SIMULATION STUDIES TO PREDICT DRUG PRECIPITATION *IN VIVO*

APM Forum, 5th June 2013

PURDUE UNIVERSITY

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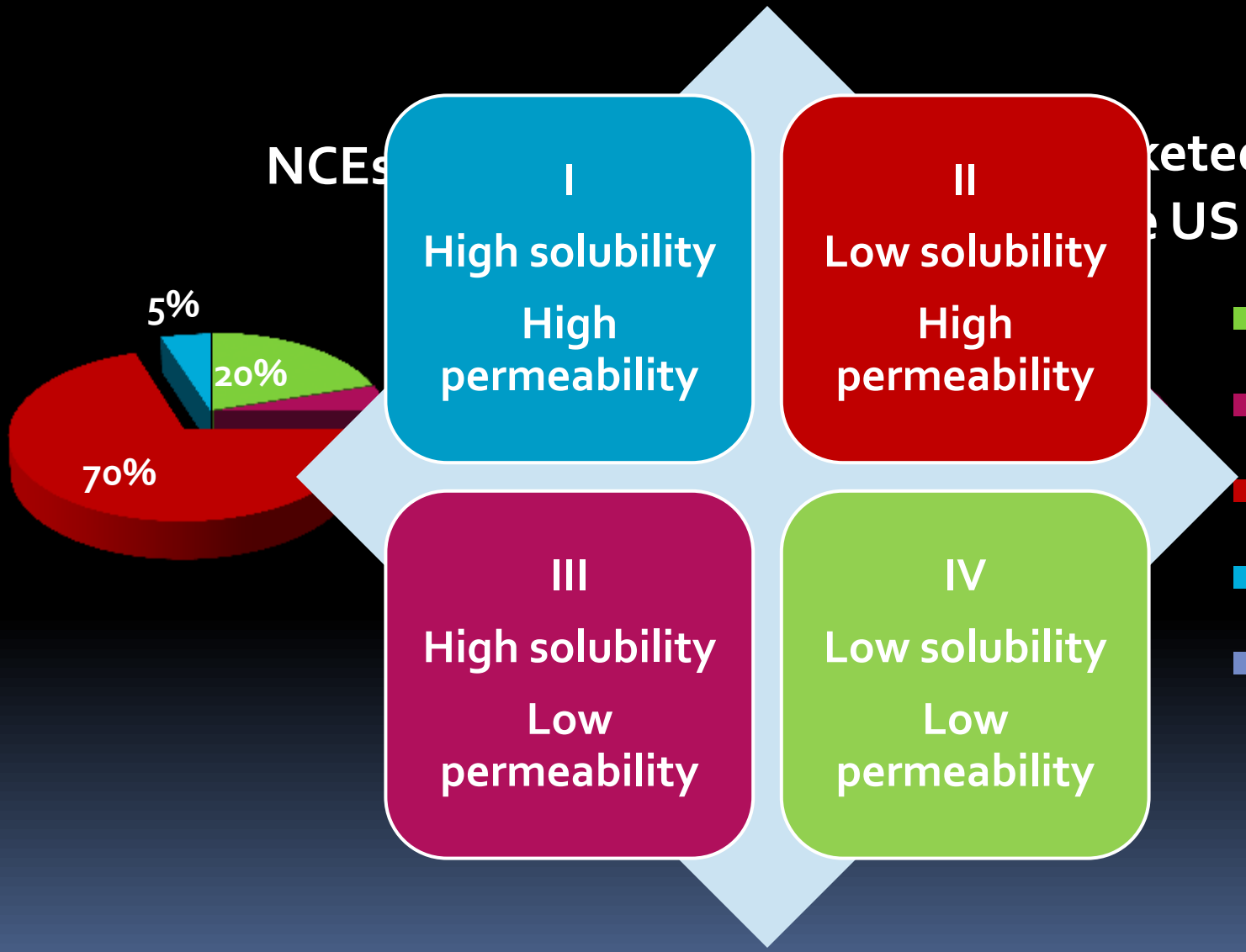
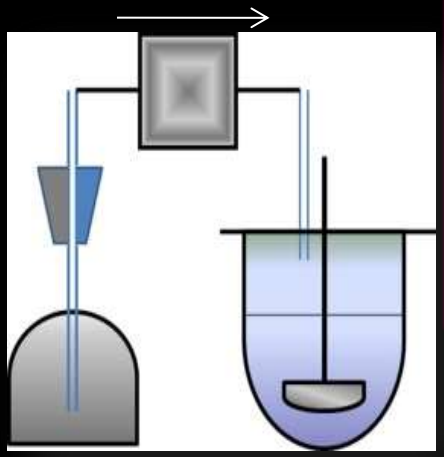
Motivation


NCEs
keted Drugs
e US
I
High solubility
High permeability
II
Low solubility
High permeability
III
High solubility
Low permeability
IV
Low solubility
Low permeability
5%
20%
70%
Class IV
Class III
Class II
Class I
Unclassified

