Novel process intensification approaches in crystallization systems

Zoltan K. Nagy

Davidson School of Chemical Engineering
Purdue University, West Lafayette, IN, USA

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Dalian University of Technology
Dalian, P.R. China

Technology moves on…

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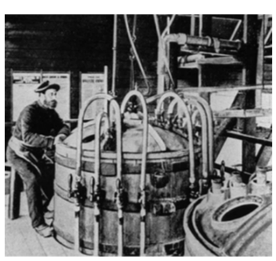
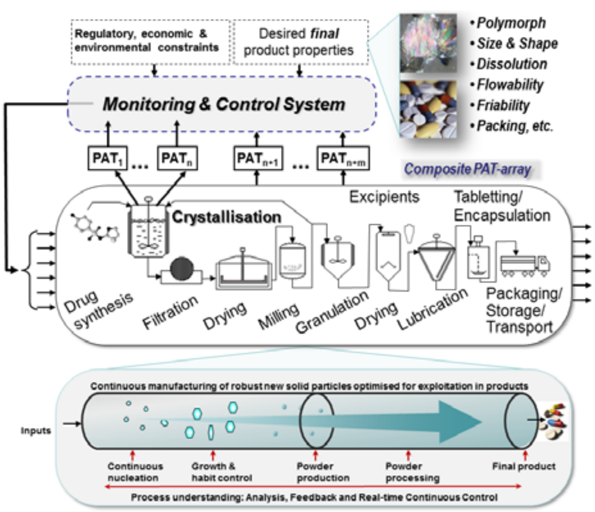
Today



Pharmaceutical processing then **and now…**

Holistic systems view of Integrated & Continuous Manufacturing of Pharmaceuticals

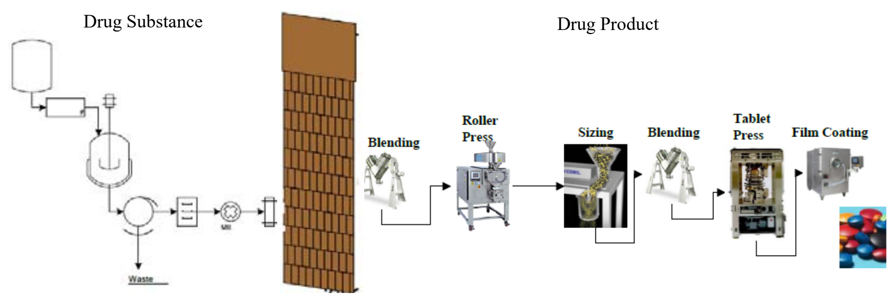


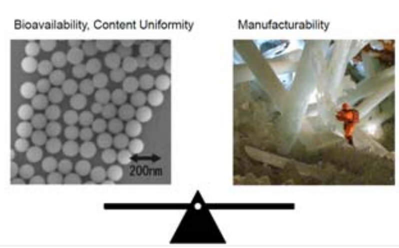
- Integrated
- Intensified
- Monitored
- Controlled

Advanced control enables a new generation of integrated, intensified & intelligent manufacturing systems with drastically improved flexibility, predictability, stability & controllability

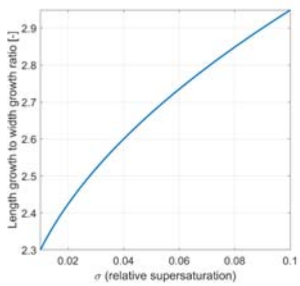
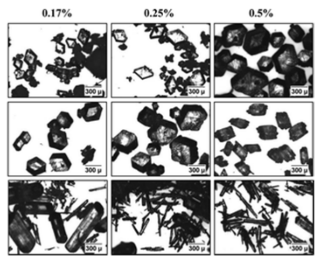
Nagy&Braatz, Handbook of Ind. Cryst., 2013; Nagy&Braatz, Annu. Rev. Chem. Biomol. Eng., 2012

Fully integrated novel crystallization design concepts



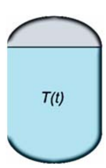
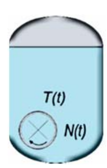
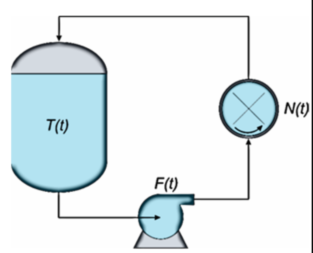


Shape control – “standard” approaches

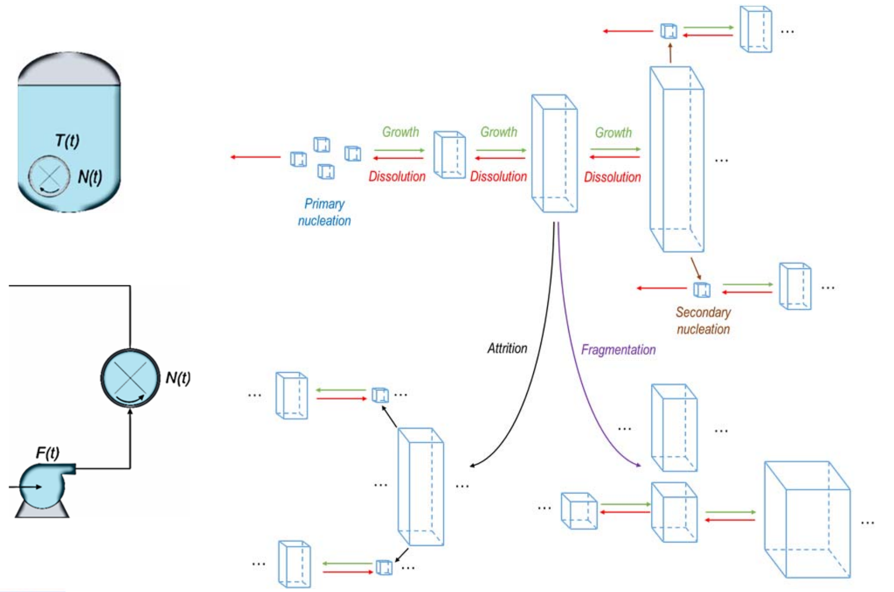
Supersaturation/temperature dependency of growth rates	Growth rate modifier	Mechanical force
		
Always available Almost never helps	Not always available Helps, when available	Always available ???

AR Klapwijk, E Simone, ZK Nagy, CC Wilson, Crystal Growth & Design 16 (8), 4349-4359

Shape control by integrated wet milling

Crystallizer only (standard)	Internal milling (integrated process)	External milling (integrated system)
		
Easy to operate Limited impact on shape	Easy to operate Breakage by wet milling May not be effective enough	Strong breakage Flowrate dynamics Transfer line

Model structure: the mechanisms

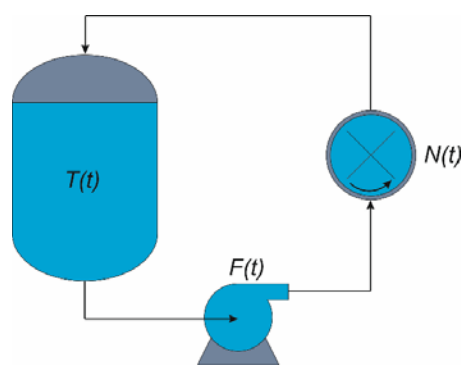


Process intensification via integrated crystallizer-wet mill optimization – size control

- **Crystallizer: crystallization**
  - **- primary nucleation**
  - **- growth**
  - **- dissolution**
- **Wet-mill: breakage**
  - **- fragmentation**
  - **- attrition**
- **Temperature: controller, no energy balance written up**

Un-seeded system

(automated seed generation)



Scheme of the integrated crystallizer-wet mill system with the most important design parameters

Szilágyi, Botond, and Zoltán K. Nagy. 2018. *Crystal Growth & Design*: acs.cgd.7b01331

Optimization of an Integrated Batch Crystallizer – Wet Mill system for CSD Control

- **Modeling and optimization of crystallizer + wet mill system**
- **Addition of wet mill → increase overall system flexibility and attainable CSD**
- **Dynamic optimization of (1) T-profile, (2) circulation flow rate and (3) wet mill rotation speed → better CSD than that in crystallizer only**
- **Model based optimization → significant process improvement**

$$\frac{\partial n_c(L,t)}{\partial t} + G(\sigma)\frac{\partial n_c(L,t)}{\partial L} = B(\sigma)\delta(L - L_n) + \frac{F}{V_c}[n_{wm}(L,t) - n_c(L,t)]$$

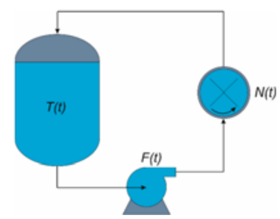
PBE in the crystallizer,

where c: crystallizer + w: wet mill

$$B(\sigma) = \begin{cases} k_b\sigma^b, \text{ if } c_c \geq c_s(T) \\ 0, \text{ if } c_c < c_s(T) \end{cases}$$

$$G(\sigma) = \begin{cases} k_g\sigma^g, \text{ if } c_c \geq c_s(T) \\ -k_d\sigma^d, \text{ if } c_c < c_s(T) \end{cases}$$

$$\sigma = \begin{cases} \frac{c_c}{c_s(T)} - 1, \text{ if } c_c \geq c_s(T) \\ 1 - \frac{c_c}{c_s(T)}, \text{ if } c_c < c_s(T) \end{cases}$$



Integrated crystallizer-wet mill optimization

- **Selection function**

$$S(\lambda) = \lambda^{\beta}\frac{\rho_{imp} l_{imp}^2 h_{imp} N_{imp}^3 d_{imp}^5}{768\pi}$$

- **Breakage function (fragmentation)**

$$b_f(L|\lambda) = k_f\frac{1}{\sqrt{2\pi\sigma_f^2}} exp\left[-\frac{(L-\lambda/2)^2}{2\sigma_f^2}\right]$$

