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Co-Processed API Product and Process Development, Optimization, and Scale-up

Nima Yazdanpanah

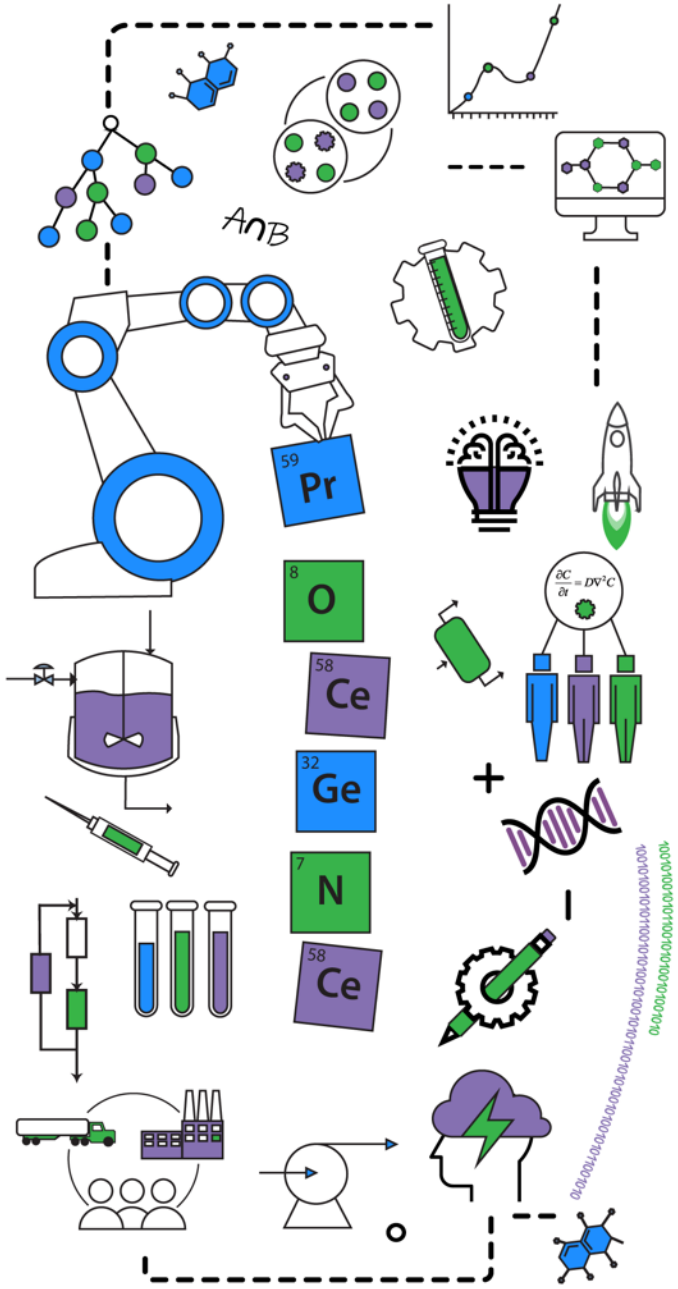
Procegence, Chevy Chase, MD, USA

FDA/M-CERSI Co-Processed API Workshop – July 13, 2022

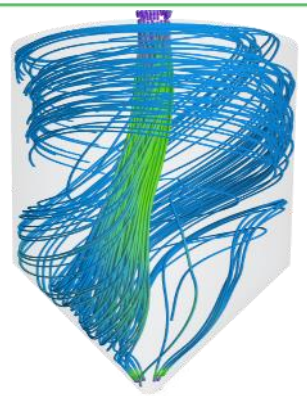
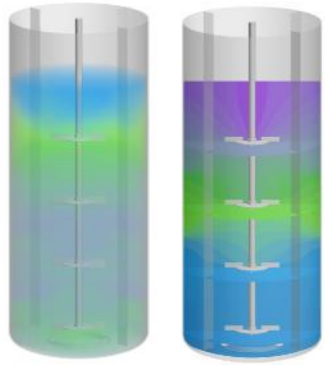
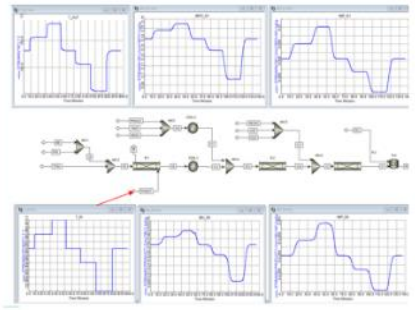