Physical Models of the GI Tract

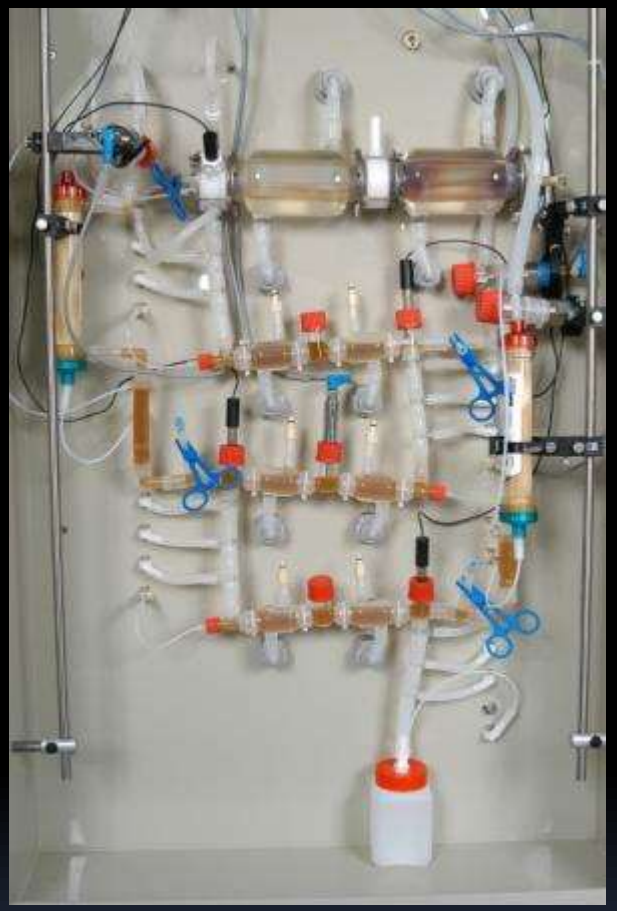


Donor phase Acceptor phase

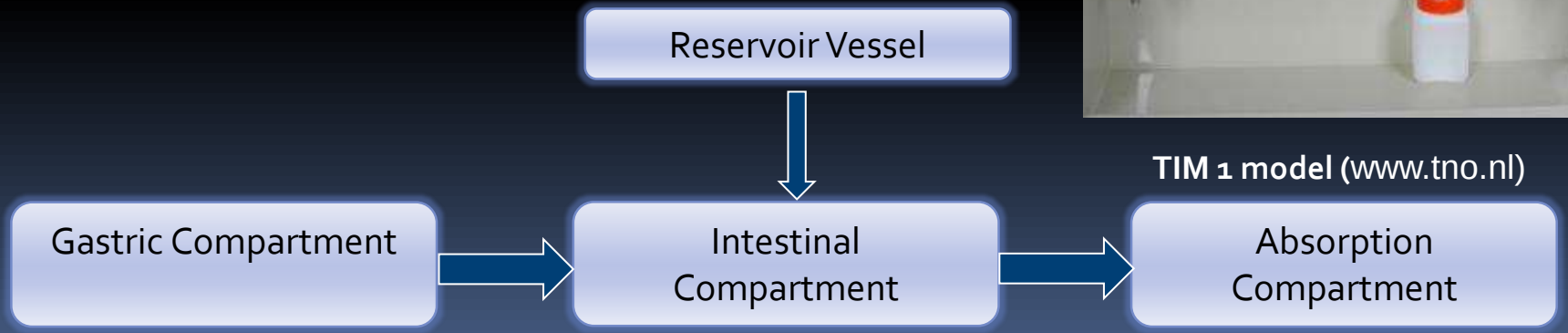
Experimental set up to examine dipyridamole precipitation

Physical modeling of the GI tract:

- Two compartment model
- Multi-compartmental dissolution system

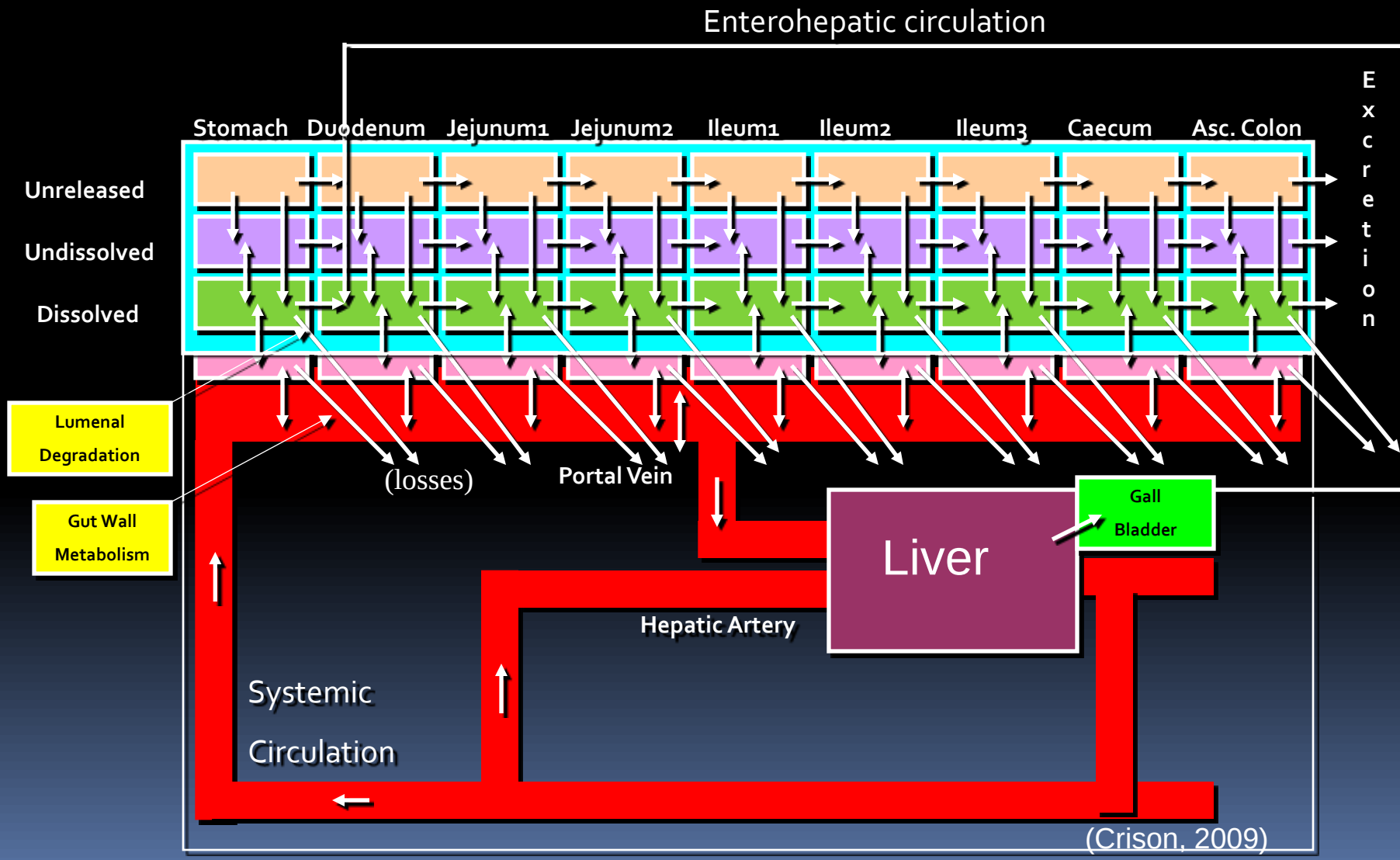


TIM 1 model (www.tno.nl)



Scheme of a multicompartment dissolution system

ACAT Model



(Crison, 2009)

Current Commercial Software

Simulation Parameters: Human

Species | **Absorption** | Distribution | Metabolism & Excretion

GI-Anatomy | GI-Physiology | Active Transport | Metabolism | Controlle

Dissolution function	PARTICLE	
Total amount of drug	50,00	mg
Density of drug material	1,00	g/cm³
Aqueous diffusion coefficient	5,00	x 1E-6 cm²/s
Thickness of unstirred water layer	20,00	µm

Particle

○ Monodisperse ◉ Polydisperse

Particle size distribution	Normal	
Mean particle radius	10,00	µm
Standard deviation of particle radius	3,00	µm
Number of bins	11,00	
Lower bound of particle radius	1,00	µm
Upper bound of particle radius	19,00	µm
Treat precipitated drug as	Soluble	
Immediately dissolve particles smaller than	10,00	nm