- **Breakage function (attrition)**

$$b_a(L|\lambda) = k_a\delta(L - L_n)$$

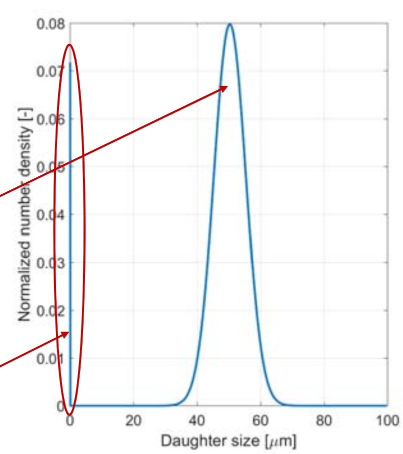


Figure. Daughter distribution of a λ = 100 μm crystal

Integrated crystallizer-wet mill optimization

- ***System optimization with multiple objectives***

$$SSE(\boldsymbol{T},\boldsymbol{F},\boldsymbol{N}) = \underbrace{\int_0^{L_{max}} \left[\frac{|n_T(L,t_{end}) - n(L,t_{end})| + \varepsilon}{n_T(L,t_{end}) + \varepsilon}\right]^2 dL}_{\text{Target CSD realization}} + \underbrace{\int_0^{t_{end}} \left[w_1\left(\frac{dT}{dt}\right)^2 + w_2\left(\frac{dF}{dt}\right)^2 + w_3\left(\frac{dN}{dt}\right)^2\right] dt}_{\text{Smooth profiles}} + \underbrace{\int_0^{t_{end}} [w_4F + w_5N]\, dt}_{\text{Minimal flow and stirring}} + T_{fin} \overset{!}{=} min$$

- ***Numerical details: Enhanced hierarchical optimization framework***

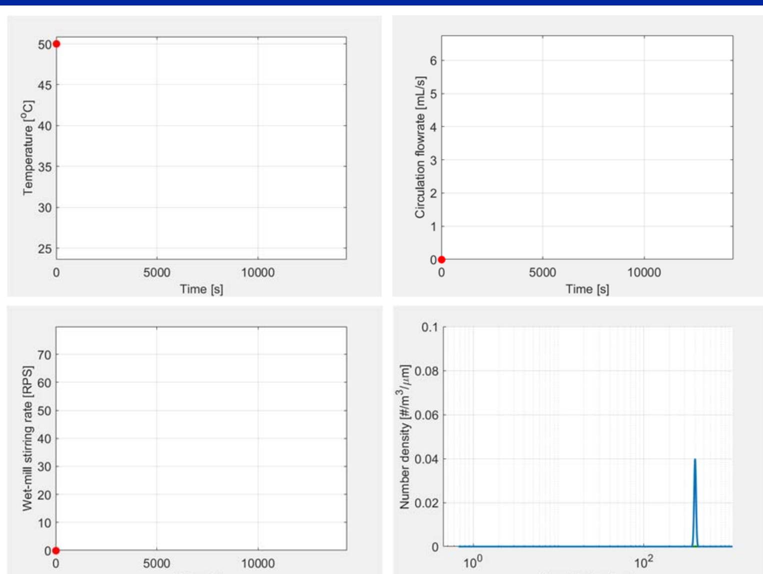
Table. Potential accuracy domains

Accuracy	CFL	Mesh size	Computing platform
Low	CFL > 0.5	N < 500	CPU only
Moderate	CFL > 0.3 CFL < 0.5	N > 500 N < 1000	CPU + GPU; CPU only
High	CFL < 0.3	N > 1000	CPU+GPU

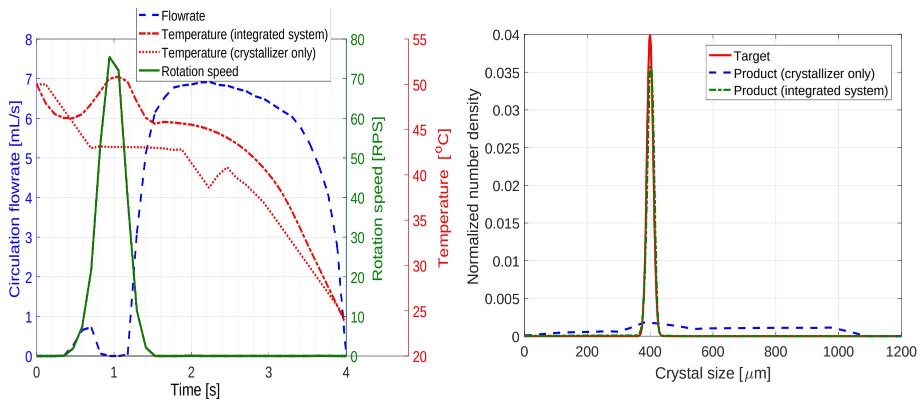
Table. Multi-level optimization

Level	Accuracy	Algorithm	Points/profile
1	Low	Interior-point	15-25
2	Moderate	Interior-point	20-30
3	High	SQP	25-35

Integrated crystallizer-wet mill optimization

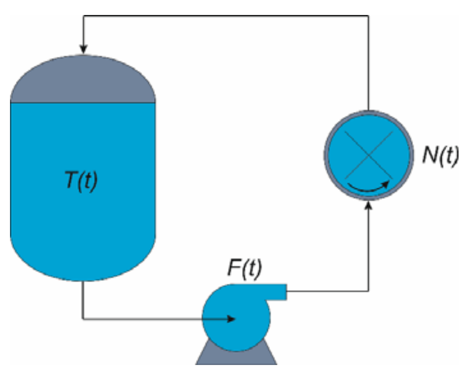


Integrated crystallizer-wet mill optimization



Process intensification via integrated crystallizer-wet mill optimization – size & shape control

- **Crystallizer: crystallization only**
  - **- primary nucleation**
  - **- growth**
  - **- dissolution**
- **Wet-mill: breakage + crystallization**
  - **- fragmentation (binary br.)**
  - **- attrition (secondary nuc.)**
  - **- primary nucleation**
  - **- growth**
  - **- dissolution**
- **Temperature: controlled in the crystallizer, energy balance in the wet-mill (no heat losses)**



Schematic representation of the integrated crystallizer-wet mill system with the most important design parameters

The model-equations

- **Population balance models:** *$L_1 \rightarrow$ crystal length, $L_2 \rightarrow$ crystal width,* **L** *= (L_1, L_2)*

$$\frac{\partial n_c(\mathbf{L},t)}{\partial t}+\sum_{i=1}^{2} G_i \frac{\partial n_c(\mathbf{L},t)}{\partial L_i}=B\delta(\mathbf{L}-\mathbf{L}_n)+\frac{n_{wm}(\mathbf{L},t)-n_c(\mathbf{L},t)}{\tau_c}$$

$$\frac{\partial n_{wm}(\mathbf{L},t)}{\partial t}+\sum_{i=1}^{2} G_i \frac{\partial n_{wm}(\mathbf{L},t)}{\partial L_i}=B\delta(\mathbf{L}-\mathbf{L}_n)-S(\mathbf{L})n_{wm}(\mathbf{L},t)+\iint b(\mathbf{L}|\mathbf{Y})S(\mathbf{Y})n_{wm}(\mathbf{Y},t)d\mathbf{Y}+\frac{n_c(\mathbf{L},t)-n_{wm}(\mathbf{L},t)}{\tau_{wm}}$$

- **Mass and energy balances**

$$\frac{dc_c}{dt}=-k_v\rho_c\left(\iint G_1 L_2^2 n_c(\mathbf{L},t)d\mathbf{L}+2\iint G_2 L_1 L_2 n_c(\mathbf{L},t)d\mathbf{L}\right)+\frac{c_{wm}-c_c}{\tau_c}$$

$$\frac{dc_{wm}}{dt}=-k_v\rho_c\left(\iint G_1 L_2^2 n_{wm}(\mathbf{L},t)d\mathbf{L}+2\iint G_2 L_1 L_2 n_{wm}(\mathbf{L},t)d\mathbf{L}\right)+\frac{c_c-c_{wm}}{\tau_{wm}}$$

$$\frac{dT_{wm}}{dt}=\frac{P_{stirr}(N)}{V_{wm}c_{p,sol}\rho_{sol}}-\frac{k_v\rho_c H_c}{c_{p,sol}\rho_{sol}}\left(\iint G_1 L_2^2 n_{wm}(\mathbf{L},t)d\mathbf{L}+2\iint G_2 L_1 L_2 n_{wm}(\mathbf{L},t)d\mathbf{L}\right)+\frac{T_c-T_{wm}}{\tau_{wm}}$$

- **HR-FVM for growth and dissolution**
- **Finite volume approximation of breakage-integrals**

PURDUE

Szilágyi, B.; Lakatos, B. G. Comput. Chem. Eng. 2017, 98, 180−196.

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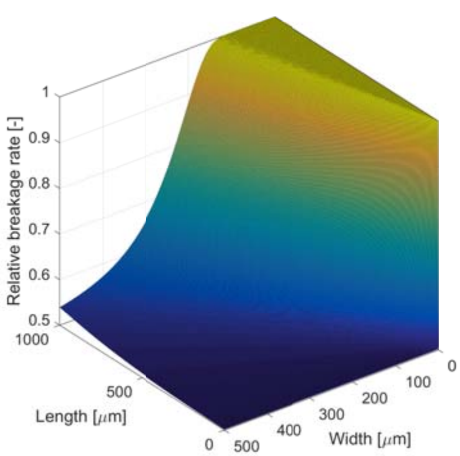
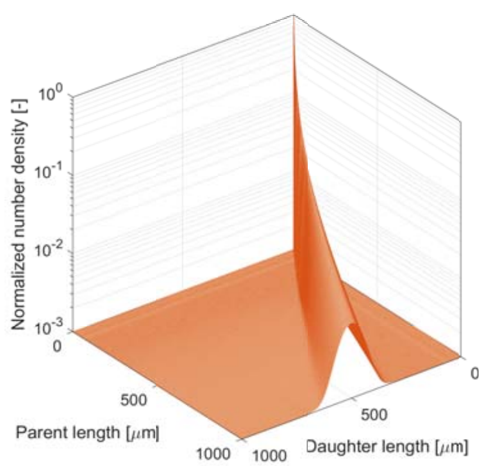
Illustration of breakage mechanisms



Aspect-ratio dependent selection function: probability that a crystal with a given size will suffer a breakage event



Fragmentation function: distribution of the daughter crystal sizes, coming from a parent crystal, as a function of parent crystal size

PURDUE

Sato K, Nagai H, Hasegawa K, Tomori K, Kramer HJM, Jansens PJ. Chem Eng Sci 2008; 63: 3271-3278.

