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Optimization of Continuous Crystallization Processes to Maintain Content Uniformity

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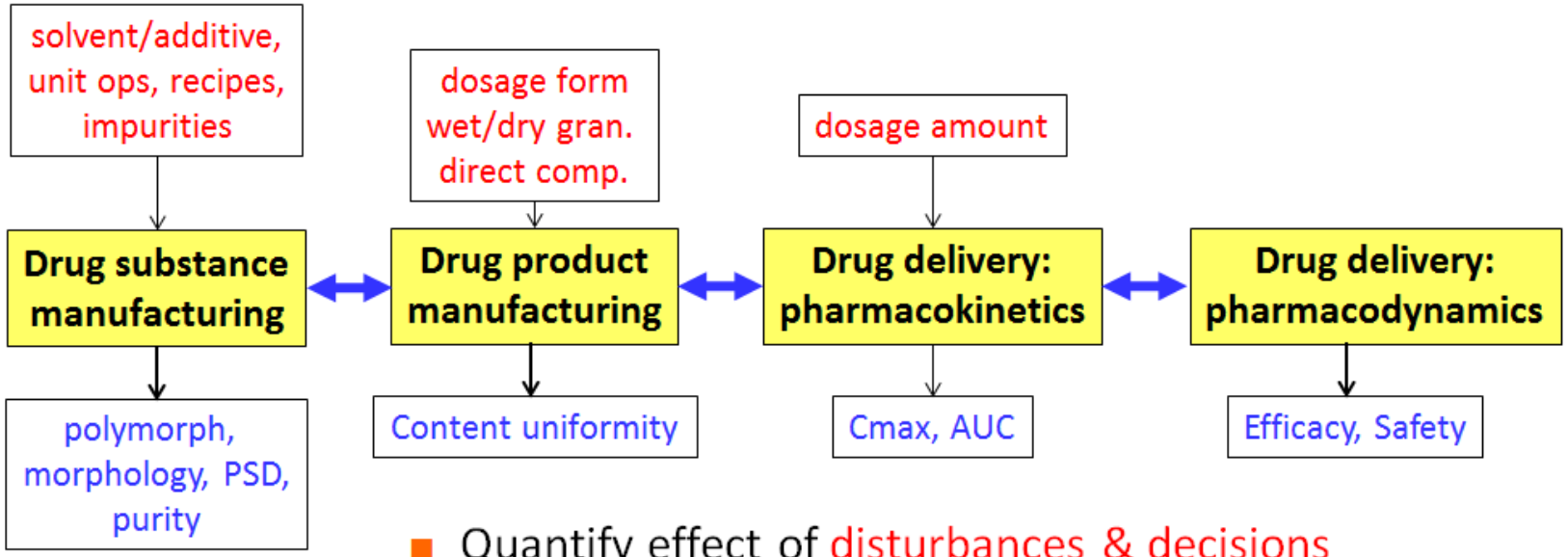
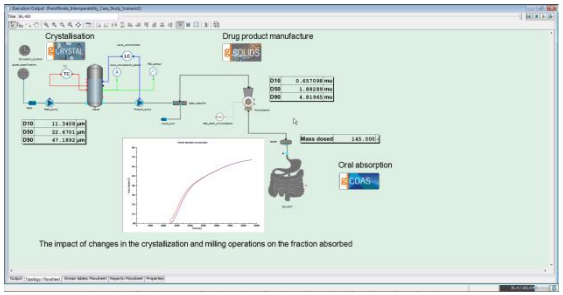
Desire End to End Understanding of Process Changes to Product Performance

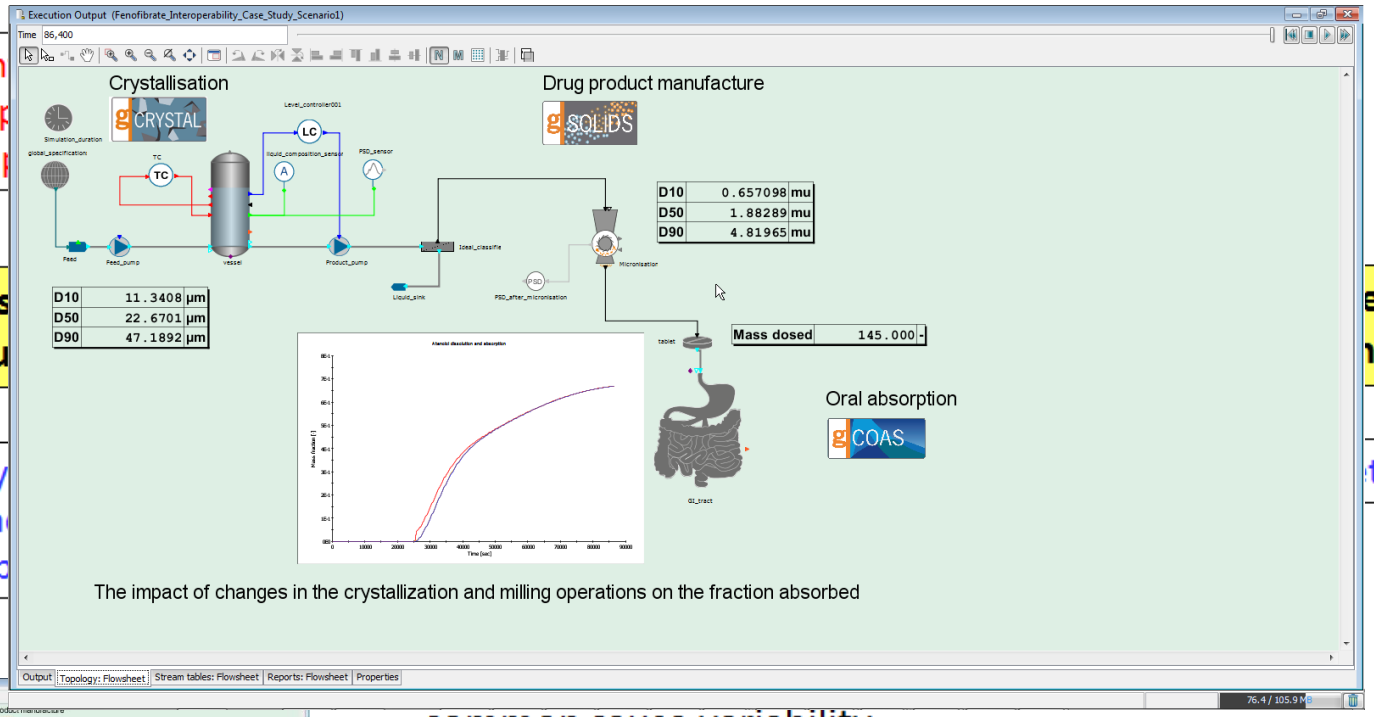


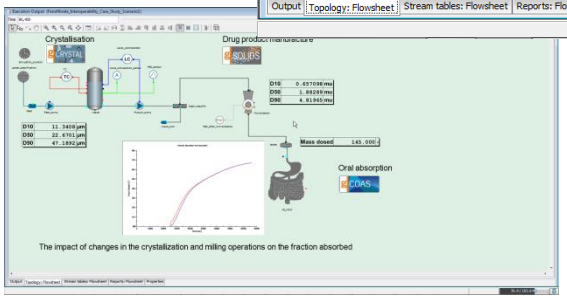


- Quantify effect of disturbances & decisions
  - uncertainty in process knowledge
  - common cause variability

  on Key Performance Indicators
  - Critical Quality Attributes
  - process economics, operability, safety

Desire End to End Understanding of Process Changes to Product Performance





- common cause variability

on Key Performance Indicators

- Critical Quality Attributes
- process economics, operability, safety

Systems Based Pharmaceutics

- A holistic approach to the development and optimization of drug manufacture and drug delivery.
- A single model based framework for the modelling of:
  - drug substance manufacture
  - drug product manufacture
  - oral absorption and pharmacokinetics
  - *Beginning to end manufacturing process.*
- Considers the impact of changes to the crystallization process on downstream unit operations (ie drug product operations such as roller compaction, tablet compression), on quality indicators (ie dissolution testing) and performance expectations (ie absorption modeling).
- A framework to support optimization across the complete manufacturing system.

Objective

To optimize a continuous crystallization process such that:

1. Physical property control is achieved via crystallization conditions.
2. Drug product quality constraints (e.g. unit dose uniformity) are met.
3. Process meets manufacturing requirements for yield and productivity.

- Utilize a population balance model coupled with product constraints (unit dose uniformity in a drug product) and manufacturing constraints (filtration time).
  - Determine optimal processing conditions to maximize yield.
- Illustrative example:
  - Model low dose drug with crystallization kinetics for paracetamol.
    - High growth, low nucleation

Physical Property Control for Pharmaceuticals: Solid Oral Dosage Forms

- Drug substance physical properties, namely particle size can effect:
  - Content uniformity.