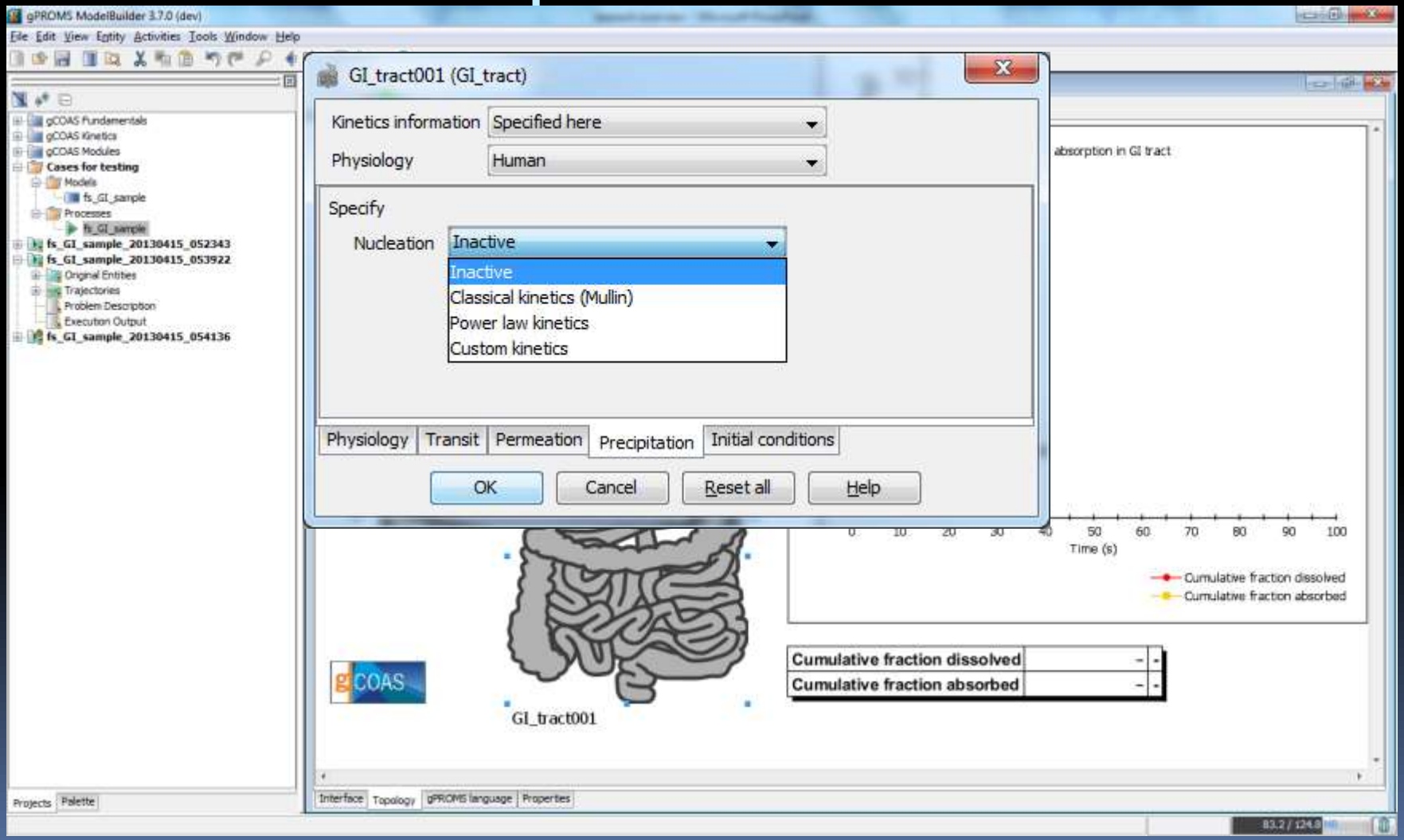
Bayer Technology Services

PK-SIM®

Tab … **Plus™ simulation**

Gen…	…arameters	Pharmacokinetics
MW…	…conditions	Body weight: 70 kg
clog…	…del: log D model	First pass extraction (fixed): 12.5%
pK_a…	…it time: 0.1 h	Blood to plasma concentration ratio = 1
Dos…	…250 mL	Clearance: 0.15 L/(h kg)
Low…	…transit time: 3.3 h	Vc: 1.9 L/kg
Mean precipitation time: 1800 s	Small intestine radius: 1.2 cm	–
Particle density: 1.2 g/mL	Small intestine length: 300 cm	–
Effective permeability: 4.4×10^{-4} cm s^{-1}	Colon volume: 1200 mL	–
Effective particle radius: 5 µm	–	–

gCOAS : a tool to Predict Oral Absorption



gCOAS: Nucleation Models

- **Classical nucleation:**
  - $J_{prim} = lnA_0 \left(\frac{-16\pi(\alpha\sigma)^3 v^2{}_0}{3k^3T^3 lnS^2}\right)$
  - Parameters to be estimated: pre-exponential factor and the surface energy correction factor.
- **Power law kinetics:**
  - $J_{prim} = lnk_n \left(\frac{\Delta C}{\rho_c}\right)^n \exp\left(\frac{-E_{A,n}}{RT}\right)$
  - Parameters to be estimated: nucleation coefficient, nucleation order, and the activation energy.
- **Custom kinetics:**
  - E.g., extracting nucleation rates from probability distribution functions of induction time
  - $P(t) = 1 - \exp(jV\left(t - t_g\right))$
- Input induction time (900 s)

gCRYSTAL: a Tool to Estimate Crystallization Kinetic Parameters

- Case study: felodipine precipitation
- Objectives:
  - Extract the nucleation and growth kinetic parameters of felodipine to use as inputs in gCOAS
  - Quantify the inhibitory effect of HPMC on both the nucleation and growth rates of felodipine

Abbou Oucherif, K., Raina, S., Taylor, L. S. & Litster, J. D. Quantitative analysis of the inhibitory effect of HPMC on felodipine crystallization kinetics using population balance modeling. *CrystEngComm* (2013).doi:10.1039/c2ce26490k

Experimental Methods

- 18 mL 50 mM pH 6.8 buffer at 25 °C
- Felodipine supersaturations of 5 and 10
- HPMC concentrations: 0 to 3.5 ppm.
- Seeded experiments: 2 mg of seeds were prepared by grinding with a mortar and pestle
- Particle size characterized via a Malvern Mastersizer laser diffractometer (Worcesteshire, UK).
- Concentration measured using Ocean Optics 6 channel fiber optic system

Alonzo, D. E. *et al.* Characterizing the Impact of Hydroxypropylmethyl Cellulose on the Growth and Nucleation Kinetics of Felodipine from Supersaturated Solutions. *Crystal Growth & Design* **12**, 1538–1547 (2012).

Modeling Approach

- Extract the growth kinetic parameters from seeded experiments
  - Power law kinetics used to model crystal growth
  - $G = k_g \left(\frac{\Delta C}{\rho_c}\right)^g \exp\left(\frac{-E}{RT}\right)$
- Use growth data to extract the nucleation kinetic parameters from unseeded experiments
- Power law kinetics used to model crystal nucleation
  - $J_{prim} = lnk_n \left(\frac{\Delta C}{\rho_c}\right)^n \exp\left(\frac{-E_{A,n}}{RT}\right)$

gCRYSTAL : Estimation of PSD Parameters

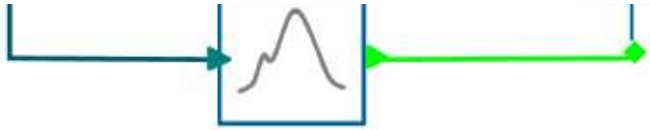
global specifications

TOP

Model Parameters

- Probability of parameter lying between (Final Value -α% Confidence Interval) and (Final Value +α% Confidence Interval) = α%
- The t-value shows the percentage accuracy of the estimated parameters, with respect to the 95% confidence intervals.

Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
Flowsheet. PSD_input_predicted.peak(1).L0_g	11.263	11.751	1	30	2.284	2.849	4.217	3.953	1.205
Flowsheet. PSD_input_predicted.peak(1).sd_g	2.30738	2.23454	1	5	0.3345	0.4174	0.6178	5.528	0.1765
							Reference t-value (95%):	1.89502	

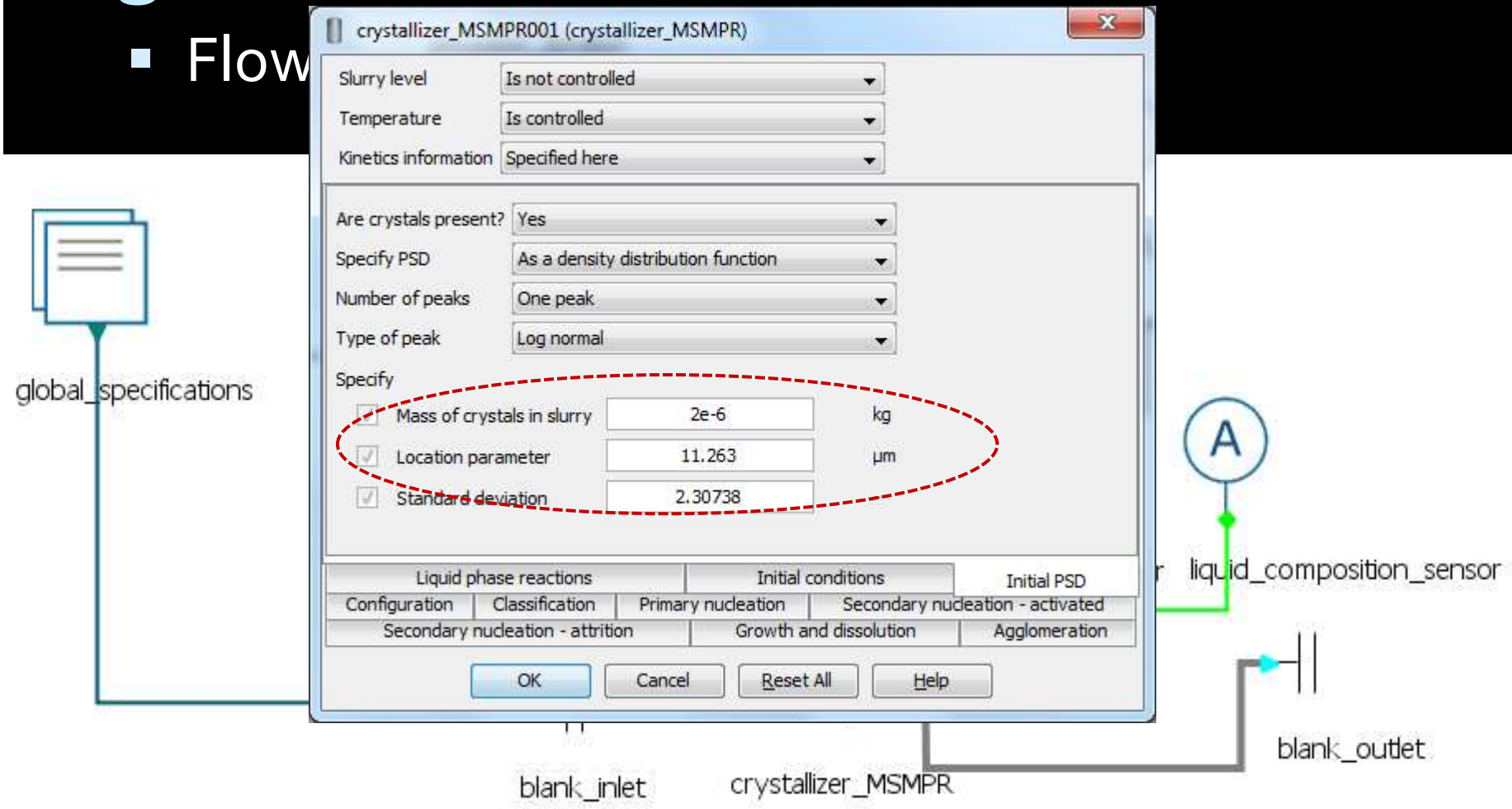


PSD_input_measured

simulation_duration001

Modeling Approach in gCRYSTAL

- Flow

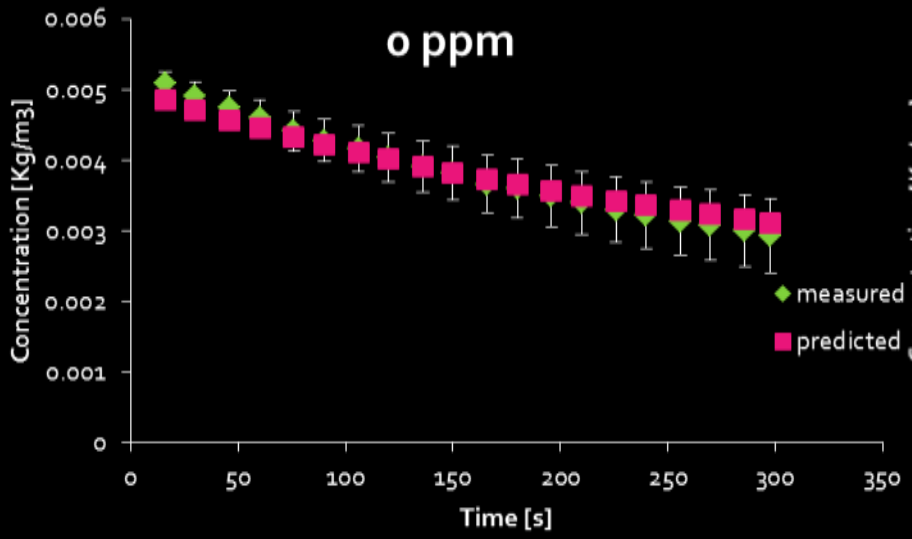


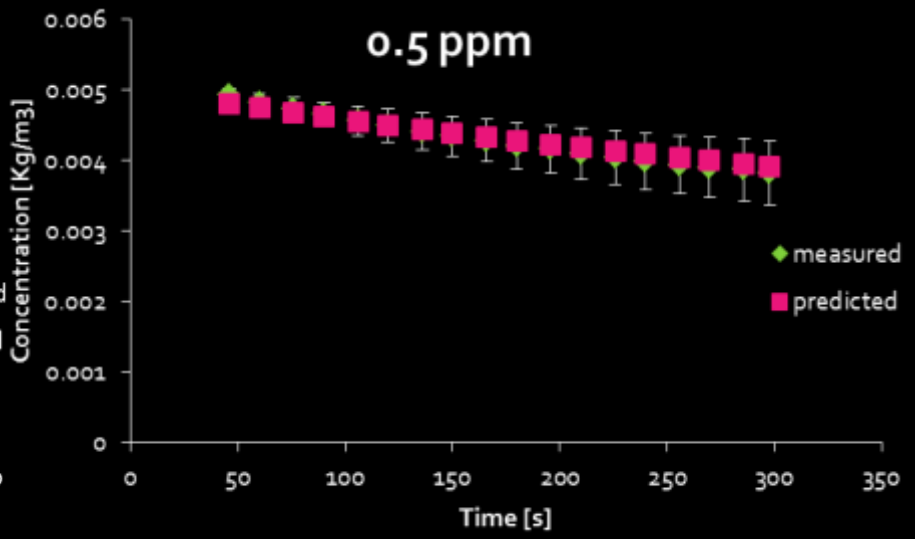
Results: growth kinetics

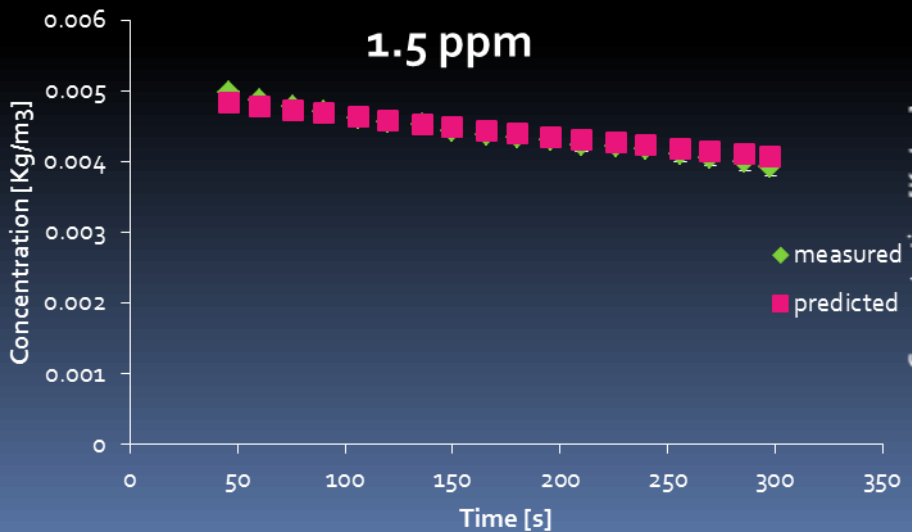
