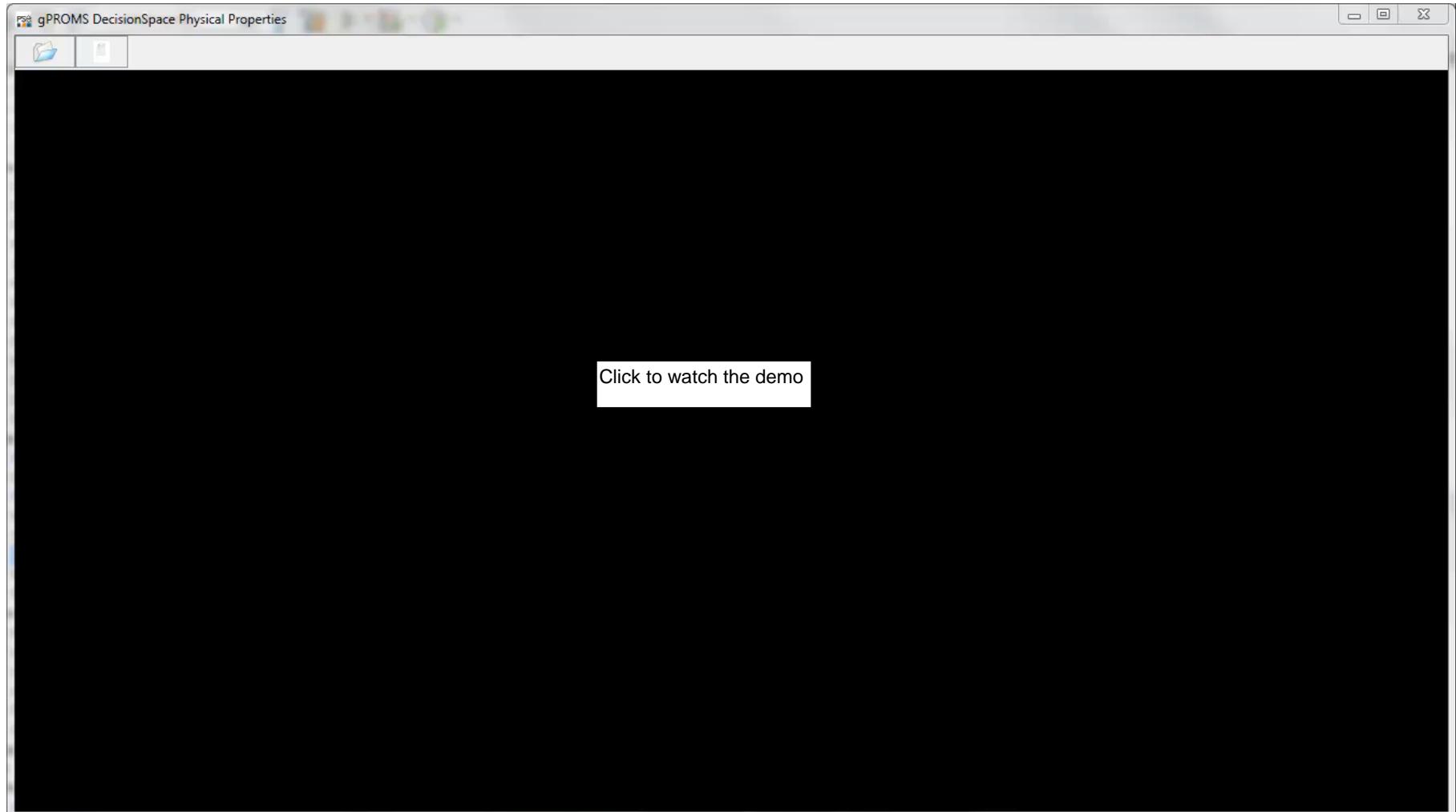
Phase hierarchy - -

Tablet dissolution

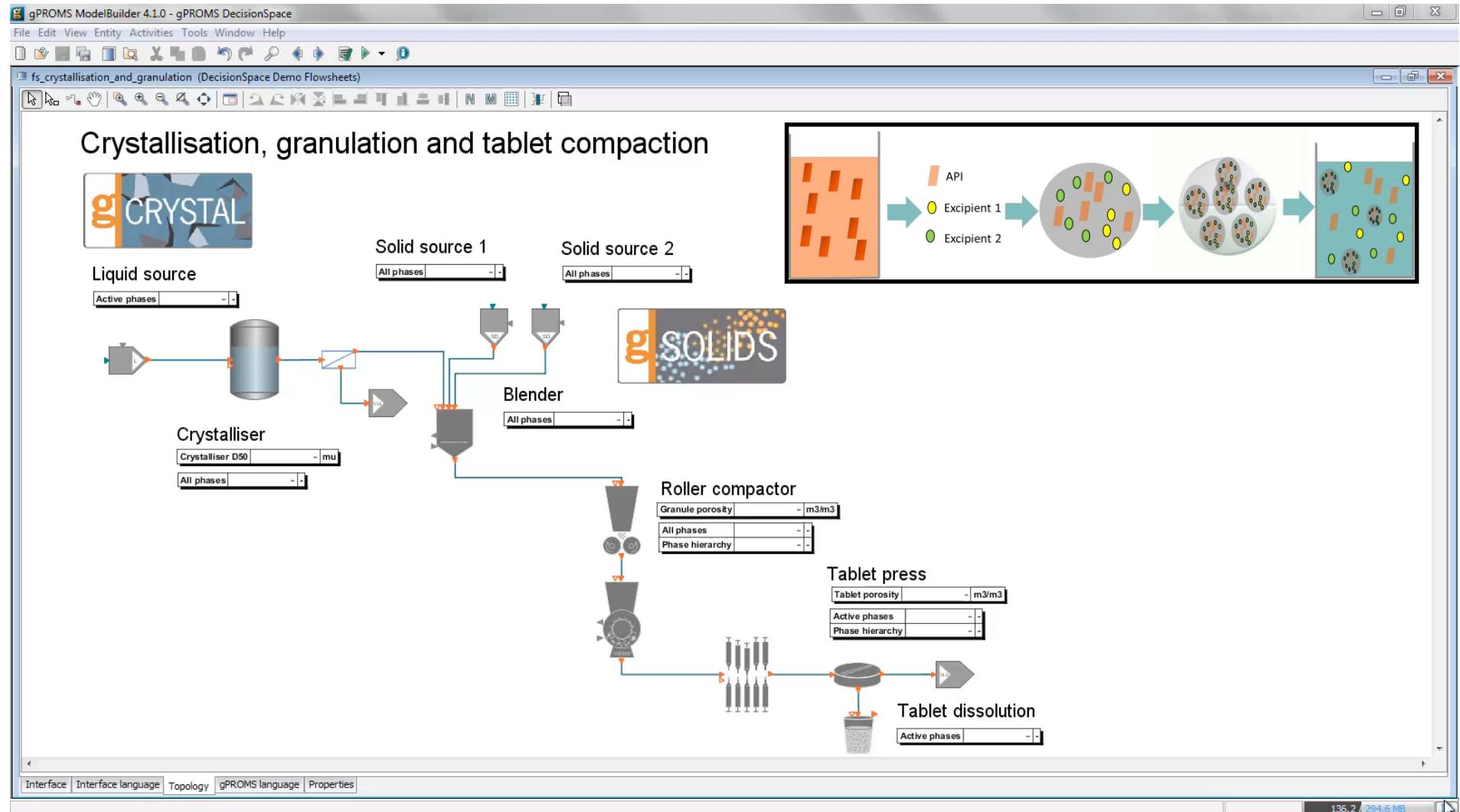
Active phases - -