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HR-FVM: grid dependence, computational cost

- Non-uniform grid: constant increment of cell width from fine (nucleon) to large crystal size. Inflation: max/min cell width. Inflation = 1: uniform grid

Error	Inflation	Grid size	t_{GPU} (s)	t_{CPU} (s)	Ratio
0	100	300	3317	-	-
0.5	71	218	670.26	59900	89.3
1	55	172	267.31	14079	52.7
3	28.5	98	43.84	907.46	20.7
5	18.4	69	20.24	240.91	11.9

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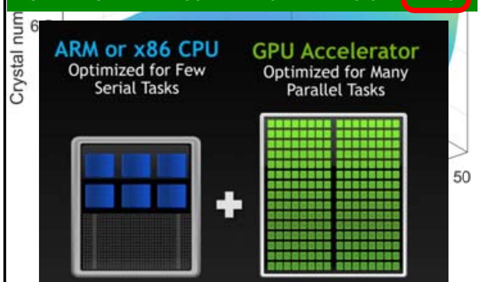
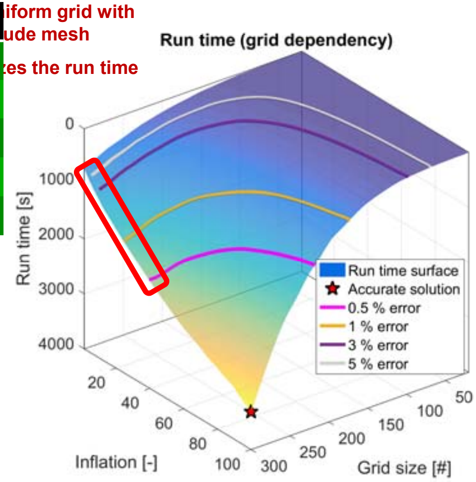
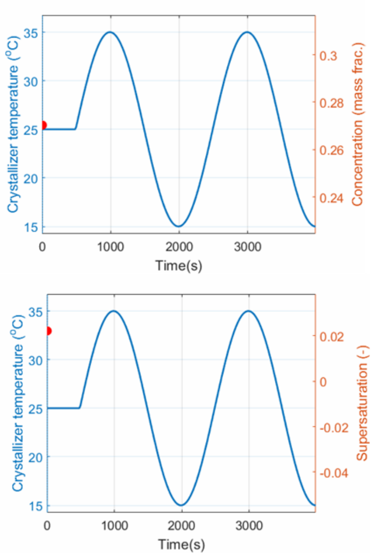
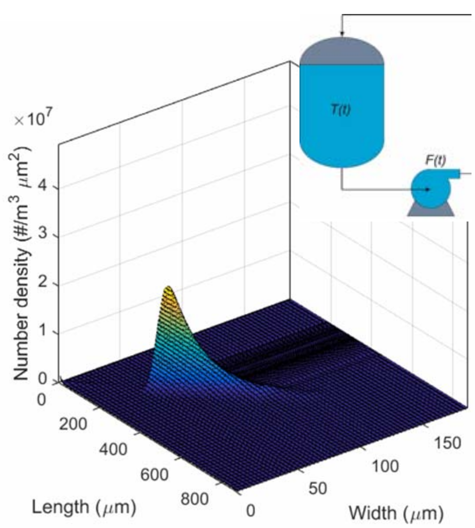




Szilágyi, B.; Nagy, Z. K. Cryst. Gro. Des., 2018, 91, 167−181.

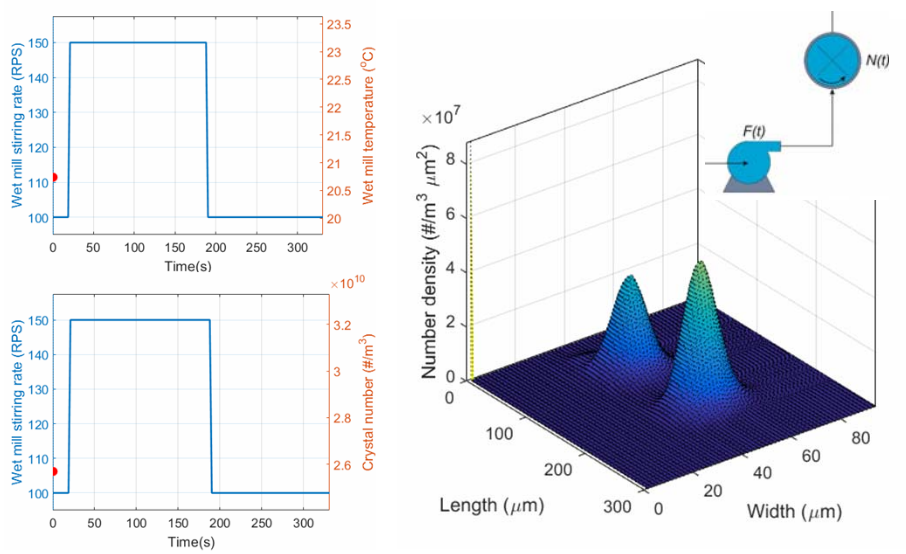
Input variation: crystallizer temperature cycle





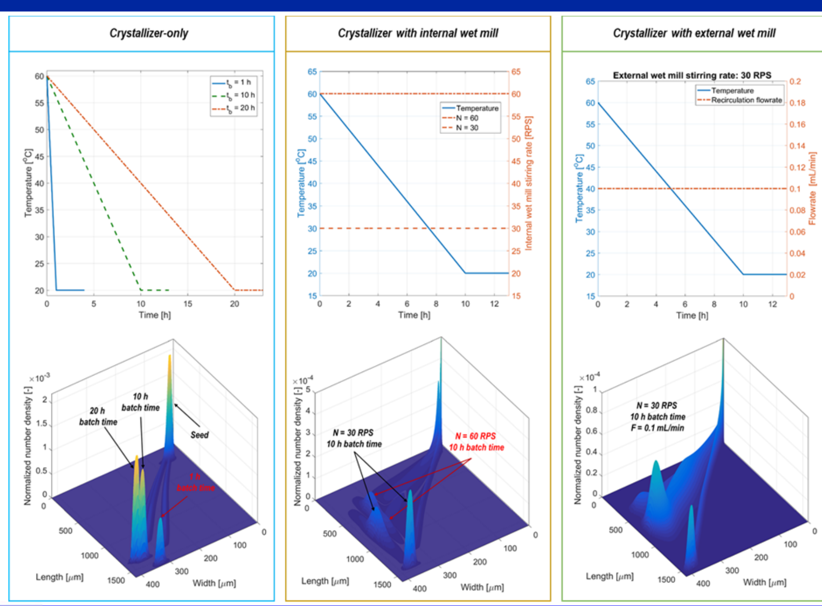
Visualization of the crystallizer dynamics during crystallizer temperature cycles

Input step-simulation: wet mill RPS

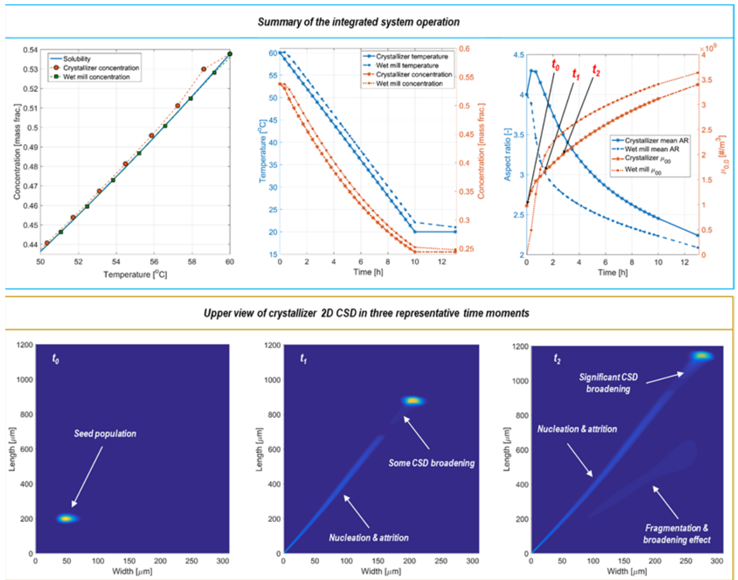


Visualization of the wet-mill dynamics after step-changes in the wet-mill stirring rate

System analysis: comparative study



System analysis: the integrated system



Advantages of integrated system

Configuration	Subsystem: Crystallizer	Subsystem: Wet-mill	Subsystem: Pump
Crystallizer only	Nucleation, growth, (fines) dissolution	-	-
Crystallizer + internal wet-mill (hypothetical)	Nucleation, growth, (fines) dissolution	Breakage	-
Crystallizer + external wet-mill	Nucleation, growth, (fines) dissolution	Breakage Continuous fines dissolution (with RPM = 0) Partial large crystal dissolution (for crystallizer CSD broadening, RPM = 0)	Dynamic feeding (and seeding) of the crystallizer from the wet-mill

Significantly broader operating space

System optimization

- ***Seeded crystallization. Optimize the crystallizer and the integrated systems to reach a specific 2D CSD***

$$SSE(\boldsymbol{T},\boldsymbol{F},\boldsymbol{N}) = \int_0^{L_{max}} \left[\frac{|n_T(L,t_{end}) - n(L,t_{end})| + \varepsilon}{n_T(L,t_{end}) + \varepsilon}\right]^2 dL + \quad \Rightarrow \text{Target CSD}$$

$$\int_0^{t_{end}} \left[w_1\left(\frac{dT}{dt}\right)^2 + w_2\left(\frac{dF}{dt}\right)^2 + w_3\left(\frac{dN}{dt}\right)^2\right] dt + \quad \Rightarrow \text{Smooth profiles}$$

$$\int_0^{t_{end}} [w_4F + w_5N]\, dt + T_{fin} \overset{!}{=} min \quad \Rightarrow \text{Minimal flow and stirring}$$