- High correlation between growth order and growth coefficient
- Growth order fixed to 1.6
- Felodipine growth is a hybrid between mass diffusion and surface integration controlled growth

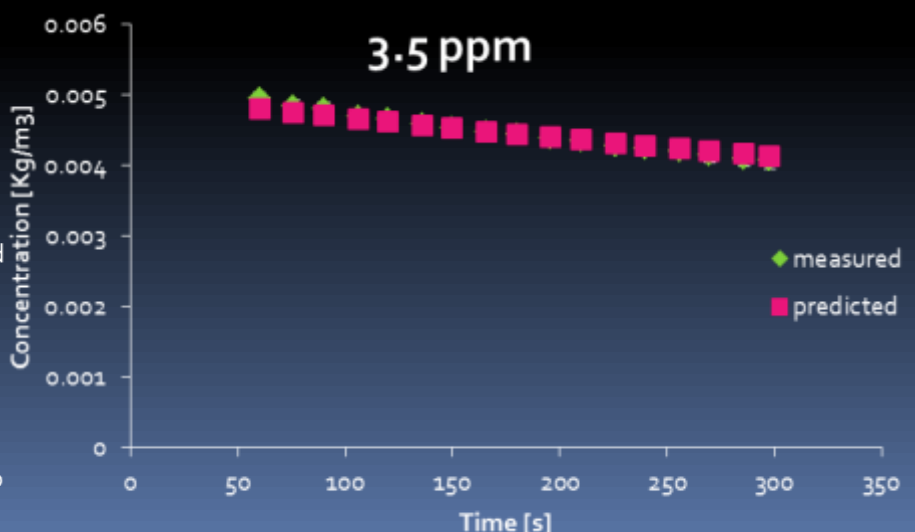
HPMC Concentration [µg/mL]	Growth order	Growth coefficient	95% confidence interval
0	1.6	0.14122	0.03148
.2	1.6	0.12878	0.01462
.5	1.6	0.0644	0.0167
1.5	1.6	0.052235	0.004368
2.5	1.6	0.050515	0.01847
3.5	1.6	0.04856	0.006527

Results: growth kinetics (cont'd)

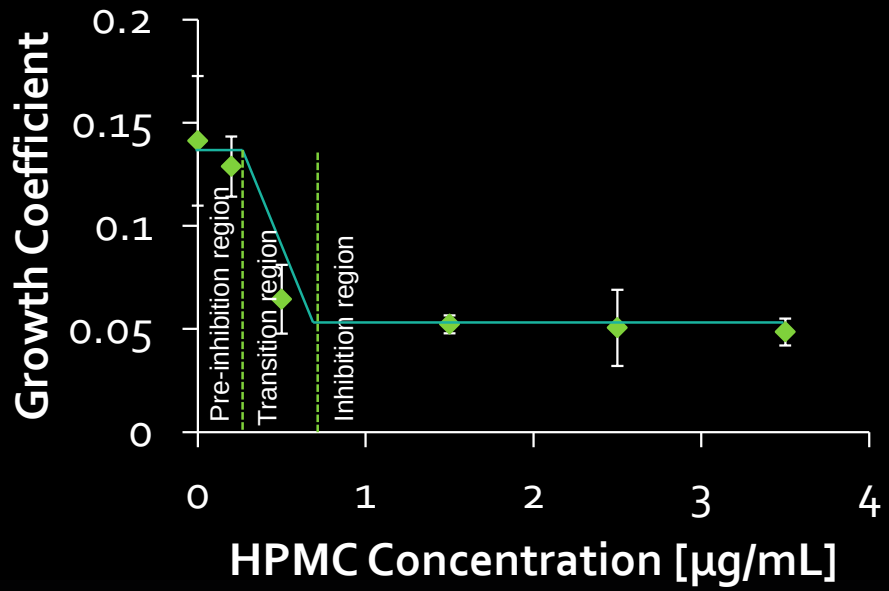


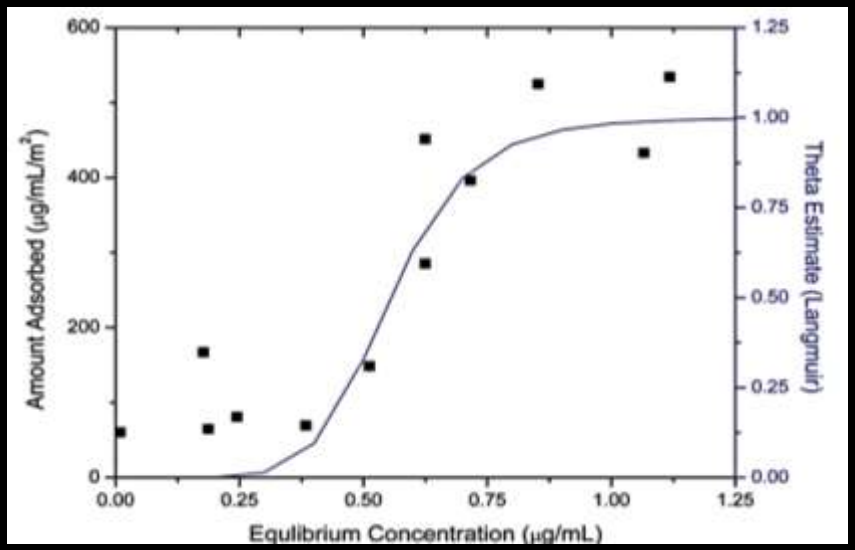






Results: growth kinetics (cont'd)