Definition of physical properties

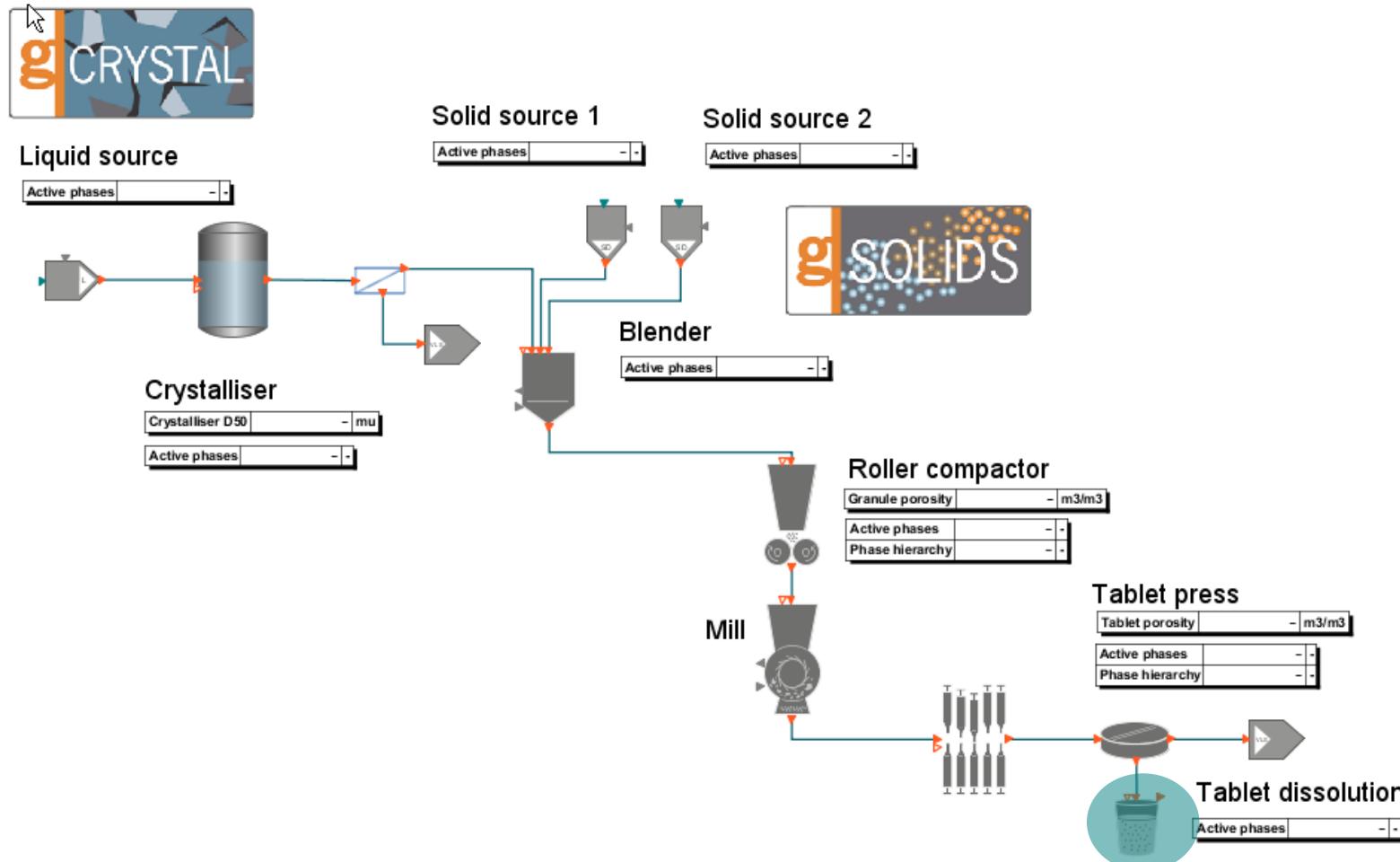


Structured phases and databases



Let's look at some simulations...