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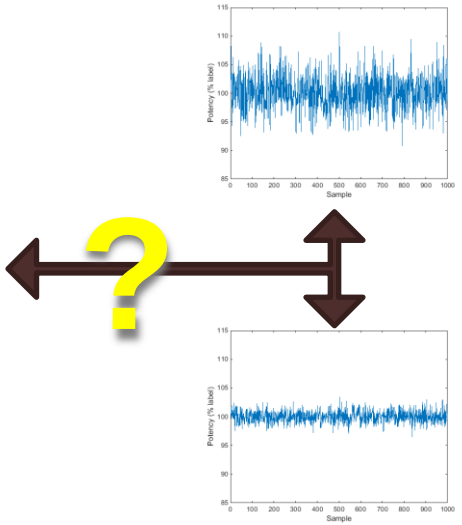
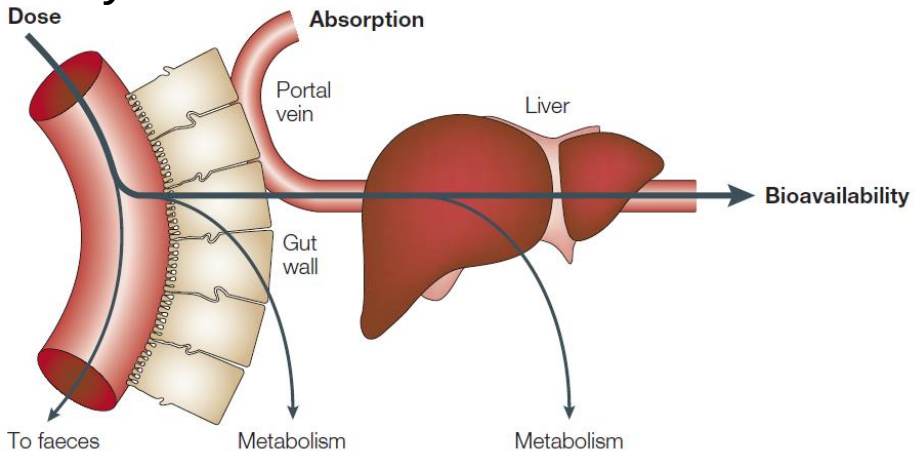


  - Bioavailability



van de Waterbeemd, H, and Gifford, E. (2003). *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. **2**, pp 192-204

Content Uniformity

- The USP guidance for acceptable Uniformity of Dosage Units
  - USP38-NF33 S1, <905>Uniformity of Dosage Units
  - Tier 1 (n= 10) testing
    - Provided the mean potency is within 1.5% of target, then a tablet RSD for potency not more than 6.25%
  - Tier 2 (n=30) testing
    - Provided the mean potency is within 1.5% of target, then a tablet RSD for potency not more than 12.5%
    - No tablet potency outside 75%-125% for up to n=30 tablets

- In brief, RSD < 6.25%

Content Uniformity Model

- Content uniformity models are used to predict volumetric diameter needed to meet USP Stage 1 criteria for tablets
- Model assumptions:
  - Random, dilute mixture (Poisson distribution)
  - Spherical particles
  - Representative PSD of drug substance in dosage unit
  - No segregation etc.

$$C_v = y\left(\frac{\pi\rho}{6G}\right)^{1/2}\left(\sum_i f_i D_i^3\right)^{1/2}$$

$f_i \equiv$ Mass fraction of drug existing as particles of diameter, d_i

$G \equiv$ Dose

$\rho \equiv$ True density

$y \equiv$ Mass fraction of excipient

Johnson MCR 1972. Particle size distribution of the active ingredient for solid dosage forms of low dosage. Pharm Act Helv 47A:546-559.

Content Uniformity Model

$$G = \sum_i np_i m_i \equiv \text{Mass of drug in a sample}$$

$$\text{var}(G) = \sum_i np_i m_i^2$$

$$np_i m_i = p_i M$$

$$\text{var}(G) = M \sum_i p_i m_i$$

$$m_i = \frac{\pi}{6} d_i^3 \rho$$

$$\sigma(G) = \left(\frac{\pi \rho M}{6} \right)^{1/2} \left(\sum_i p_i d_i^3 \right)^{1/2}$$

$$p_i = f_i \frac{G}{M}$$

$$C_v = \left(\frac{\pi \rho}{6G} \right)^{1/2} \left(\sum_i f_i d_i^3 \right)^{1/2}$$

- Spherical particles
- Ideal mixing
- Small drug fraction
- Sampling corresponds to a Poisson distribution

$n \equiv$ Total number of particles in the sample

$m_i \equiv$ Mass of drug in a particle of diameter, d_i

$p_i \equiv$ Number fraction of drug existing in the sample as particles of diameter, d_i

$f_i \equiv$ Mass fraction of drug existing as particles of diameter, d_i

$M \equiv$ Total sample mass

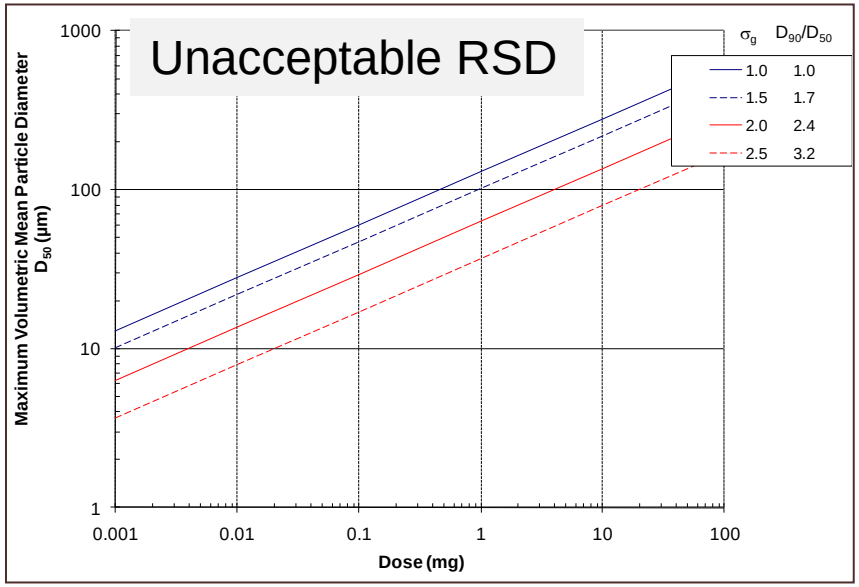
Johnson MCR 1972. Particle size distribution of the active ingredient for solid dosage forms of low dosage. Pharm Act Helv 47A:546-559.

Content Uniformity Models

USP38-NF33 S1, <905> Uniformity of Dosage Units.

- Rohr's et al model:
  - Assumes log-normal PSD
  - Design tool – target x_{90}.

$$d_{50} = \sqrt[3]{\left(\frac{6Dose}{\pi\rho}\right)\exp\left(-4.5\ln^2\sigma_g\left(\frac{RSD}{100}\right)^2\right)}\ 10^3$$

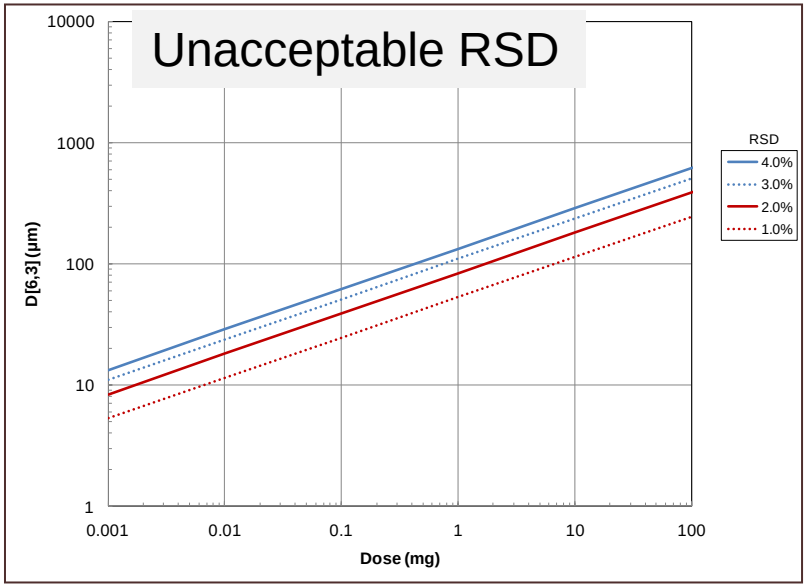


$C_v = 3.84\%$ $\rho = 1.3\ \text{g/cm}^3$

Rohr BR, *et al* (2006). *J of Pharm. Sci.* 95(5) pp 1049-1059.