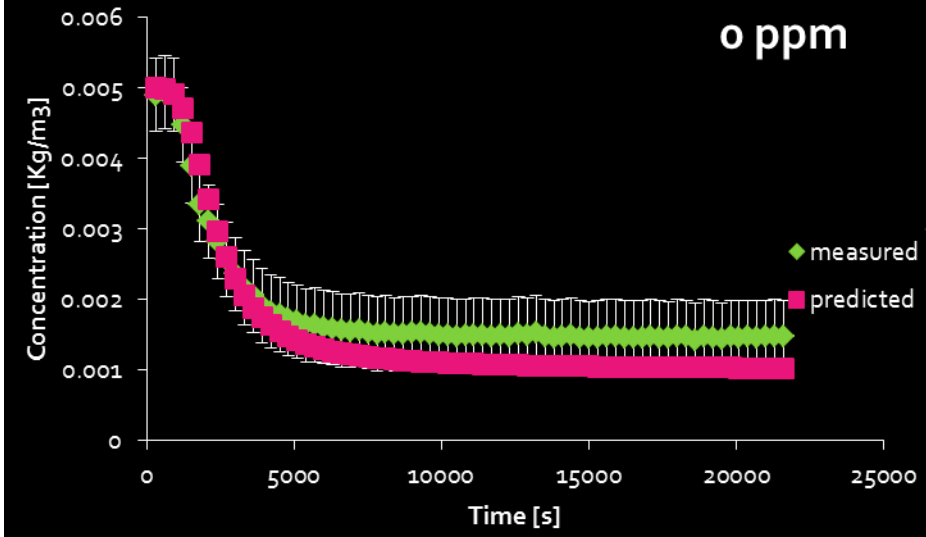


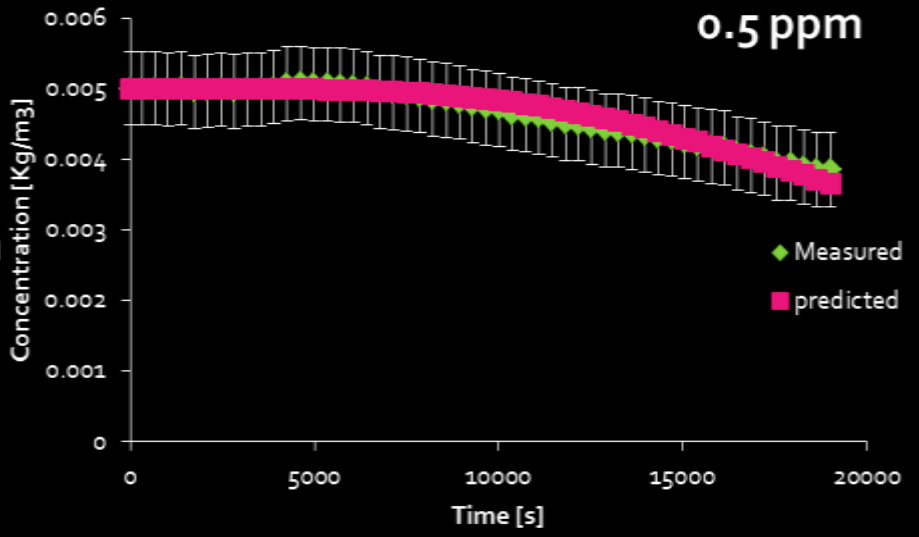
Results: nucleation kinetics

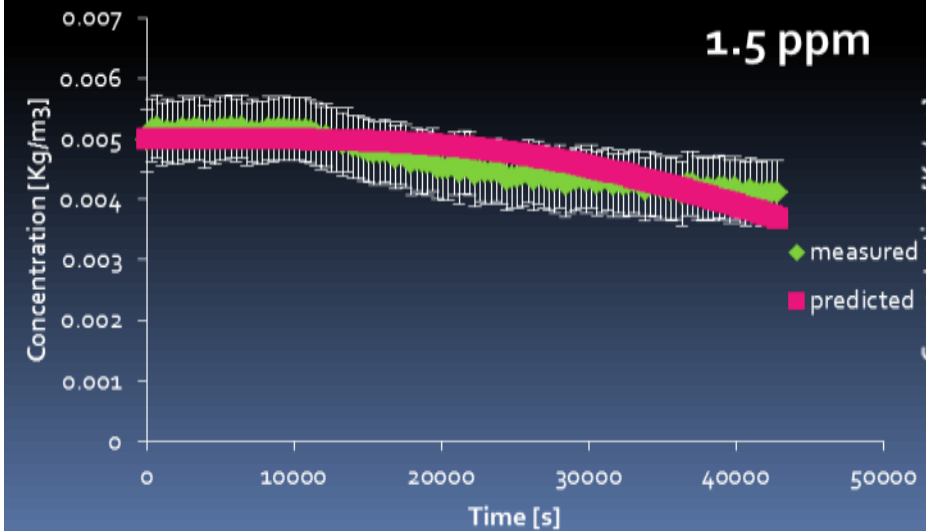
- Nucleation order fixed to 1
- Direct correlation between HPMC concentration and effect on the nucleation rate

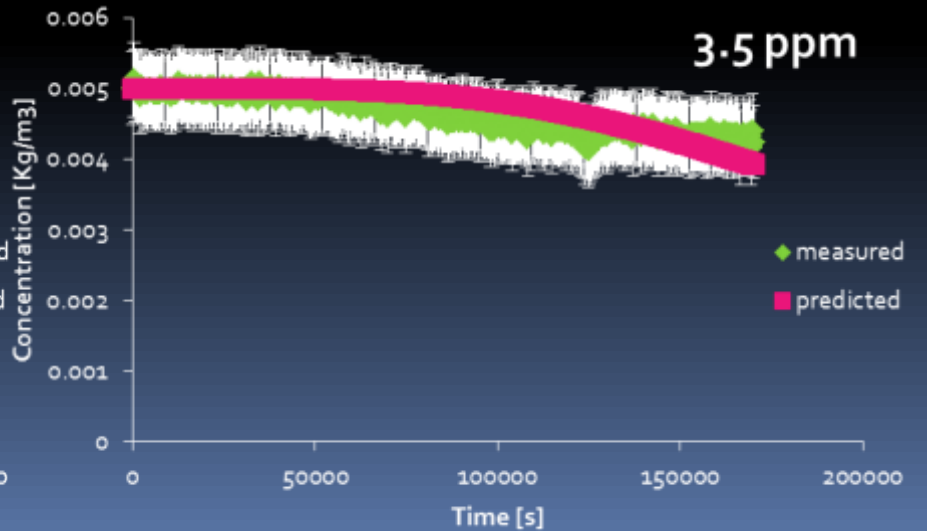
HPMC Concentration [µg/mL]	Nucleation order	Nucleation coefficient	95% confidence interval
0	1	37.66	0.487
0.5	1	30.94	0.102
1.5	1	28.26	0.068
2.5	1	28.62	0.269
3.5	1	22.63	0.012

Results: nucleation kinetics (cont'd)