Crystallisation, granulation and tablet compaction



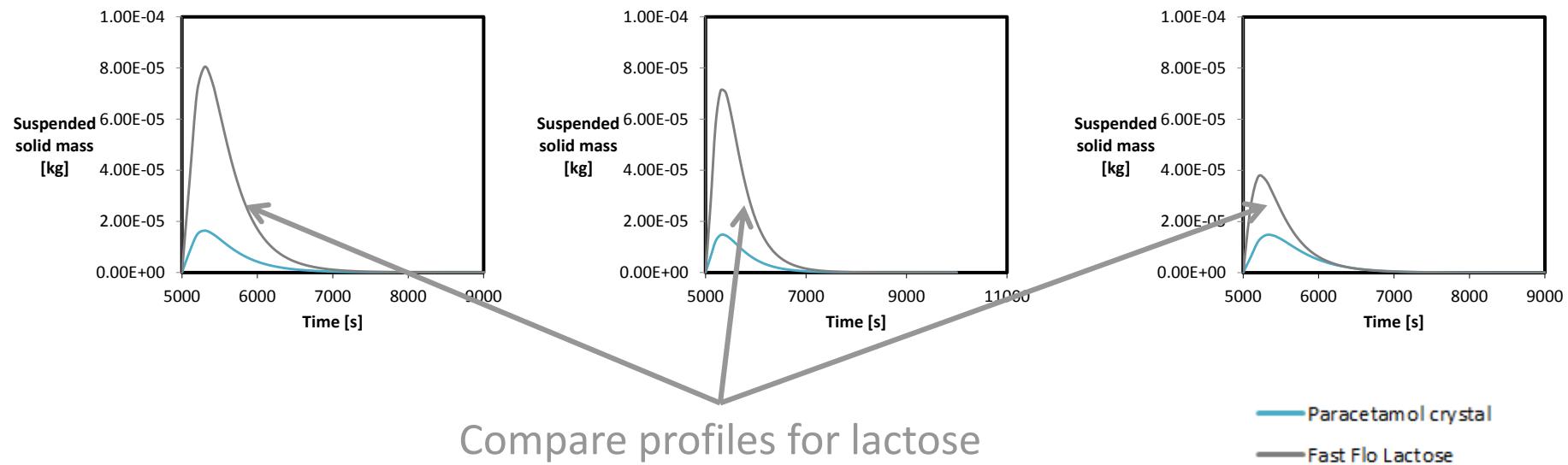
Impact of upstream processing on formulation properties