- D[6,3] model:
  - No assumptions about PSD shape.

$$RSD = \sqrt{\frac{\pi}{6}\cdot D[6,3]^3\cdot\frac{\rho}{Dose}}$$



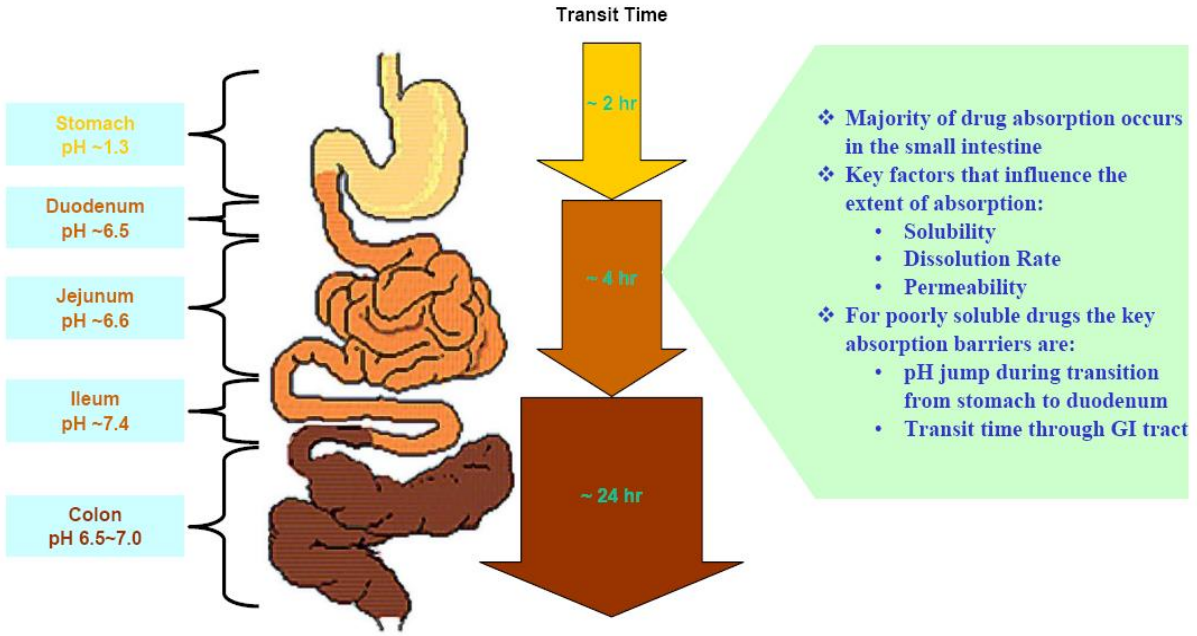
Hilden, J. *et al* (2012). *J Pharm. Sci.* 101(7) pp 2364-2371.

Absorption

- Dependent on solubility (thermodynamic), dissolution rate (kinetic) and permeability.

Class I • High solubility • High permeability • Generally well absorbed	**Class II** • Low solubility • High permeability • Solubility / dissolution limited absorption
Class III • High solubility • Low permeability • Permeability limited absorption	**Class IV** • Low solubility • Low permeability • Generally poorly absorbed

BCS I if entire dose dissolves in 250ml (pH 1 to pH 8)



Amidon, G. L. et al. (1995). *Pharm Res,* **12**, 3, pp 413-420.

Martin, A. (1993). *Physical Pharmacy*, 4th Ed. Lea and Febinger, Philadelphia.
Martinez, M.N. and Amidon, G. J. (2002). *J. Clin. Pharmacol.,* **42**, pp 620-643.

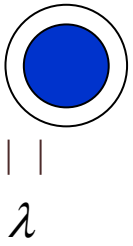
Dissolution Rate Limited

- Drug substance physical properties, namely particle size effects:
  - Absorption/bioavailability of the drug substance can be impacted by the dissolution rate of the drug substance according to the Noyes Whitney Equation:

$$\frac{dm}{dt} = \frac{D_{AB}}{\lambda} A\left(C^* - C_b\right)$$

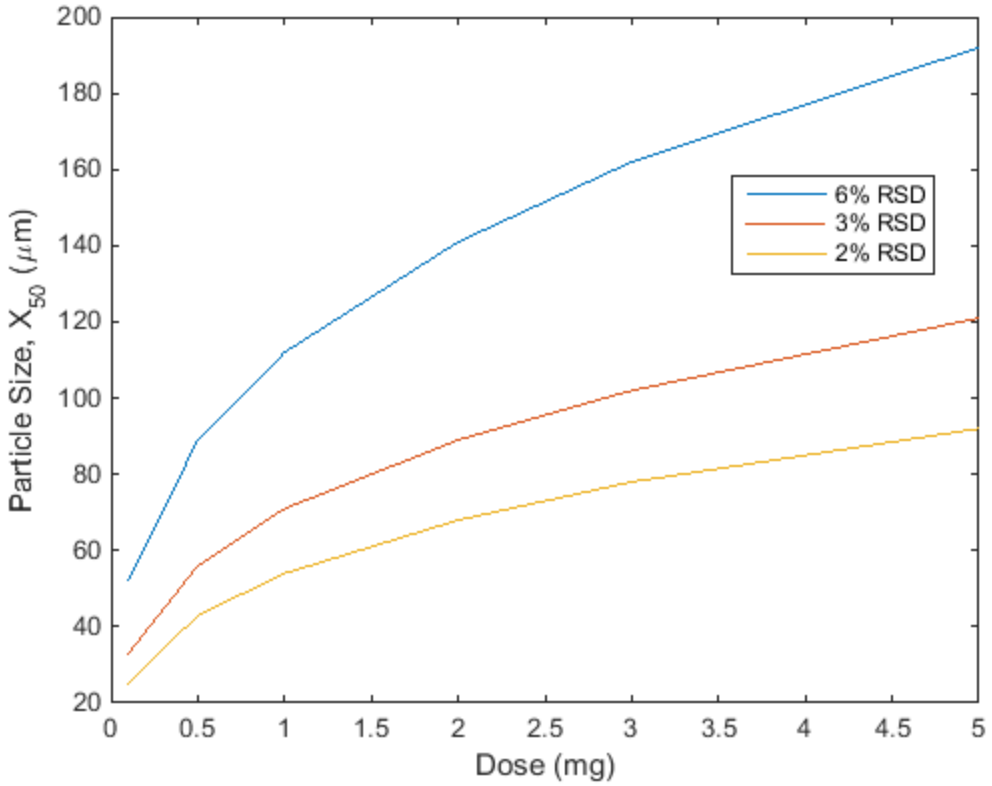
$$A = \left(Dose\right) SSA$$

$$SSA \propto \frac{1}{D}$$

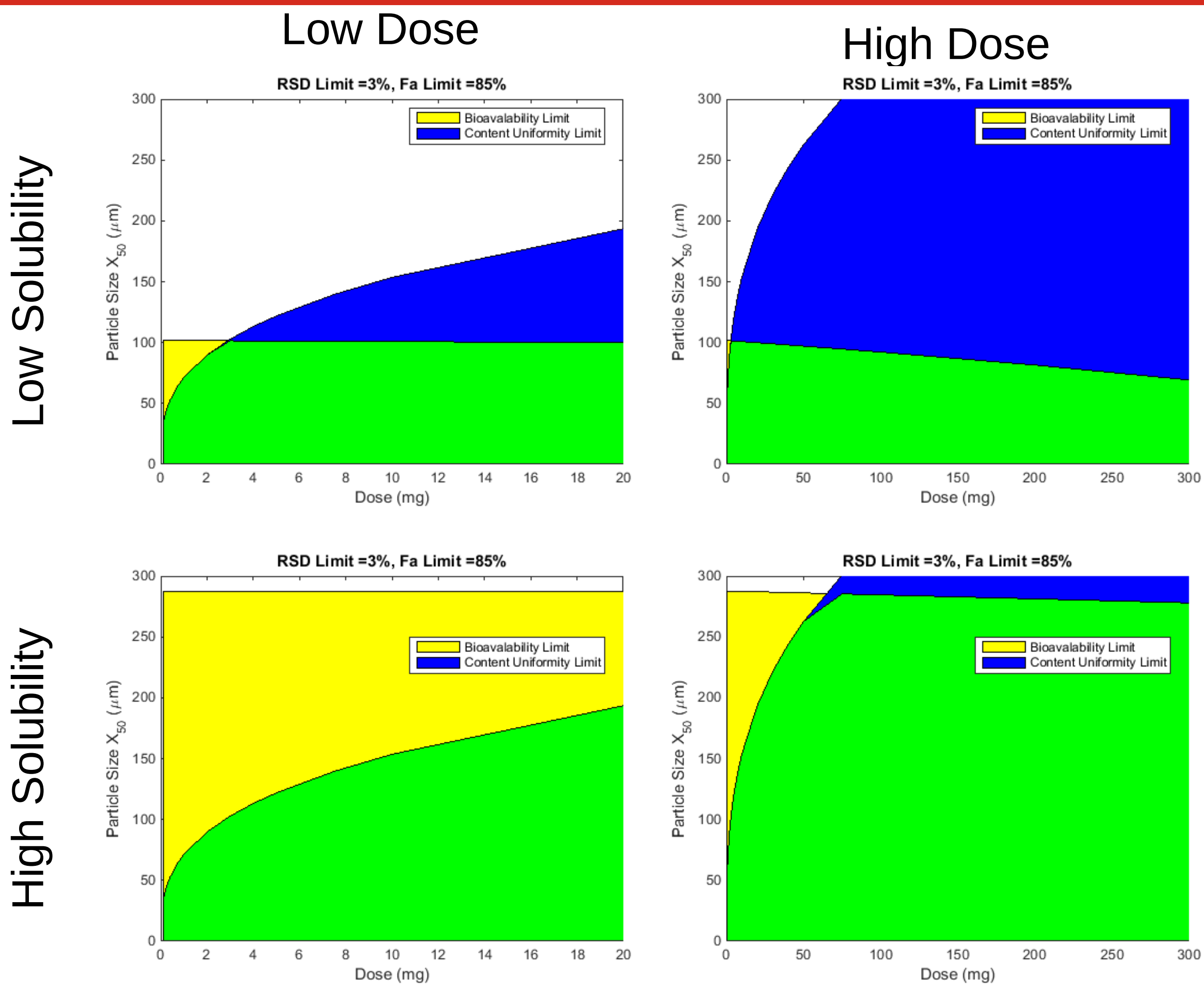


Impact of Particle Size on Content Uniformity as a Function of Dose

- True density of 1.33 g/cm^3, log-normal distribution with a standard deviation of 1.72, $X_{90}/X_{50} = 2$



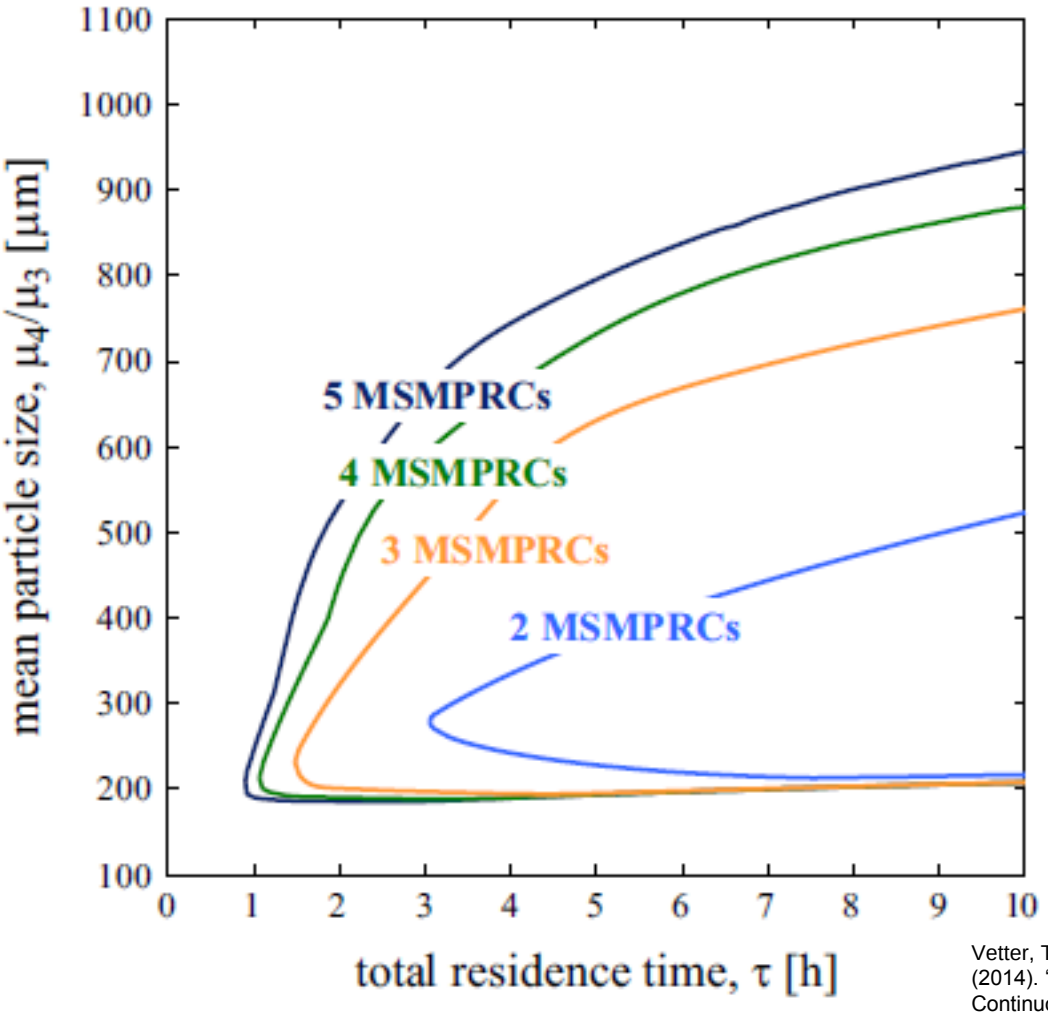
Allowable and Attainable Regions



Oh D-M, Curl RL, Amidon GL 1993. Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: A mathematical model. Pharm Res 10(2):264-270.

Vetter, T., Burcham, C. L., and Doherty, M. F. (2014). "Regions of Attainable Particle Sizes in Continuous and Batch Crystallization Processes." *Chem. Eng. Sci.*, **106**, 167-180.

Allowable and Attainable Regions



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Impact to Manufacturability – Filtration Time

- Filtration time[1]:

$$t = \left(\frac{\mu c \alpha}{2A^2 \Delta p} \right) V(t)^2 + \frac{\mu R_m}{A \Delta p} V(t)$$

$$c = \frac{c_s}{1 - \left[m_F / m_c - 1 \right] c_s / \rho}$$

- Cake resistance dependence upon particle size[2]:

$$\alpha = \frac{18}{\rho} \frac{K}{d_{vg}^2 \exp\left(4 \ln^2 \sigma_g\right)} \frac{\nu(\varepsilon)}{\varepsilon^2}$$

$$\nu(\varepsilon) = \frac{10(1-\varepsilon)}{\varepsilon}$$

t	time
V	Filtrate Volume
μ	Filtrate Viscosity
α	Cake Resistance
A	Filter Cross Sectional Area
Δp	Pressure Drop over the Filter
R_m	Filter Media Resistance
m_F	Wet Cake Mass
m_c	Dry Cake Mass
c_s	Concentration of Solids in the Slurry
$\rho_{filtrate}$	Density of the Filtrate
ε	Cake Porosity
ρ	True Density of the Solid Phase
d_{vg}	Volume equivalent diameter on a number basis
K	Dynamic Shape Factor
σ_g	Lognormal Standard Deviation
ν	Void Fraction

1. McCabe, W. L., Smith, J. C., and Harriott, P. (1985). *Unit Operations of Chemical Engineering*, 2nd ed., McGraw-Hill, New York, pp. 873-877.
2. Endo, Y. and Alonso, M. (2001) 'Physical meaning of specific cake resistance and effects of cake properties in compressible cake filtration', *Filtration & Separation*, pp. 42-46.

Modeling the Crystal Size

- Population Balance Model

$$\frac{\partial n(L,t)V}{\partial t} = F_{in}n_{in} - F_{out}n(L,t) - V\frac{\partial\left(G(L)n(L,t)\right)}{\partial L} + (B-D)V$$

  - Birth (B)
    - Nucleation
      - Primary
        - Homogeneous (from solution)
        - Heterogeneous
      - Secondary
        - From existing crystals
          - Attrition
          - Activated
  - Death (D)
    - Dissolution
  - Birth and death
    - Attrition, breakage and agglomeration
  - Growth (G)