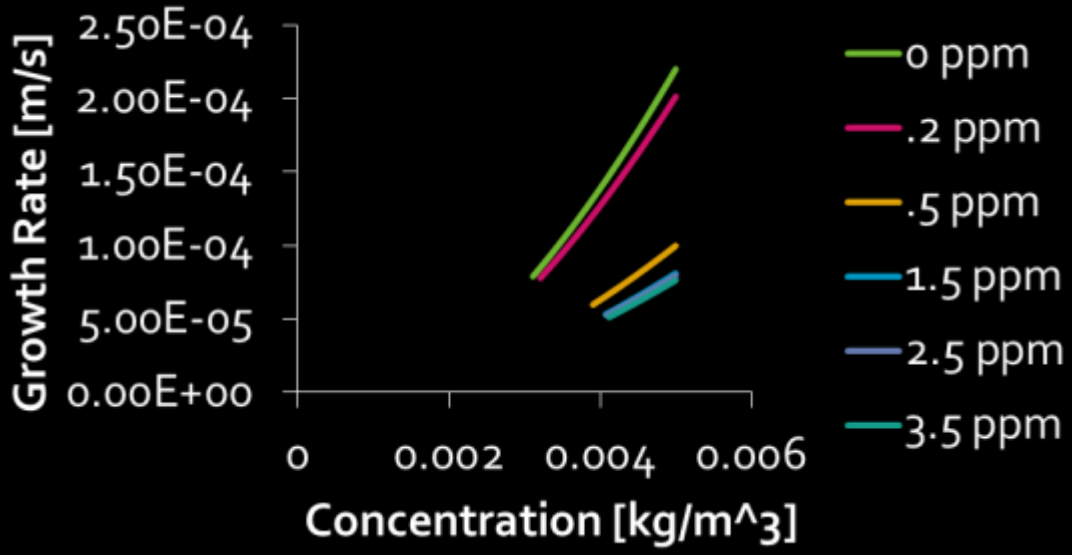


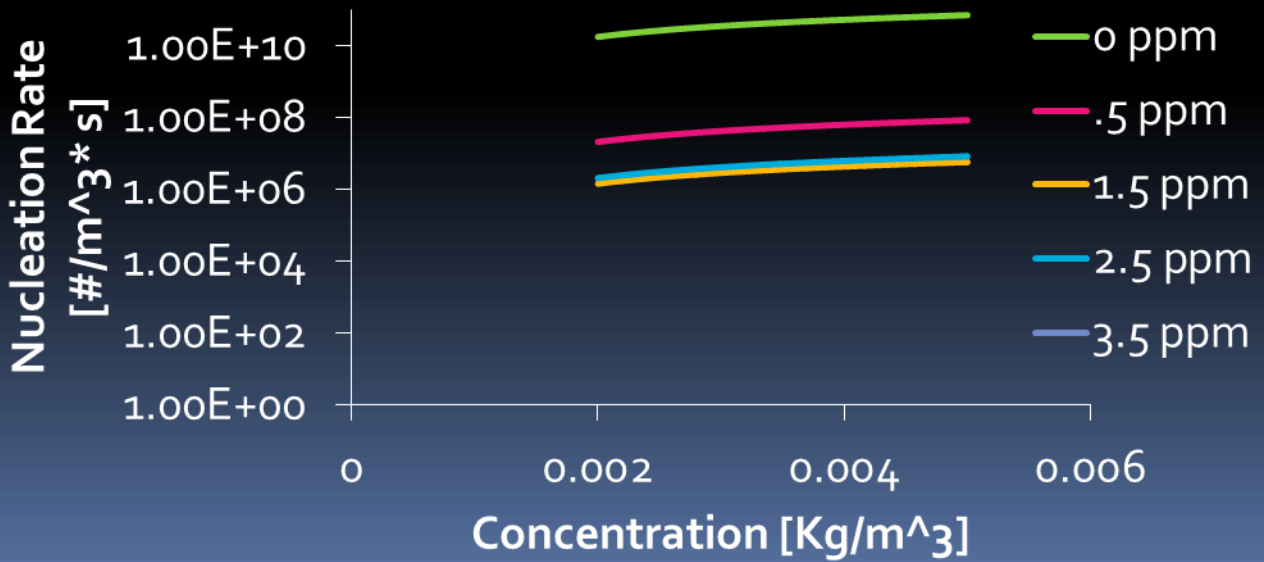






Result Highlights





Result Highlights

- HPMC has a much greater effect on inhibiting nucleation:
  - up to an 8 order decrease in nucleation rate vs. only a decrease by a factor of 2 for the growth rate
- Practical applications:
  - Better understanding of stabilization mechanism of inhibitors (decouple the effect of additives on nucleation and growth)
  - Develop better formulation strategies by facilitating the screening of polymers

Future Work

- Conduct crystallization experiments of poorly soluble APIs in the presence of bile salts
- Use estimated crystallization kinetic parameters as inputs in gCOAS
- Predict API concentration and fraction of drug absorbed as a function of time and location in the GI tract

Acknowledgments

- PSE
- Lilly Endowment Grant
- Dr. Lynne Taylor's research group
- Dr. Litster's research group

Thank you!

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Obtaining Nucleation Rates from PDFs of induction times

- Probability of forming a nuclei follows a Poisson distribution:

$$P_m = \frac{N_m}{m!}\exp(-N)$$

- Probability that there is at least 1 nucleus:

$$P_{\geq 1} = 1 - P_0 = 1 - \exp(-N)$$

- Nucleation rate is:

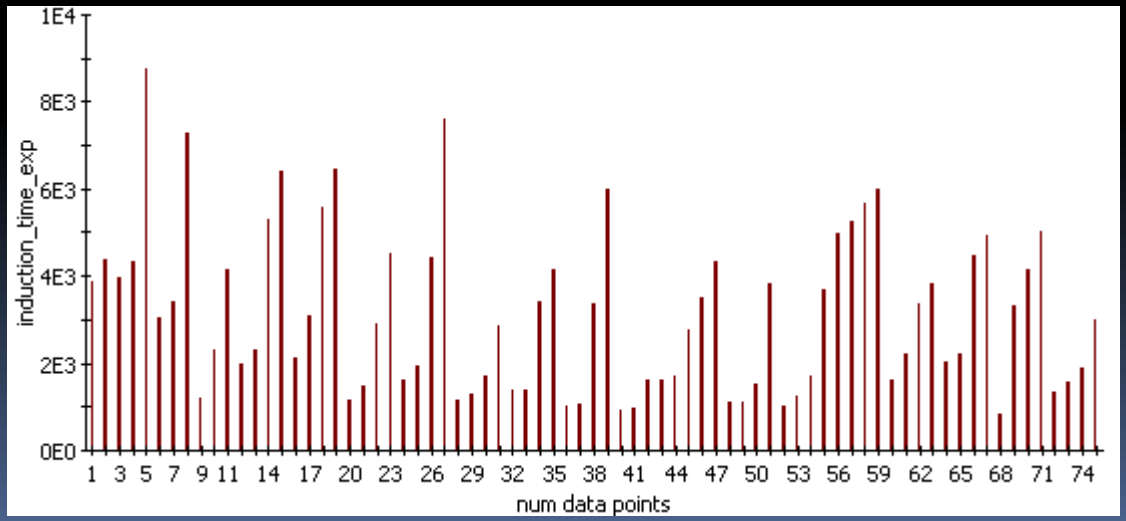
$$N = JVt_j$$

Nucleation time $t_j = t - t_g$

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

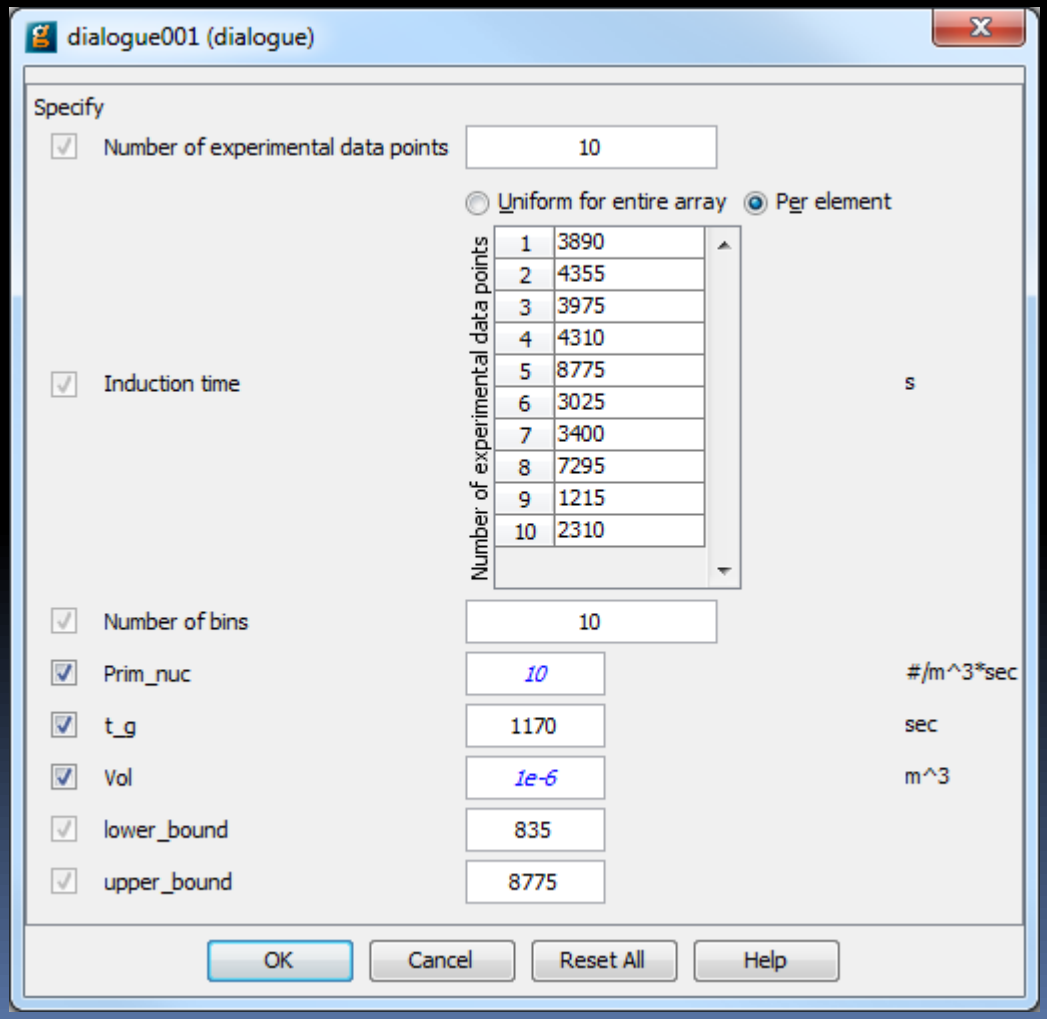
Case study:

- m-aminobenzoic acid crystallization
- Experiments conducted at isothermal conditions
- Constant supersaturation
- Induction times measured with the Crystal 16



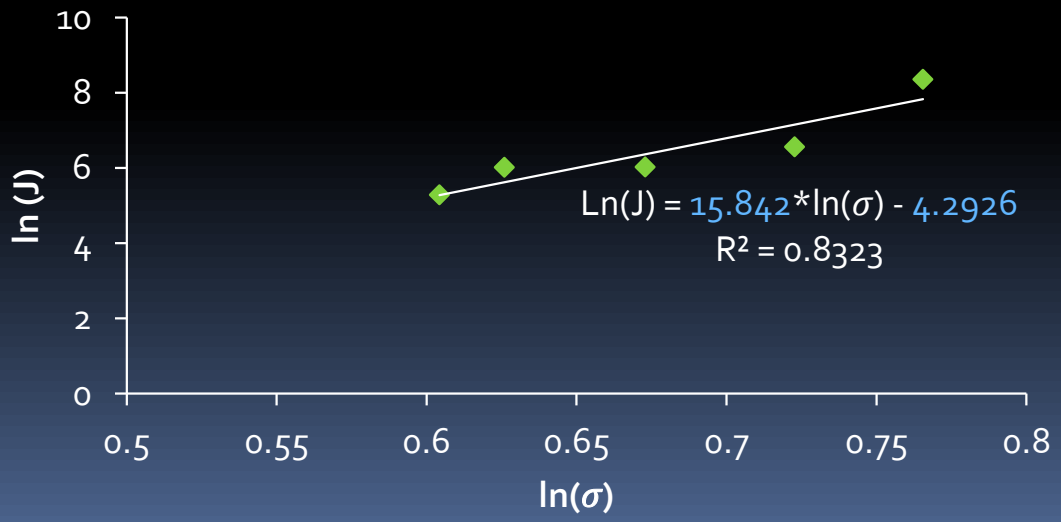
Jiang, S., & Ter Horst, J. H. (2011). Crystal Nucleation Rates from Probability Distributions of Induction Times. *Crystal Growth & Design*, *11*(1), 256–261. doi:10.1021/cg101213q

Parameter Estimation in gPROMS



Extracting Crystallization Kinetics

Supersaturation (σ)	Nucleation rate (J) [#/m^3*s]	Standard deviation [#/m^3*s]	Growth time [s]	Standard deviation [s]
1.96	414.75	30.24	2092	123.2
2.06	709.84	51.43	924.82	55.07
1.87	411.73	30.11	2076.9	125.3
2.15	4274.8	395	325.27	11.76
1.83	198.36	18.01	3697.2	235.8



$J = k_n(\sigma)^n$

$k_n = \exp(-4.2926)$

$n = 15.842$

Felodipine as a Case Study

Objective: quantify the ability of hydroxypropylmethyl cellulose (HPMC) to inhibit both the nucleation and growth of a model amorphous compound, felodipine.

- Significance of the study: stabilize amorphous solid dispersions via the use of carrier polymers to inhibit crystallization
- Benefits of amorphous materials:
  - Enhanced dissolution rates
  - Higher supersaturation levels in the GI tract

Obtaining Nucleation Rates from PDF

- Probability of forming a nuclei follows a Poisson distribution:

$$P_m = \frac{N_m}{m!}\exp(-N)$$

- Probability that there is at least 1 nucleus:

$$P_{\geq 1} = 1 - P_0 = 1 - \exp(-N)$$

- Nucleation rate is:

$$N = JVt_j$$

Nucleation time $t_j = t - t_g$

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

Project Road Map