T → Temperature profile in the crystallizer (crystallizer operation)

F → Circulation flowrate profile (pump operation)

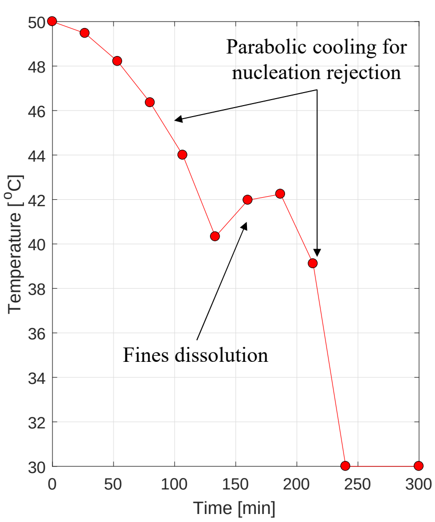
N → Wet mill stirring rate profile (wet-mill operation)

- ***Global optimization algorithm (evolutionary strategy)***

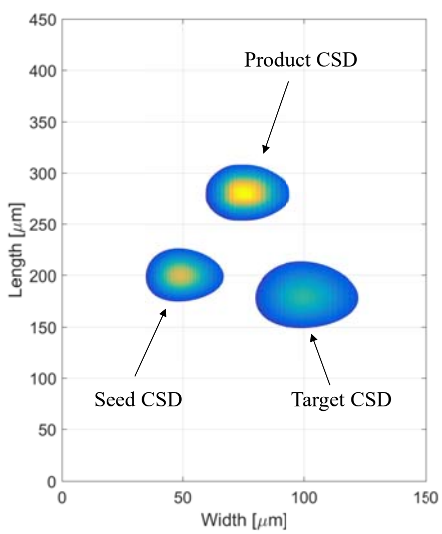
PURDUE

N. Hansen, S.D. Müller, P. Koumoutsakos, Evol. Comput. 11 (2003) 1e18.

System optimization results – crystallizer only



Optimal crystallizer temperature profile



Seed, target and achieved 2D CSD by the crystallizer-only configuration

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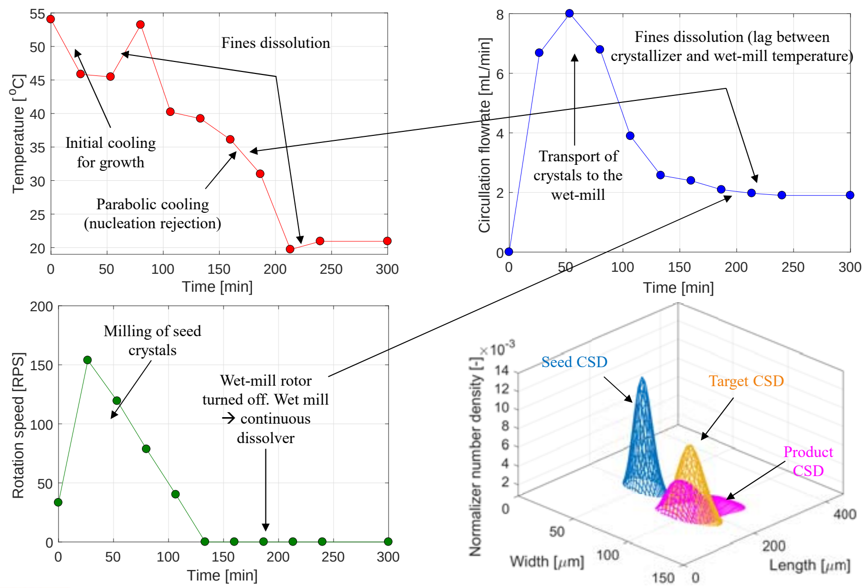
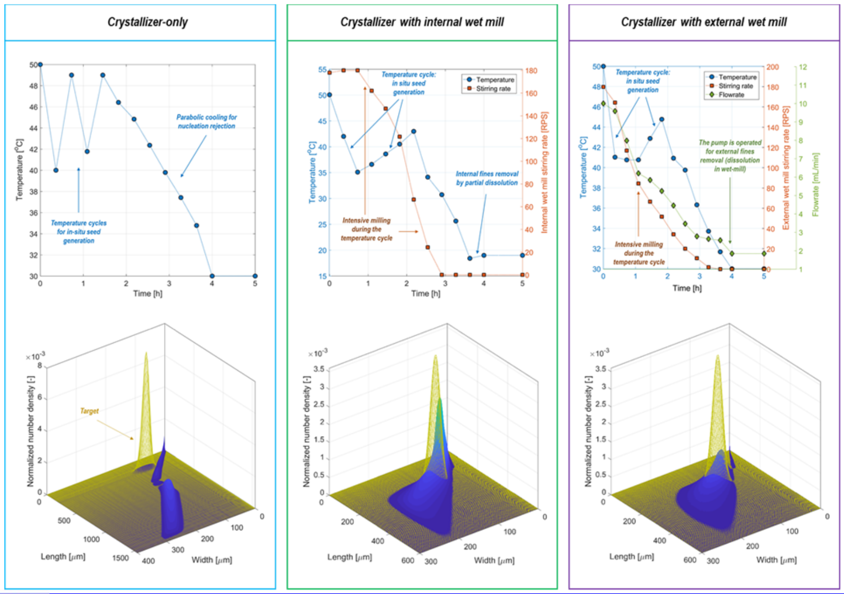
System optimization results – integrated system



System optimization: results summary

Configuration	Seed loading	$\sum_i \Omega_i$	O_1 (2D CSD)	O_2 (smooth T prof.)	O_3 (smooth N prof.)	O_4 (smooth F prof.)	O_5 (minimum N)	O_6 (minimum F)
Crystallizer only	0	152054	151530	524	-	-	-	-
	0.005	124165	123760	405	-	-	-	-
	0.02	32375	32121	254	-	-	-	-
Crystallizer with internal wet mill	0	6125	4743	522	656	-	204	-
	0.005	2212	1324	313	218	-	357	-
	0.02	1463	705	153	180	-	425	-
Crystallizer with external wet mill	0	5185	3949	200	197	149	333	357
	0.005	1781	1028	264	172	133	94	90
	0.02	820	397	206	19	69	93	36

System optimization: unseeded system

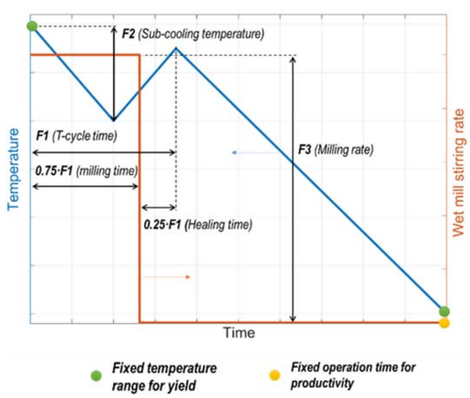


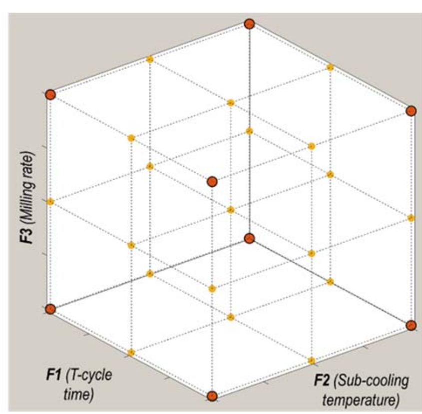
Generalization: application of DoE/QbD

Step 1: The crystallizer is cooled to trigger nucleation and growth. Milling is applied to reduce AR.

Step 2: Heating for partial dissolution and healing. The mill is turned off during this step.

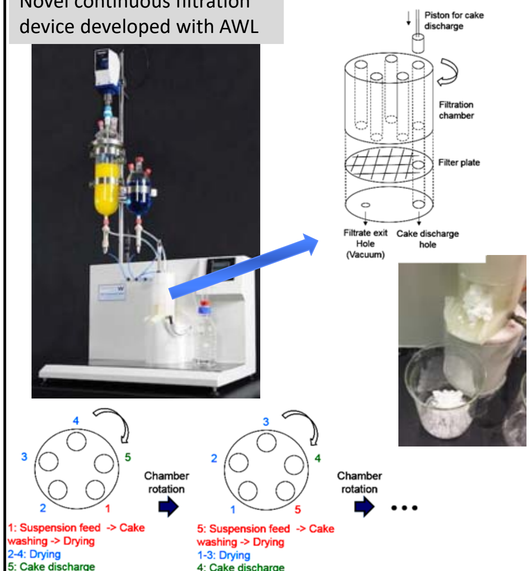
Step 3: Traditional cooling crystallization.

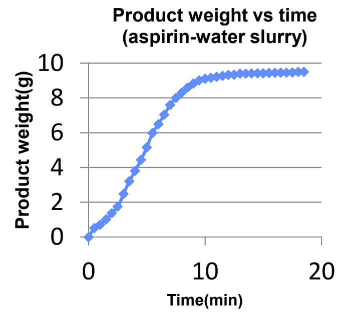




Continuous Filtration

Novel continuous filtration device developed with AWL

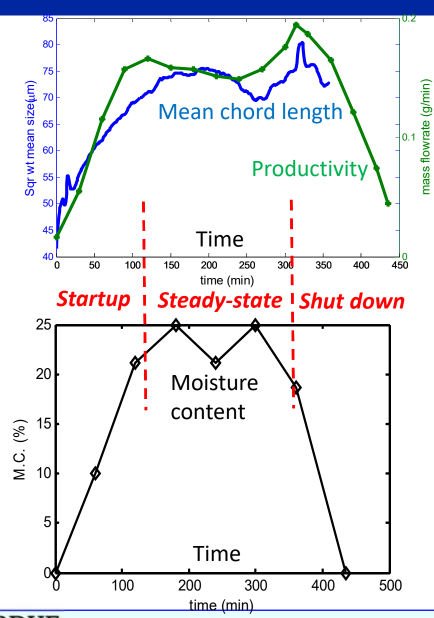




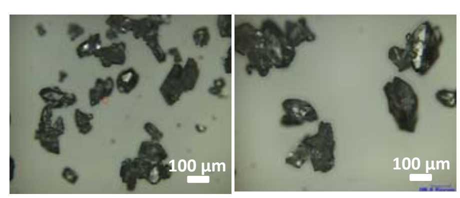
- **Good productivity** (~6 g/min)
- Crystal quality is preserved (**no breakage**)

Acevedo et al. *Chem. Eng. Proc.: Process Intensif.*, 108, 212-219, 2016.