Kinetic Models and Parameters

- Nucleation
  - Primary

$$B_{prim} = k_n' \left(\Delta C\right)^n$$

  - Secondary nucleation:

$$B_{\text{sec}} = k_N m_2 \left(\Delta C\right)^b$$

- Growth

$$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right) \Delta C^{\ g}$$

$$\text{if } C - C^* > 0$$

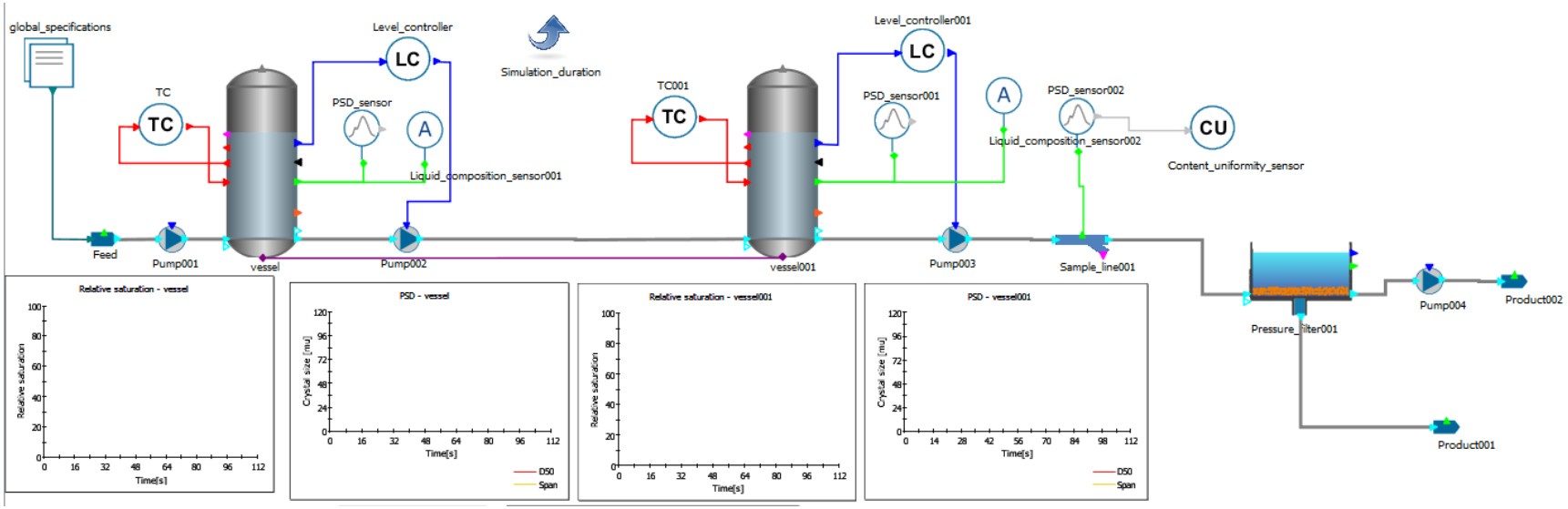
- No agglomeration, attrition, breakage.

Parameter	Value	Units
k_n'	$1.597*10^{10}$	(#/min)
n	2.276	-
k_g	9.979	$(m/s)(m^3/kmol)^g$
$E_{A,g}$	40.56	kJ/mol
g	1.602	-

Agitation Rate (rpm)	k_N (#/s m²)	b
200	$2.656*10^7$	2.232
250	$6.397*10^7$	2.339
300	$26.632*10^7$	2.314

Frawley, P.J., Mitchell, N.A., O´Ciardha, C.T., and Hutton, K.W., (2012). "The effects of supersaturation, temperature, agitation and seed surface area on the secondary nucleation of paracetamol in ethanol solutions." *Chem Eng Sci*, **75**, pp. 183–197.

Flowsheet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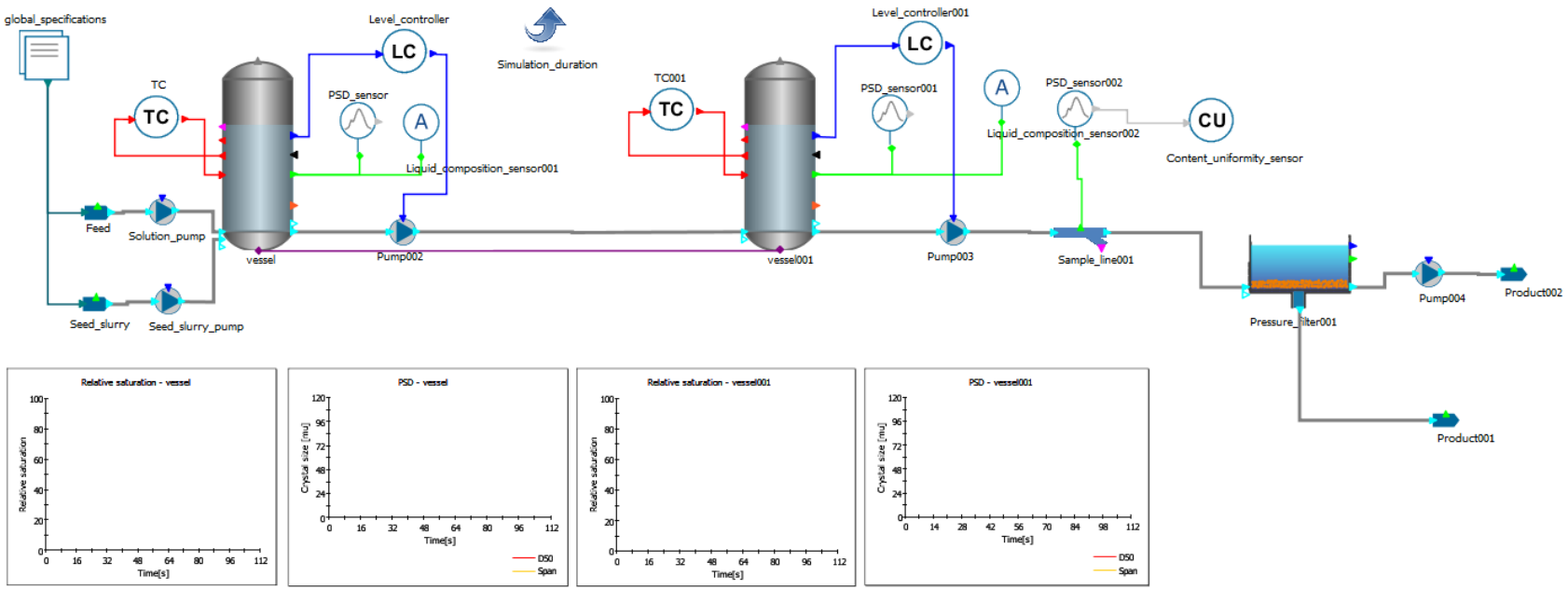
PSD_sensor001
A
PSD_sensor002
Liquid_composition_sensor002
CU
Content_uniformity_sensor
Feed
Pump001
vessel
Pump002
vessel001
Pump003
Sample_line001
Pressure_filter001
Pump004
Product002
Product001
Relative saturation - vessel
Relative saturation
Time[s]
PSD - vessel
Crystal size [mu]
Time[s]
D50
Span
Relative saturation - vessel001
Relative saturation
Time[s]
PSD - vessel001
Crystal size [mu]
Time[s]
D50
Span