Tablet dissolution profiles for lactose and paracetamol

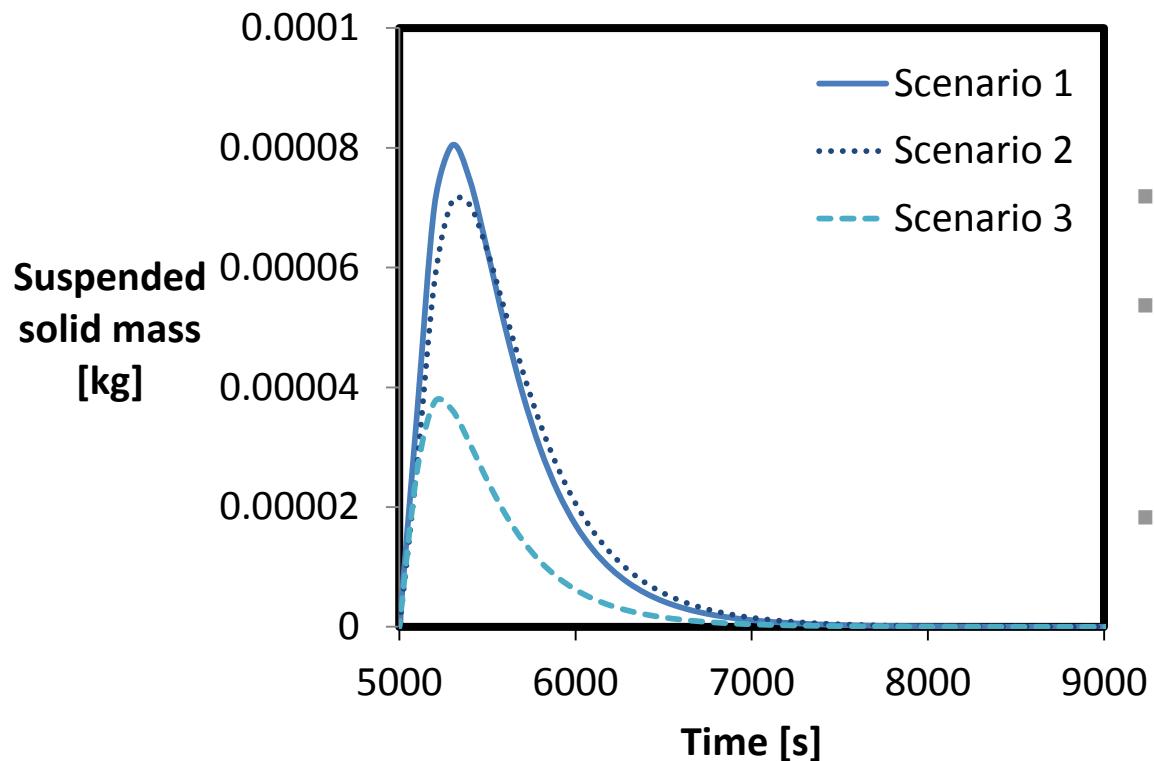
Scenario 1
Base case

Scenario 2
Higher tablet compaction pressure

Scenario 3
Lower lactose D50



Impact of upstream processing on formulation properties



Tablet dissolution profiles for lactose

- **Scenario 1:** Base case
- **Scenario 2:** Higher tablet compaction pressure -> slower tablet disintegration -> fewer suspended lactose particles
- **Scenario 3:** Lower lactose D₅₀ -> faster lactose dissolution -> less suspended lactose

Practicalities and logistics

This interoperability stuff sounds great, but I'm only interested in one product. What will it do for me?



Shared functionality, e.g.,

- Databases
 - dosage forms, equipment, physiology, materials, etc.
- pH shift crystallisation
- Oiling out crystallisation
- Co-crystals
-

Release date and backward-compatibility



- Beta release in autumn 2015
 - on a beta of v4.2 of the gPROMS platform
- Integrated framework will be backward-compatible with gCRYSTAL, gSOLIDs and gCOAS
 - licences
 - flowsheets

Crystallisation, granulation and tablet compaction

■ Novel architecture for,

- Complex phenomena
- Composite, distributed phase structures

■ Link between upstream processing conditions and product performance

■ Distil this complexity into a single, usable framework

Many thanks to...



- PSE Solids Advisory Board

- Costas Pantelides
- Sean Bermingham

PSE Product development team for Life Sciences, Food, Consumer Goods, Specialty and Agrochemicals,

- Niall Mitchell – London, gCRYSTAL
- David Slade – London, gSOLIDs
- Edd Close – London, gCOAS
- Jianfeng Li – New Jersey, gSOLIDs
- Dana Barrasso – New Jersey, gSOLIDs
- Dan Braido – New Jersey, gCOAS
- PSE Software Technology Group



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Thank you