Coupled continuous MSMPRC and Filtration



- ➢ Continuous cooling crystallization and filtration of paracetamol-ethanol system is studied.
- ➢ Steady-state is reached after 3 residence times.

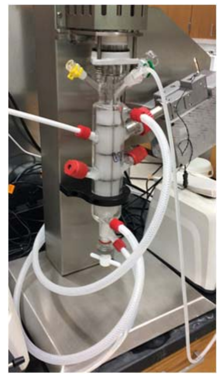


Before filtration   After filtration

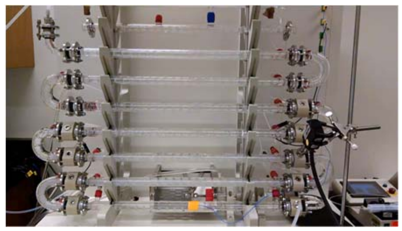
Acevedo et al. *Chem. Eng. Proc.: Process Intensif.*, 108, 212-219, 2016.

Continuous Crystallization

- Two main technologies:
  - MSMPR (cascade of MSMPRs) – stirred tank or dynamic baffled
    - **Advantages:** equipment in place, easier use of PAT
    - **Disadvantage:** similar to batch processes (large residence time distribution, low heat transfer area/volume ratio)
  - Plug flow crystallizers (PFC) – different technologies
    - **Advantages:** faster, smaller volume, higher product consistency
    - **Disadvantage:** need for new equipment, difficulty of using PAT



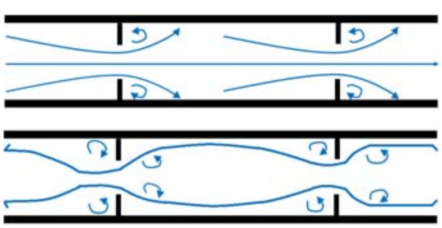
- Typical problems:
  - Optimal operation
  - Control of CQAs
  - Startup
  - Fouling



COBC Mixing Dynamics

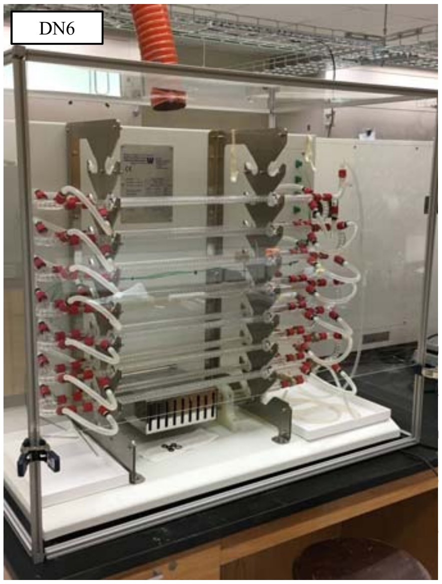
Performance Benefits

- Solid suspension at low flow rates (compared to traditional Plug Flow Reactors)
- Superior heat transfer rates
  - Control properties of solids
  - Narrow Residence Time Distributions (RTD)
- Ease of knowledge transfer
  - Linear Scalability - lab to industry
- High throughput capabilities
- Lower shear rates (compared to CSTR)
  - Lower energy input/duty
  - Breakage sensitive applications



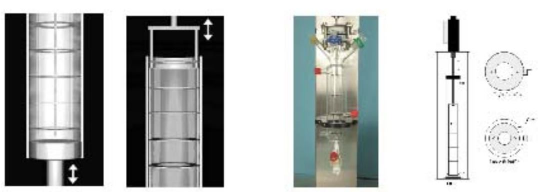
1. Ni, X.; Jian, H.; Fitch, A. W. Computational fluid dynamic modelling of flow patterns in an oscillatory baffled column. *Chemical Engineering Science, 2002, 57, 2849-2862.*
2. Lawton, S., Steele, G., Shering, P., Zhao, L., Laird, I., & Ni, X. W. (2009). Continuous crystallization of pharmaceuticals using a continuous oscillatory baffled crystallizer. *Organic Process Research and Development*, *13*(6), 1357–1363.
3. Ni, X., & Liao, A. (2010). Effects of mixing, seeding, material of baffles and final temperature on solution crystallization of l-glutamic acid in an oscillatory baffled crystallizer. *Chemical Engineering Journal*, *156*(1), 226–233.

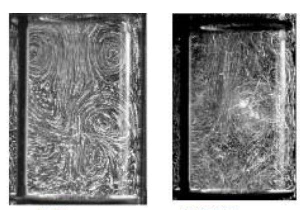
COBC Mixing Dynamics



1. Ni, X.; Jian, H.; Fitch, A. W. Computational fluid dynamic modelling of flow patterns in an oscillatory baffled column. *Chemical Engineering Science, 2002, 57, 2849-2862.*
2. Lawton, S., Steele, G., Shering, P., Zhao, L., Laird, I., & Ni, X. W. (2009). Continuous crystallization of pharmaceuticals using a continuous oscillatory baffled crystallizer. *Organic Process Research and Development*, *13*(6), 1357–1363.
3. Ni, X., & Liao, A. (2010). Effects of mixing, seeding, material of baffles and final temperature on solution crystallization of l-glutamic acid in an oscillatory baffled crystallizer. *Chemical Engineering Journal*, *156*(1), 226–233.

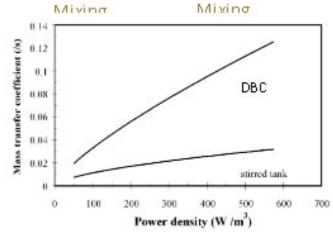
Oscillatory dynamic baffled crystallizer (ODBC)



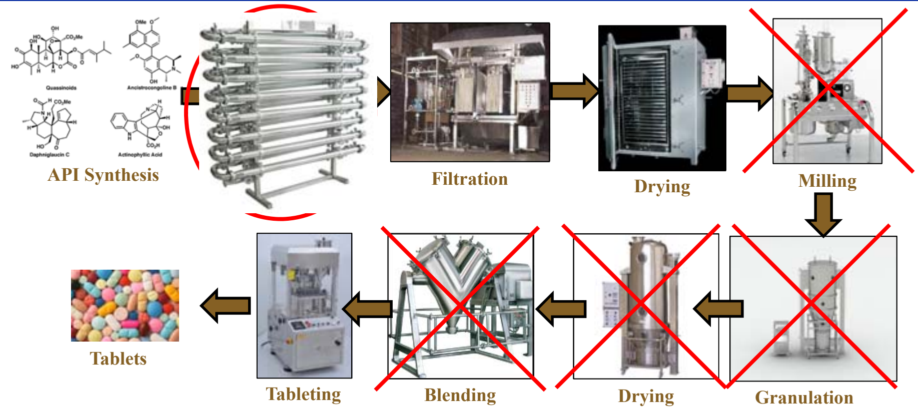


Soft Mixing Intense Mixing

- Degree of mixing can be tightly controlled
  - Oscillatory Reynolds Number: $Re_o = \frac{2\pi f x_0 \rho D}{\mu}$
  - Strouhal Number $St = \frac{D}{4\pi x_0}$
  - D: diameter of the tube
  - x_0: oscillation amplitude
  - f: oscillation frequency
  - μ: viscosity of the fluid
- Enhanced heat and mass transfer

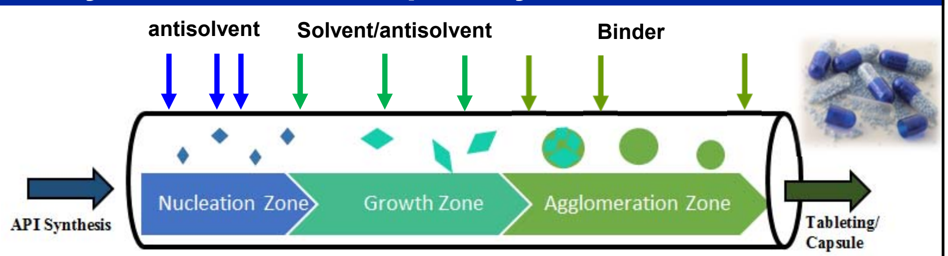


Process Intensification via continuous spherical crystallization and spatially distributed control

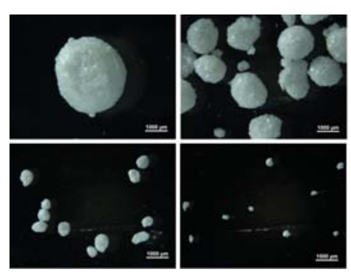


- Integrated drug substance & drug product manufacturing
- Difficult morphologies (needles, plates), slow growing (proteins, mAb, etc.) & growth inhibited systems (**biopharmaceuticals**)
- Enables design for balance between bioavailability and manufacturability

Process Intensification via continuous spherical crystallization and spatially distributed control