Flowsheet with Continuous Seeding

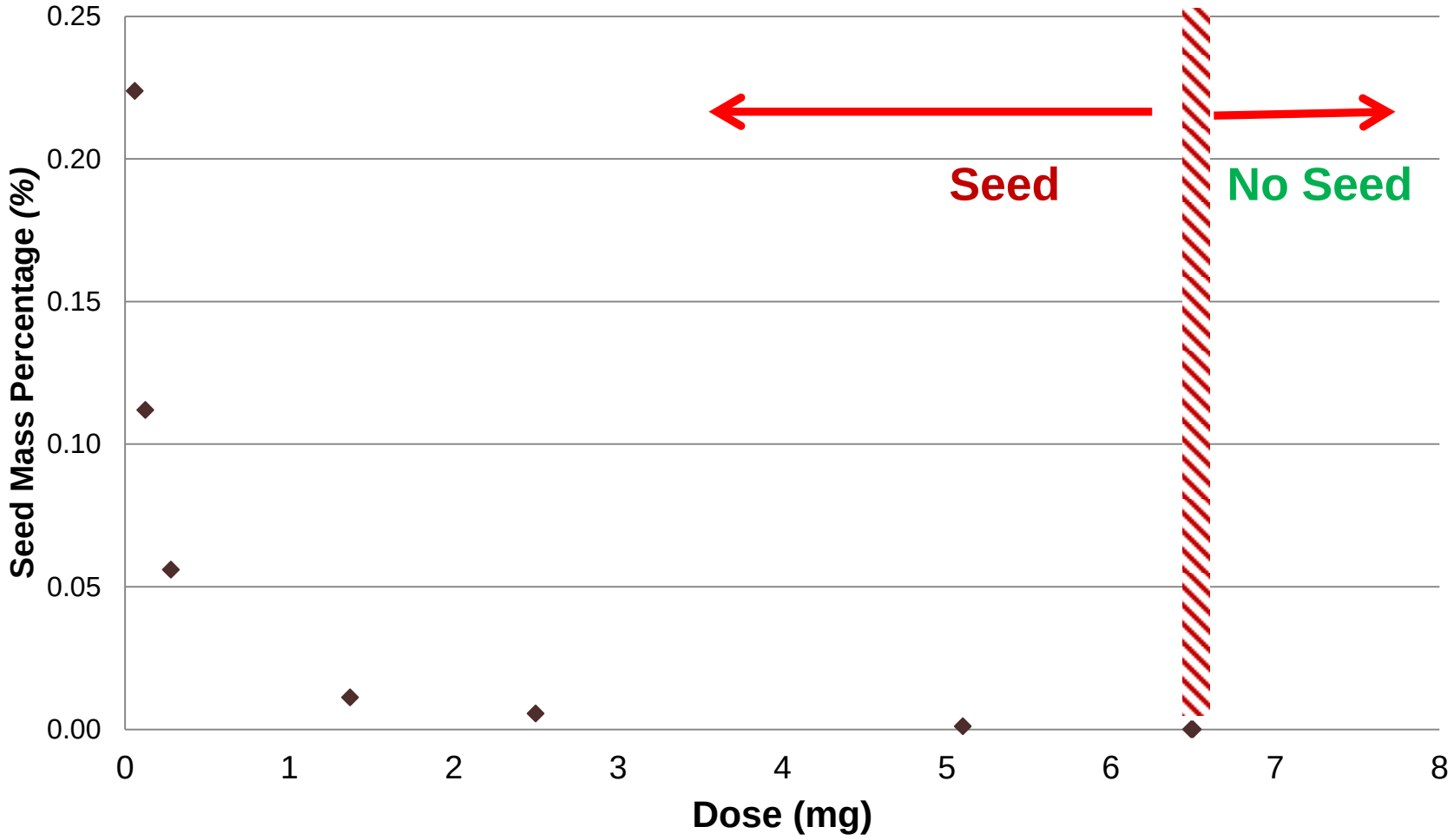


Optimization Problem

- Optimize: Maximize X_{50} of the product

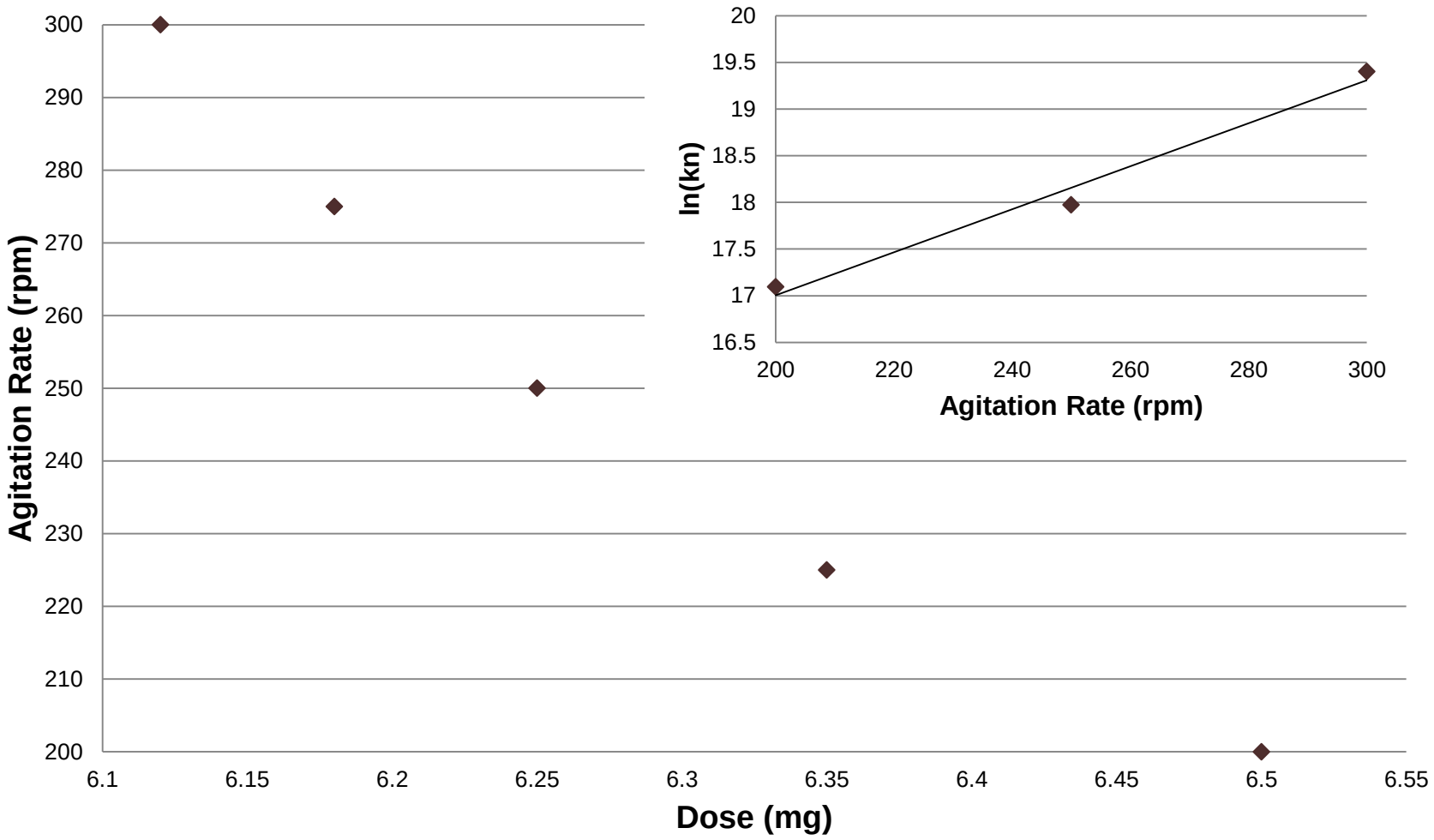
- Constraints:
  - Tablet RSD < 3%
  - Cake resistance < 10^{10} m/kg
  - Relative supersaturation < 2.0
  - Yield > 90% theoretical yield
- Controls:
  - *Fraction of seed to first MSMPR (0.01 to 0.5 wt/wt)*
  - Temperature in the first MSMPR (30 to 50 °C)
  - Residence time in the first MSMPR (40 to 270 min)
  - Temperature in the second MSMPR (5 °C)
  - Residence time in the second MSMPR (40 to 270 min)
  - Solution concentration in the feed

Attainable Dose Range (Without Continuous Seeding)