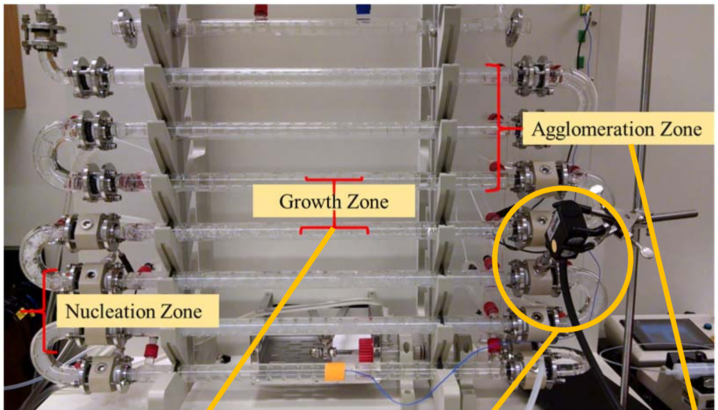


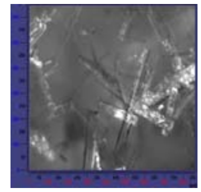
- Reconfigurable "plant" via spatially distributed control (QbC)
- Nucleation zone via crystallization or wet milling/micronization
- Tailored internal/external size (bioavailability vs. manufacturability)
- Co-agglomeration (FCD, excipient-API)
- Demonstrated in PFC and series of MSMPR

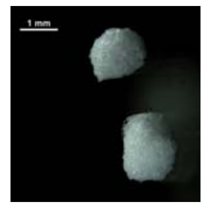


Pena & Nagy., CGD, 2015; Pena et al. CES 2017; Pena et al. CGD. 2017

Process Integration and Intensification through Oscillatory Baffled Crystallizer and Spherical Crystallization







Growth control via spatial temperature profile or distributed antisolvent

Nucleation control using FBRM-based feedback control

Agglomeration via spatial binder addition control

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Pena et al. CGD. 2017

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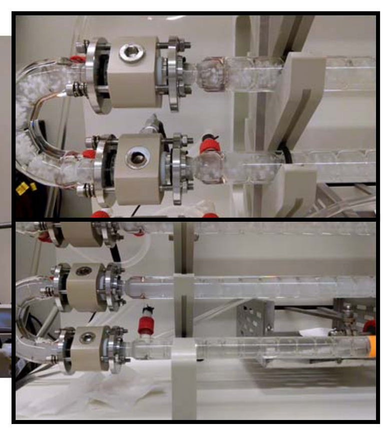
Process Integration and Intensification through Oscillatory Baffled Crystallizer and Spherical Crystallization



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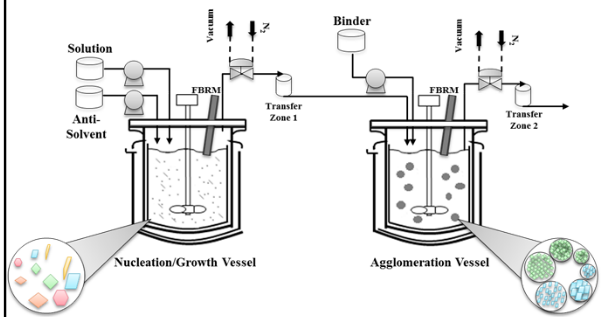
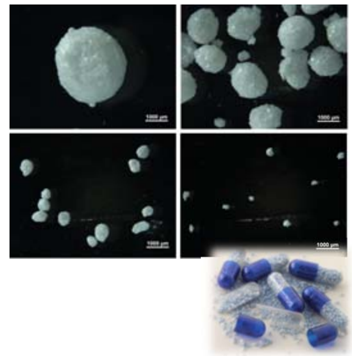
Process intensification via continuous spherical crystallization (CSC)

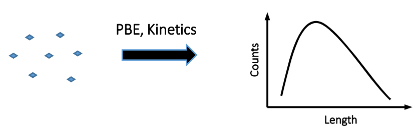




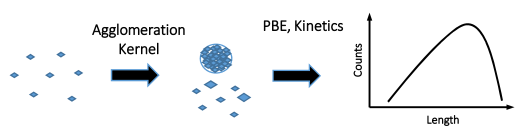
- Decoupled control of mechanisms
- Tailored internal/external size (bioavailability vs. manufacturability)
- Controlled micromeritic properties & release
- Solves processing problems (needles, growth inhibited system, etc.)
- Novel PBM formulation

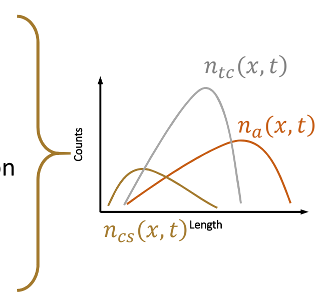
Model formulation
Tracking primary & secondary populations

- Traditional crystallization modeling with nucleation and growth



- Traditional crystallization modeling with agglomeration





- Reasons for a coupled population balance framework
  - *Loss of constituent information – lumped in single distribution*
  - *Inability to optimize and control – crystal and agglomerate properties*

Peña, R., et al. (2017). *Chem. Eng. Sci.*

Model formulation
Coupled population balance framework

- **Primary crystals:** $\frac{\partial[V(t)n_{tc}(x,t)]}{\partial t} = -\frac{\partial}{\partial x}\left(G(x)V(t)n_{tc}(x,t)\right) + \delta(x)V(t)B$
- **Crystals in suspension:**

$$\frac{\partial[V(t)n_{cs}(x,t)]}{\partial t} = -\frac{\partial}{\partial x}\left(G(x)V(t)n_{cs}(x,t)\right) + \delta(x)V(t)B - V(t)n_{cs}(x,t)\int_0^\infty \beta(x,\lambda)n_{ca}(\lambda,t)d\lambda$$

- **Agglomerates:**

$$\frac{\partial[V(t)n_a(x,t)]}{\partial t} = -\frac{\partial}{\partial x}\left(G(x)V(t)n_a(x,t)\right) + \frac{x^2}{2}\int_0^x \frac{\beta\left((x^3-\lambda^3)^{1/3},\lambda\right)n_{ca}\left((x^3+\lambda^3)^{1/3},t\right)V(t)n_{ca}(\lambda,t)}{(x^3-\lambda^3)^{2/3}}d\lambda - V(t)n_a(x,t)\int_0^\infty \beta(x,\lambda)n_{ca}(\lambda,t)d\lambda$$

- **Crystals in suspension & agglomerates:** $n_{ca}(x,t) = n_{cs}(x,t) + n_a(x,t)$

Nucleation: $B = k_b(\mathcal{N})(1 + i * M)(S-1)^{b(\mathcal{N})}$

Growth: $G = k_g(\mathcal{N})(S-1)^{g(\mathcal{N})}$

- Semi-batch operation
- Reverse anti-solvent addition

Agglomeration: **Brownian+** kernel: $\beta(L_i,L_j) = a(b + c\varepsilon^{1/2} - d\varepsilon)S^e \frac{k_a(L_i+L_j)^2}{L_iL_j}$ $\quad \varepsilon = \frac{k_{power}d_s^{\,5}N(t)^3}{V}$

Multi-objective optimization framework
Bioavailability vs Manufacturability

- Optimal control design for tradeoff between a target size (CSD) for bioavailability ($\mathcal{B}_T$) and a target size (ASD) for manufacturability ($\mathcal{M}_T$)

$\mathcal{B}_T$ – bioavailability
$\mathcal{M}_T$ – manufacturability
$\mathcal{T}$ – Temperature
$\mathcal{N}$ – Agitation Rate
$\mathcal{F}$ – Flowrate
$\mathcal{C}_{final}$ – final concentration
$\mathcal{C}_{max}$ – maximum concentraion

Bioavailability target **Manufacturability target**

$$\min_{\mathcal{T}(t),\mathcal{N}(t),\mathcal{F}_S(t)} w_1\left(\mathcal{B}_T - \mathcal{L}_{tc,10}\right)^2 + w_2\left(\mathcal{M}_T - \mathcal{L}_{a,10}\right)^2$$

s.t. $15 \le \mathcal{T}(t) \le 30\,°C$

$400 \le \mathcal{N}(t) \le 800\ RPM$

$0 \le \mathcal{F}(t) \le 2.5\ ml/min$

$-1 \le \frac{\partial T}{\partial t} \le 1°C/min$

$\mathcal{AE} \ge 50\%$

$0.25 \le \mathcal{SASR} \le 0.50$

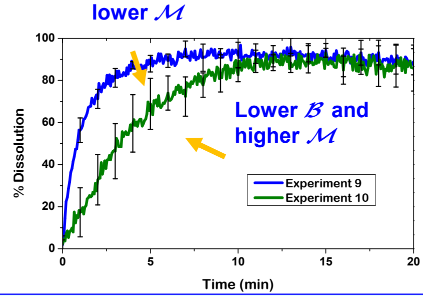
$\mathcal{C}_{final} \le 0.75 * \mathcal{C}_{max}$

$\mathcal{F}_S(0) \ge 1.0\ ml/min$

$t_{batch} = 30\ min$

Optimize temperature trajectory, dynamic agitation and antisolvent addition profiles

Higher $\mathcal{B}$ and lower $\mathcal{M}$

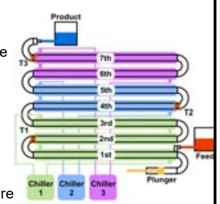


Pena et al. CES 2017

Biopharmaceutical Purification

- **Chromatographic Purification**
  - High product quality and yield
  - Very expensive
  - Throughput and scalability limitations
- **Protein Crystallization Difficulties**
  - Slow kinetics
  - Growth limited systems
- **Typical Batch Crystallizations**
  - 24+ hours
  - Low filterability
    - Usually leads to lyophilization
    - Uncontrollable agglomeration/ caking

- **Benefits of Oscillatory Systems**
  - Low shear stress
  - Enhanced micromixing
  - High surface area to volume
  - Plug flow operation
    - Narrow RTDs
- **Limitations**
  - Solid settling and clogging
  - Fouling and encrustation
  - Long residence times require long tube lengths



Batch Chromatography

*Taken from Prof Linda Wang *Purdue University*

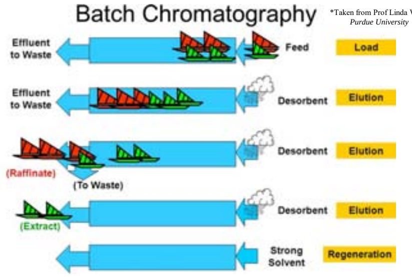


Table 5. OBR bioprocesses using cellular components.

bioprocess	cellular component	year	conclusion
protein refolding	hen egg white lysozyme	2001	OBRs are suitable refolding devices and comparable to STRs
protein renaturation	hen egg white lysozyme	2002	refolding yield in OBR comparable to STR. Uniform shear important for successful refolding
protein refolding	chicken egg white lysozyme	2006	prevention of aggregation enhances refolding during initial stages (0–4 min)

Table 8. Key barriers facing adoption of OBR technology.

design	
lengths hundreds of metres required for fully continuous operation with residence times of hours to days	

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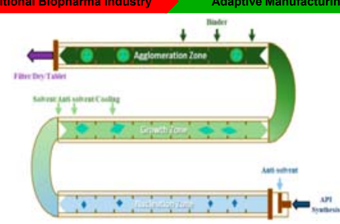
1. Abbott, M. S. R., Harvey, A. P., Perez, G. V., & Theodorou, M. K. (2013). Biological processing in oscillatory baffled reactors: operation, advantages and potential. *Interface Focus*, *3*(1), 20120036.

Motivation for Spherical Agglomeration

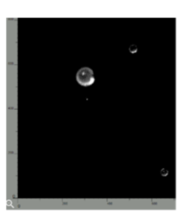
- **Protein Crystallization Difficulties**
  - Slow growth kinetics
  - On order of 5 hours to days
- **Spherical Agglomeration Demonstrated for Small Molecules**
  - Overcome tradeoff between bioavailability and manufacturability
  - Why grow crystals when you can agglomerate them?
    - Reduce crystallization time by order of magnitude
    - Process flexibility (can generate wide range of particle sizes)
    - Directly filterable
      - No longer reliant on costly chromatography

Paradigm Shift in Manufacturing Culture

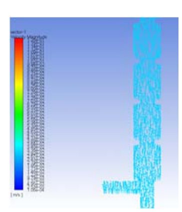
Traditional Biopharma Industry | Adaptive Manufacturing



Process Automation with Advanced Control and System Monitoring

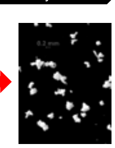


Predictive Product Quality through Process Optimization



Simultaneously Tailor Bioavailability and Manufacturability

Effective Diameter: 998nm



Average Diameter: 307 µm

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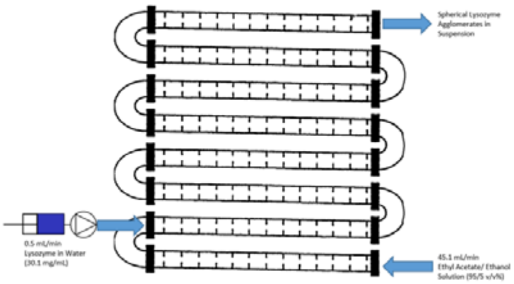
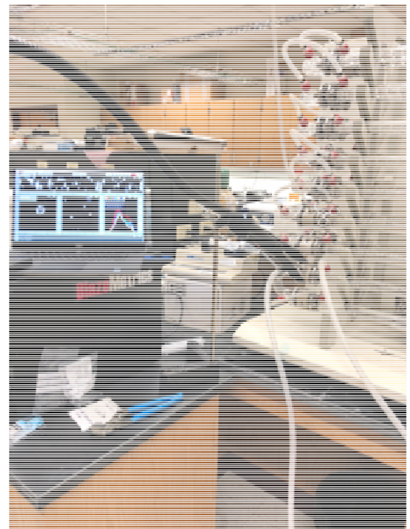
Spherical Agglomeration Overview

Spherical Crystallization System



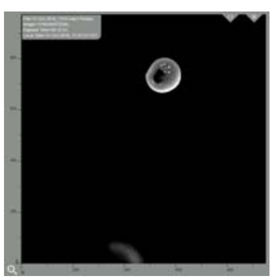


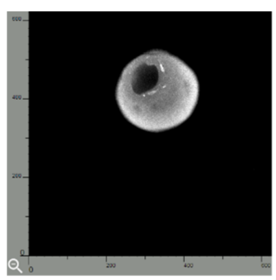
DN6

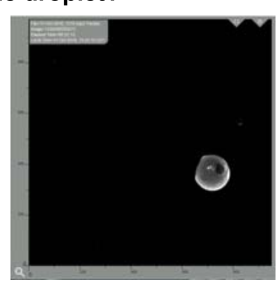
DN15

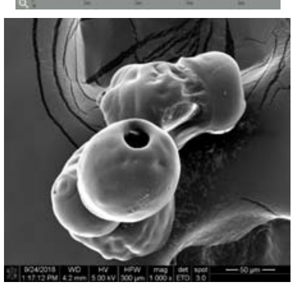
Blaze Imaging and SEM Analysis

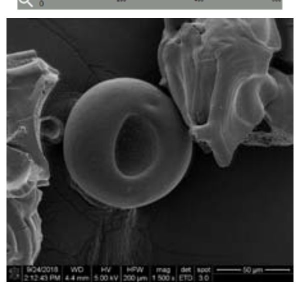
What is the fate of the solvent inside the droplet?

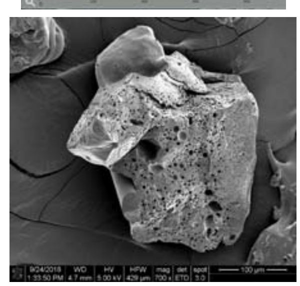




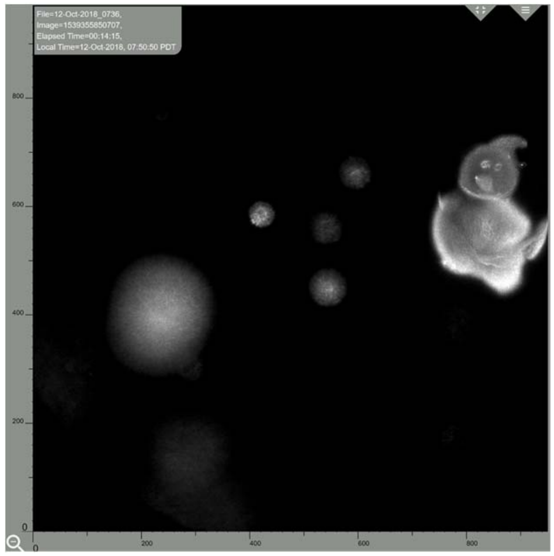








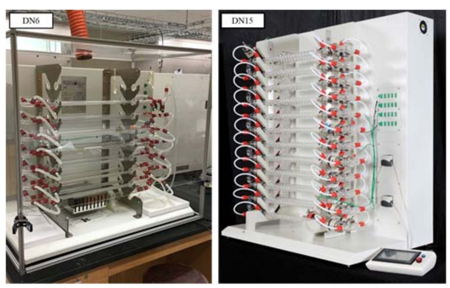
What makes spherical agglomeration work?



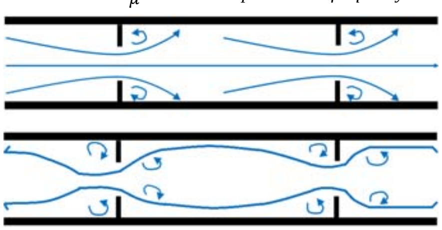
Scale-Up and Geometric Considerations

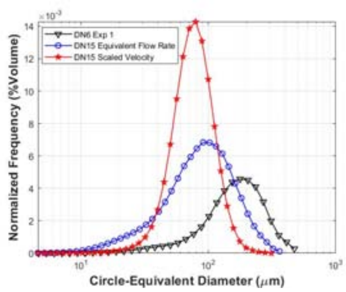
Scale-up Considerations:

- Method 1 (Blue Curve)
  - Directly transfer DN6 conditions
    - Const. injection flow rate, antisolvent flow rate
    - Scale piston conditions to keep Re_o const.
- Method 2 (Red Curve)
  - Scale axial velocity to be const
    - Change in diameter changes injection environment
  - Scale piston conditions to keep Re_o const.



$$Re_o = \frac{2\pi f x_o \rho D}{\mu};$$ *x_0 and f are the piston amplitude and frequency*

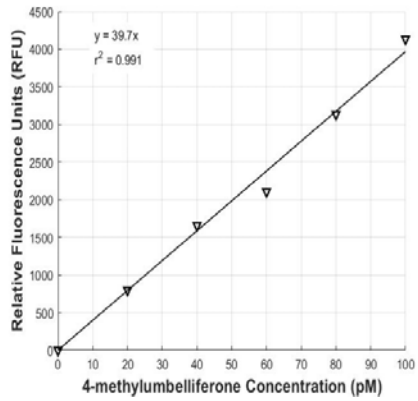


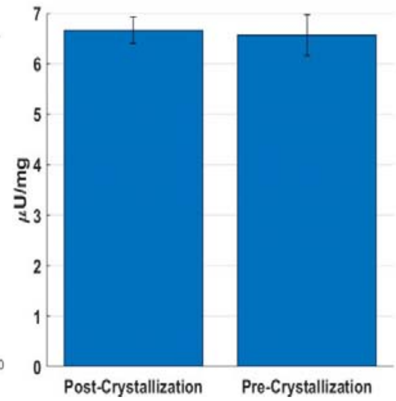


Protein Activity

Measuring Protein Activity:

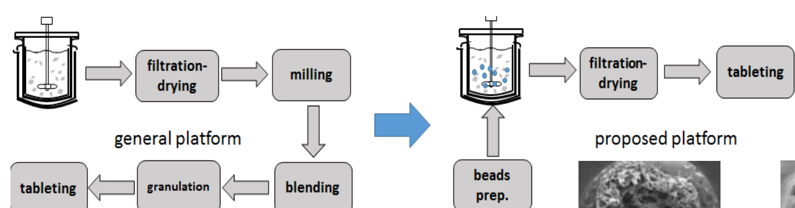
- Lysozyme is a muramidase
  - Acts on glycosidic bonds in cell walls on bacteria
    - Cleaves a synthetic analog of this bond
    - Creates a fluorescent by-product

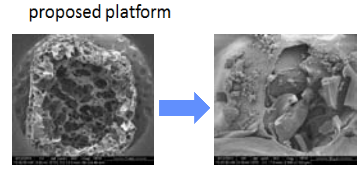




Process intensification via reverse product engineering through crystallization in porous polymer substrate