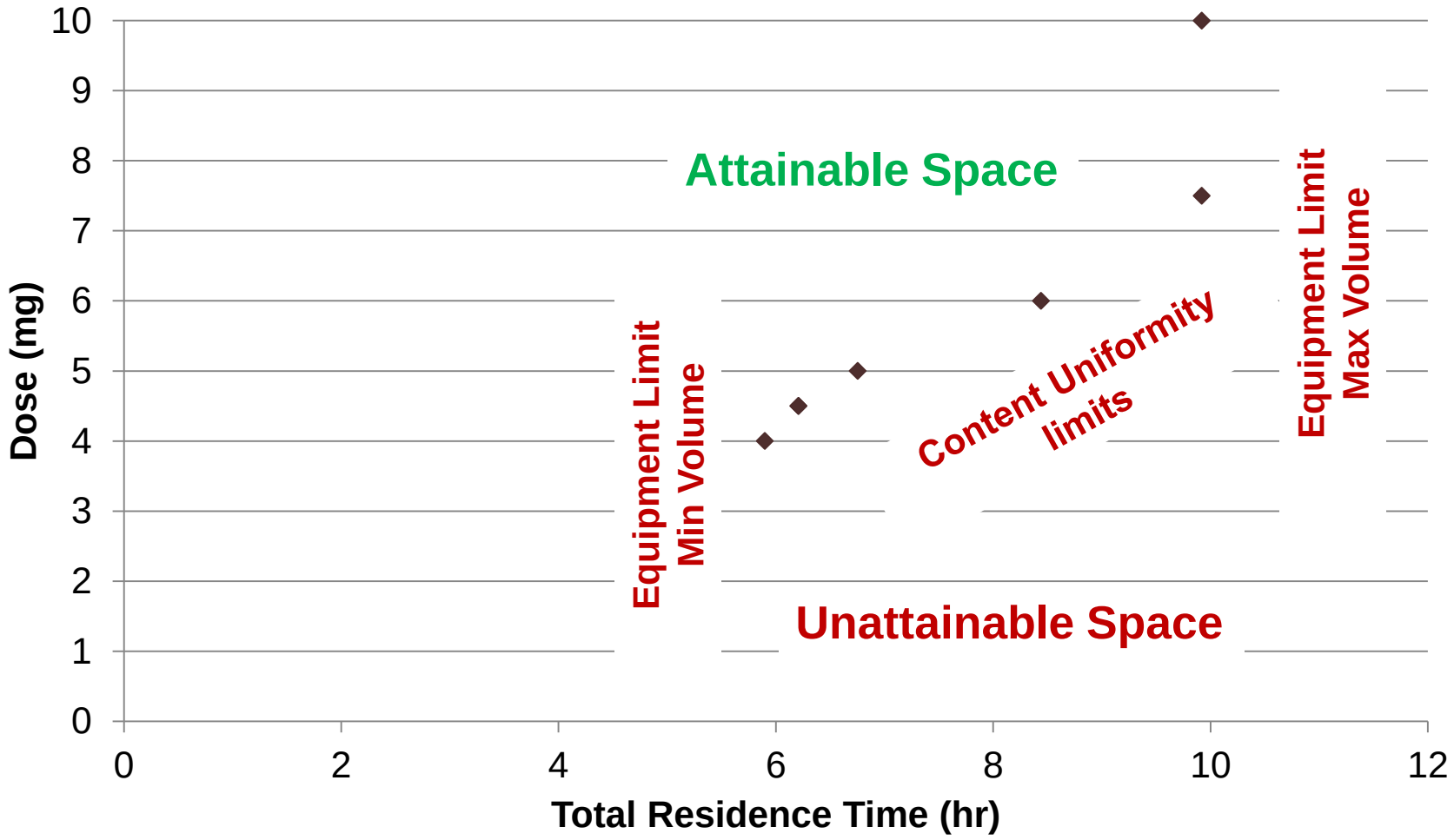
Increasing Secondary Nucleation

By Increasing Agitation Rate



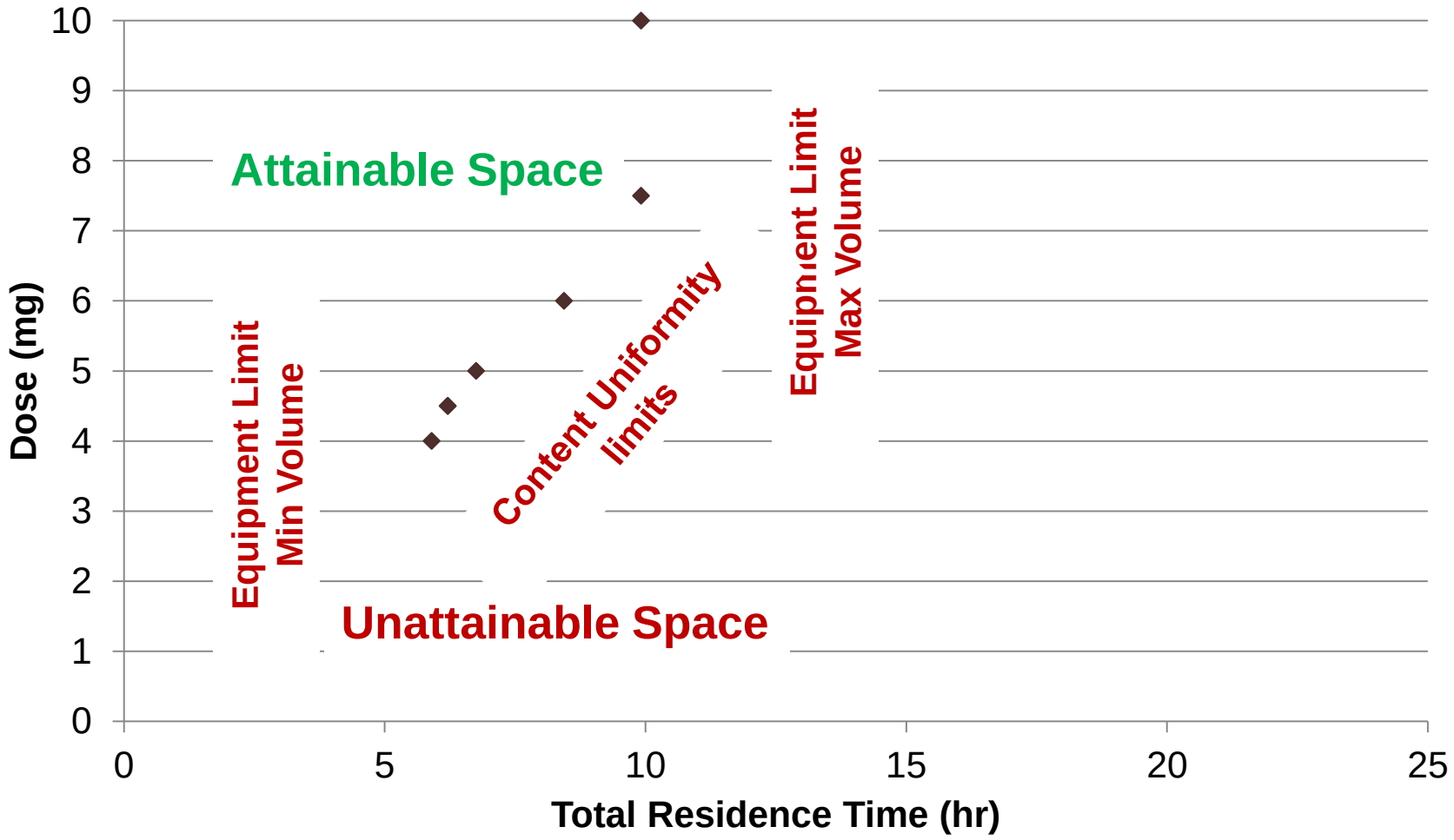
Continuously Seed MSMPR 1

0.000011 kg seed/kg feed, Fixed feed rate



4 Stages, Continuously Seed MSMPR 1

0.000011 kg seed/kg feed, Fixed feed rate



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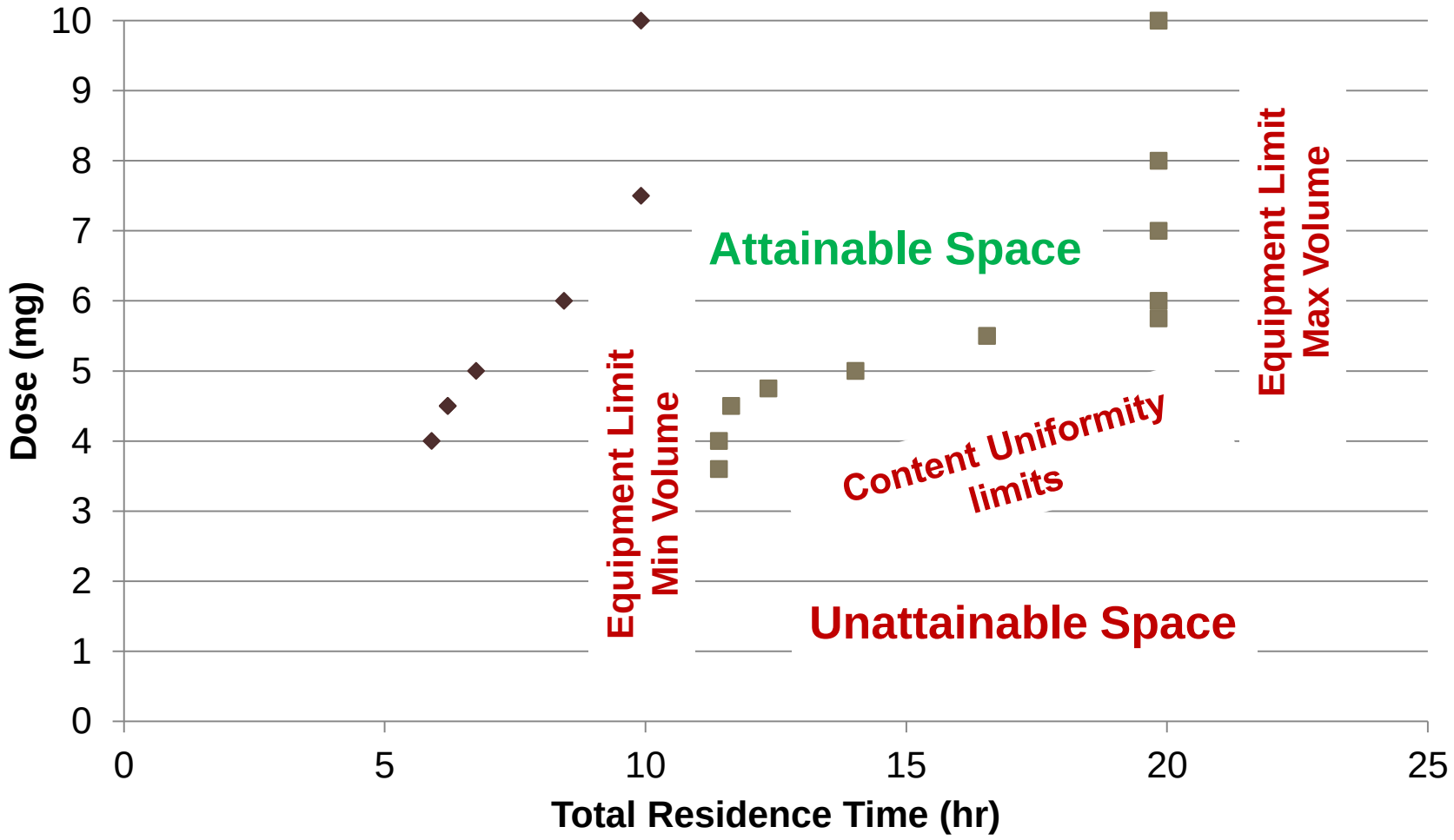
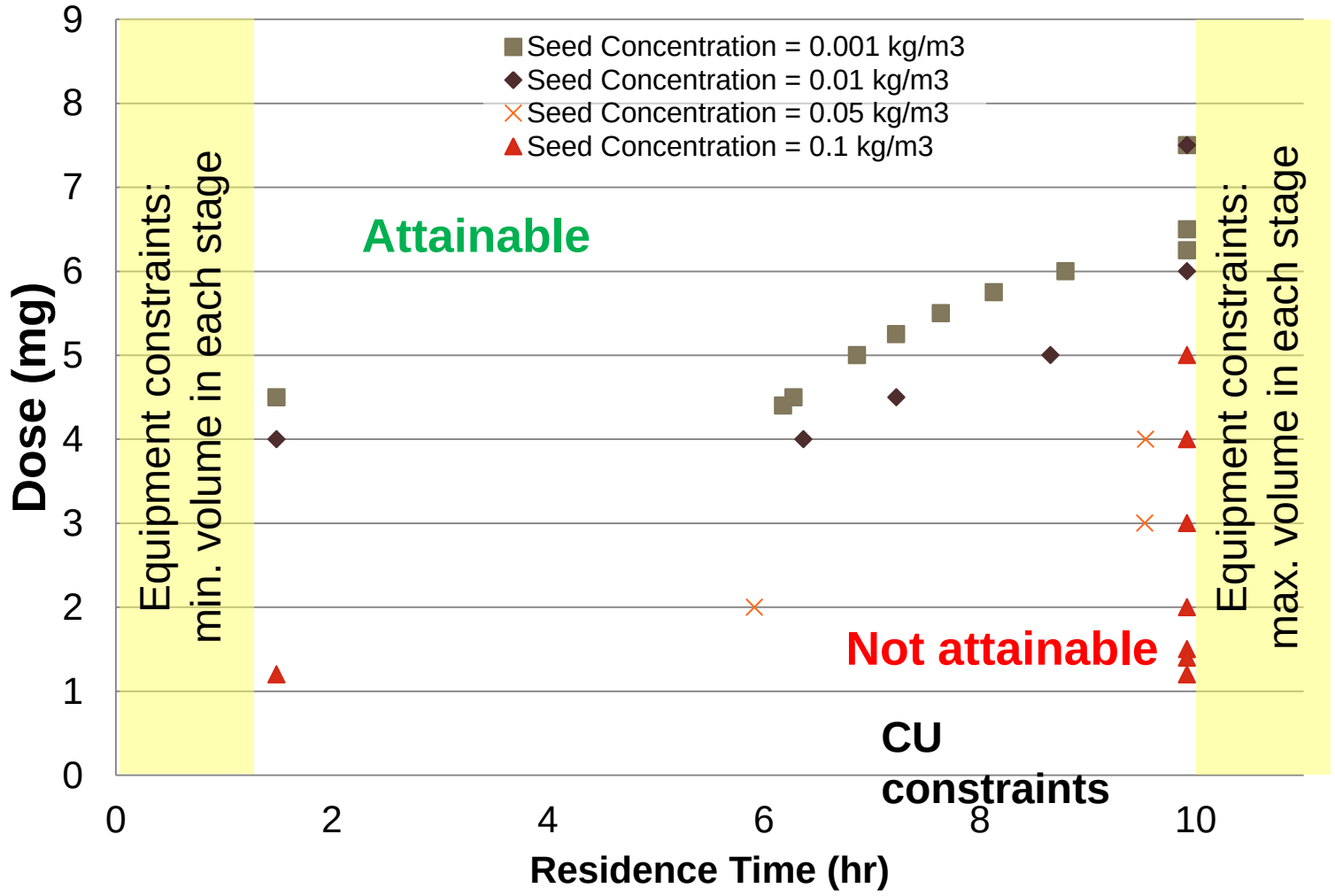
0.000011 kg seed/kg feed, Fixed feed rate



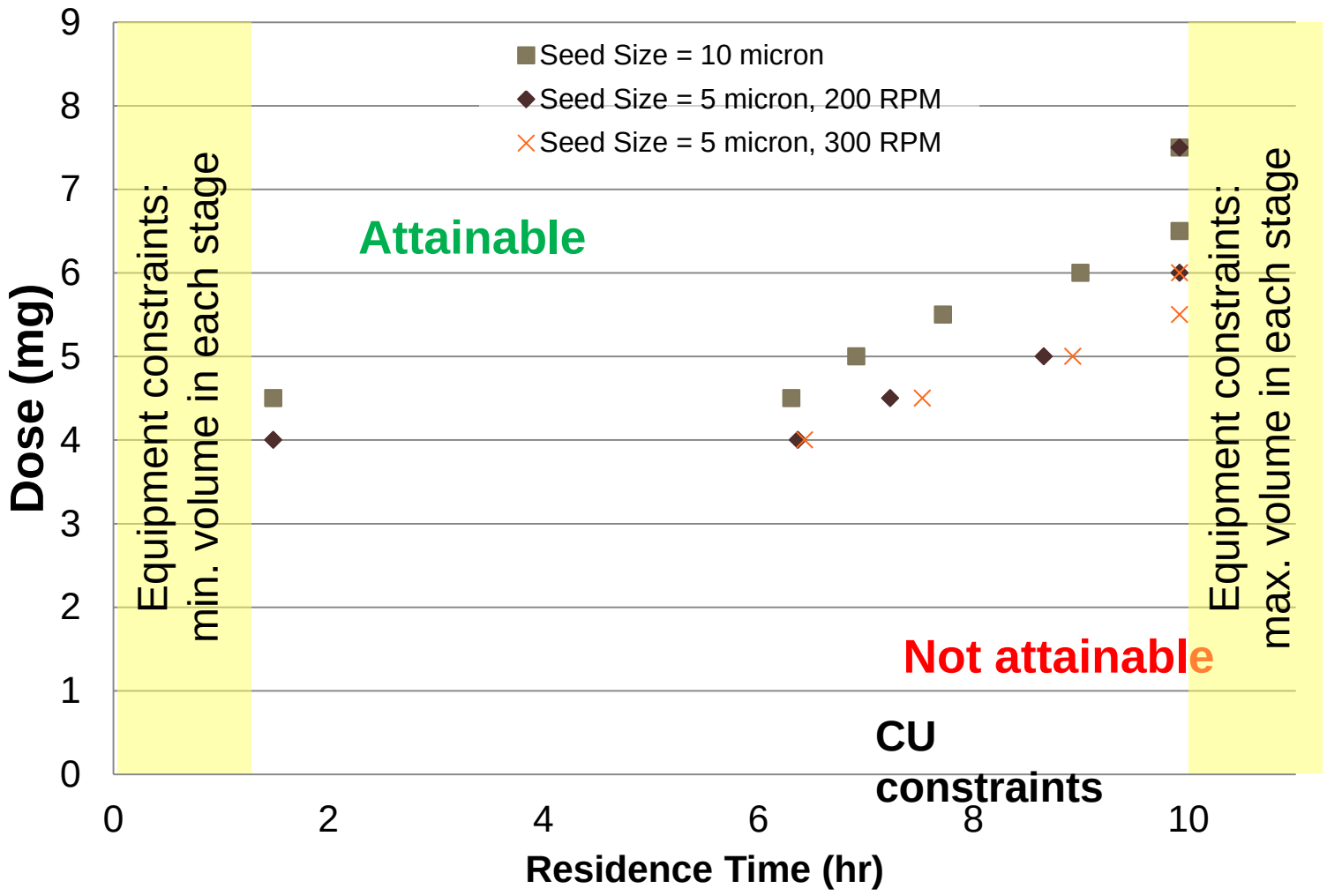
2 Stages, Continuously Seed MSMPR 1

Impact of seed load, Fixed feed rate



2 Stages, Continuously Seed MSMPR 1

Impact of Seed Size and Nucleation Rate, Fixed feed rate



Conclusions

- Integrating product quality constraints (content uniformity) with manufacturing constraints (filtration time), economic constraints (yield) with a process model (operational parameters) allows for attainable regions to be probed.
  - Minimizes experimentation.
  - Allows for “what-if” scenarios to be considered.
- For this case, with the crystallization kinetics considered,
  - Seeding is needed to meet constraints on content uniformity RSD (3%) for doses below 7 mg due.
  - Increasing nucleation by an order of magnitude (via increasing the agitation level) is not sufficient to decrease the product particle size.