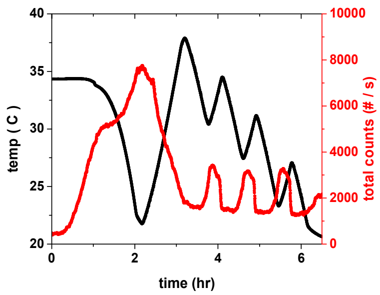
- Create porous substrate then load with API (reverse engineering)
- Decrease number processing steps
- Suitable for particles that are difficult to process (needle, plate, growth inhibited)
- Tailor product properties from controlling substrate property (e.g. porosity) and internal CSD
- Increase drug loading, eliminate bulk nucleation, control CSD

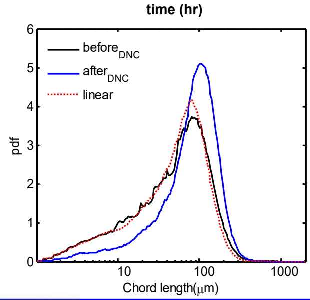


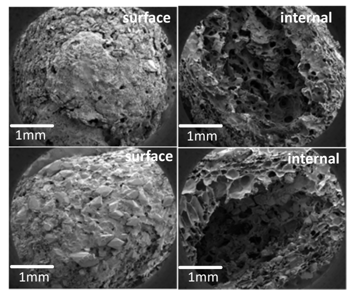


Collaboration with Chadwick group at Purdue

Process intensification via reverse product engineering through crystallization in porous polymer substrate







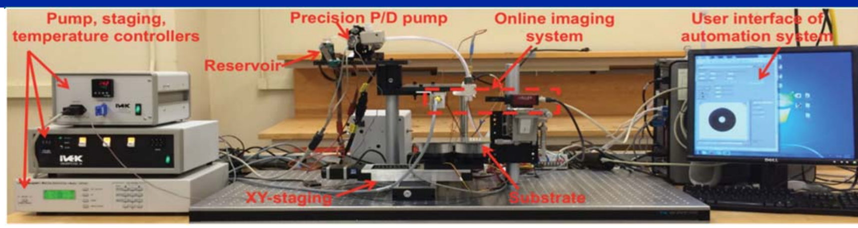
	linear		programmed	
	only	DNC	only	DNC
loading (% w/w)	49.2	53.7	68.1	68.0
stdev	10.1	2.7	9.1	1.8

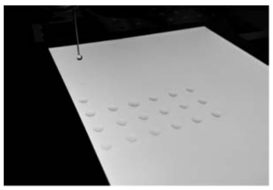
DAMP™

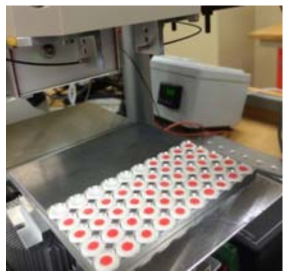
Dropwise Additive Manufacturing Process

Nagy, Reklaitis, Taylor (IPPH)

Dropwise Additive Manufacturing Process (DAMP)

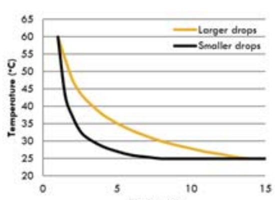


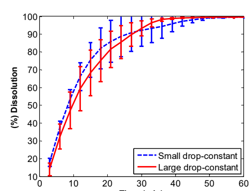




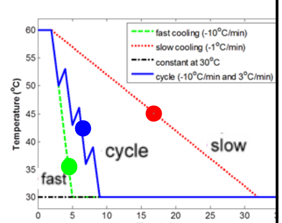
- Drop-On-Demand (DoD) fast Inkjet Printing Technology
- Placebo tablets, edible films and capsules
- Solvent and Melt based formulation

Hot Stage Microscopy study of effect of T-cycling



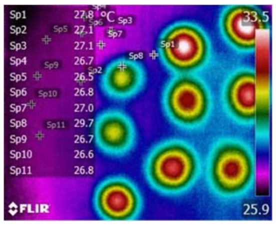


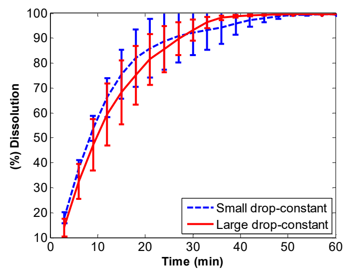
- ❑ Drop size affects the cooling profile and therefore the morphology of the drug affecting bioavailability

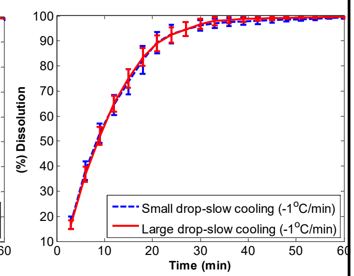


- ❑ **Fast cooling:** Increased surface area due to more nucleation sites and due to surface defects
- ❑ **T-Cycling**: Surface defects are eliminated, more uniform morphology

Monitoring and control of spatial temperature difference

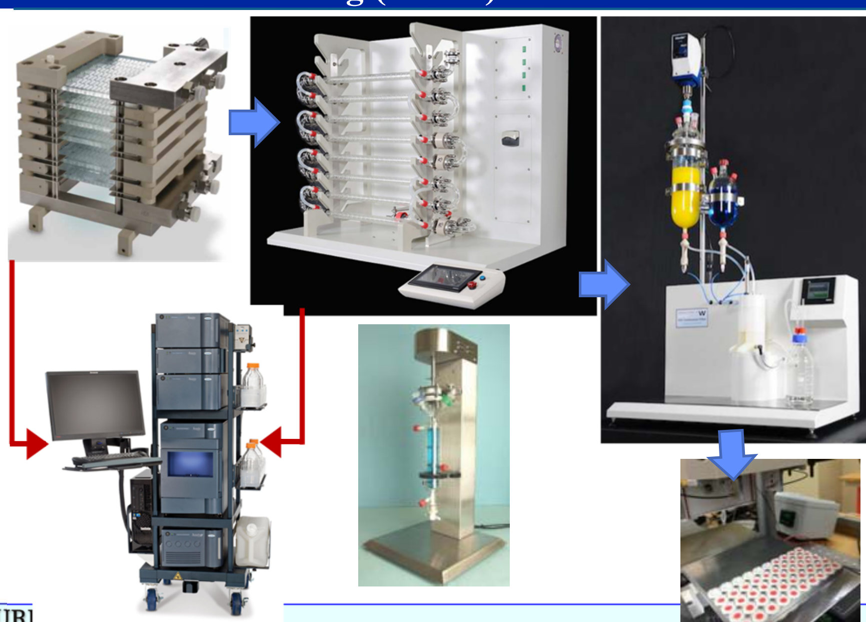






- IR camera to monitor spatial temperature distribution
- Spatial temperature control to minimize effect
- Controlled crystallinity
- Uniform dissolution profile despite difference in drop size (dose)

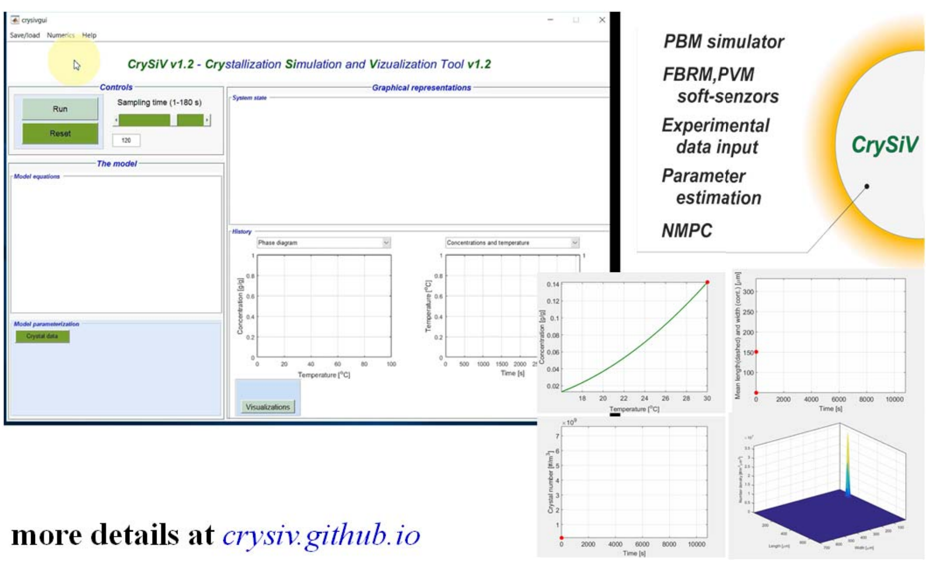
The Integrated Continuous Pharmaceutical Manufacturing (ICPM) testbed at Purdue



Conclusions

- Continuous crystallization as a method of process intensification
- Oscillatory systems have better performance then stirred tanks
- Process intensification via spatially distributed controlled crystallization
- Process intensification and integration via crystallization within porous substrate
- Designed as integrated operations (reaction-crystallization-filtration-formulation)
- Membrane crystallization
- Novel integrated manufacturing platforms (e.g. DAMP)

Exercise:
Model-based crystallization design and control



more details at *crysiv.github.io*

Exercise

A crystallization was designed to produce API crystals with mean size of **285±15 μm** as required for content uniformity. Although the product meets required mean size target the slurry at the end requires excessive filtration time.

1. Simulate the process and give possible explanations of the problem
2. Propose modifications to the current operation of the crystallization to produce similar mean crystal size but a product which most likely significantly improves

Homework:

1. How the batch time influences the crystallization process (product CSD, evolution of nucleation and growth rates)? Explain your observations. Create animated .gif file to support your answer
2. How the cooling rate influences the CSD

Note: The currently designed process can be simulated by loading the default model in CrySiv.

CrySiV GUI installation

1. Go to "crysiv.github.io"
2. "Downloads"
3. "GUI installation kit"
4. Install the software

Report any bug to: zknagy@purdue.edu

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Solution:

0.005 (default: 285); 0.01 (309); 0.03 (259); **0.02 (283)**