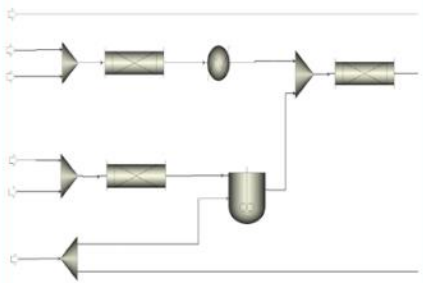
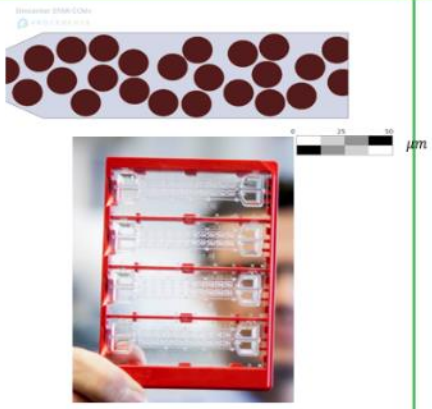
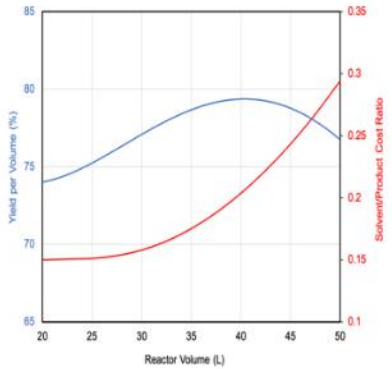
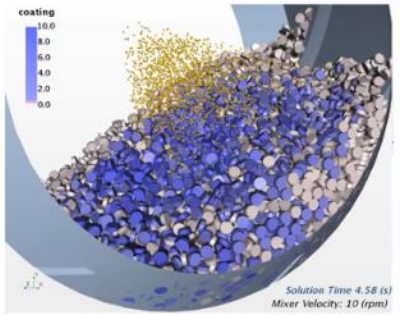
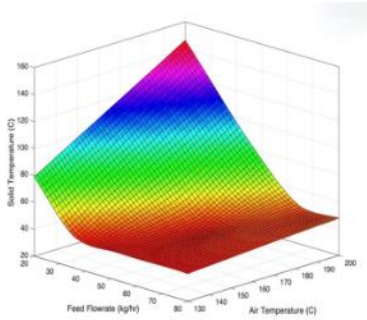
Procegence is an Advanced Manufacturing and Emerging Technology consultancy firm for Pharma, Biopharma, and Fine Chemical industries.

Through modeling & simulation, we help companies to:

- Reduce time to market
- Reduce R&D spending
- Increase R&D efficiency



Some of Our Projects

				
Spray Drying	Crystallization	Hydrogenation	Bioprocessing	Digital Twin
				
Process Development	Devices	Technoeconomic	Drug Product	CMC, QbD

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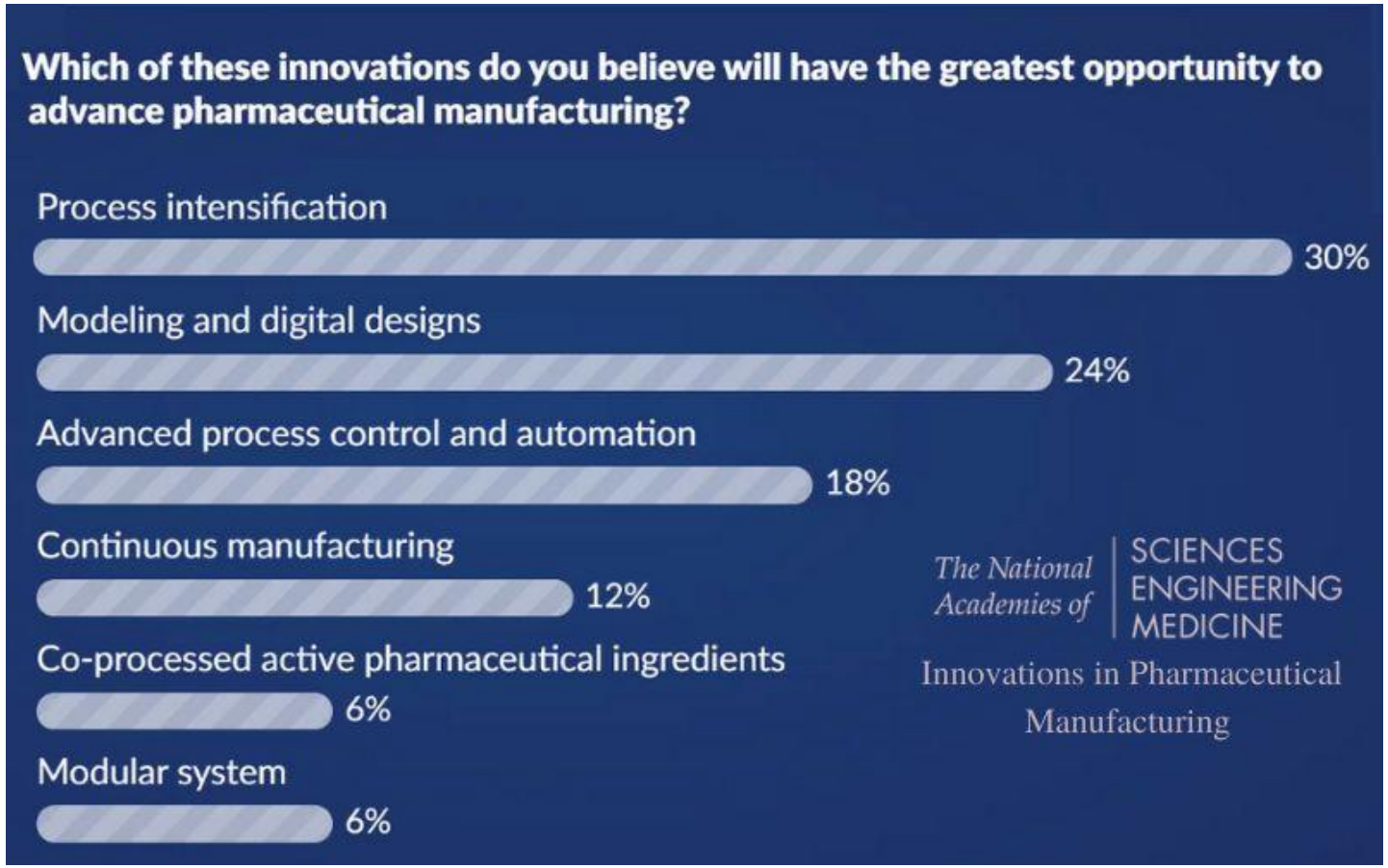

Procegence is proud to be the forefront of modernization of the Pharmaceutical manufacturing.
We have done many projects on above themes and helping our clients to step-up their games.

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Outline

- 3 case studies
  - Crystallization-Epitaxy
  - Spray drying- (in-situ crystallization)- Dry Powder Inhalation product
  - mRNA, Exosome, Liposome- encapsulation and device design optimization
- Product design
- Manufacturing, Process development
- Scale-up and technology transfer

Emphasizing on:

- Scale-up and technology transfer (and CMC)
- Scale dependent phenomena
- Lab to plant, compatibility
- CMA~CPP~CQA correlation

Case 1: Epitaxy

- Pioneer work (2014-2016) on co-processed API
- Ref to the published paper for details

CRYSTAL GROWTH & DESIGN

Article

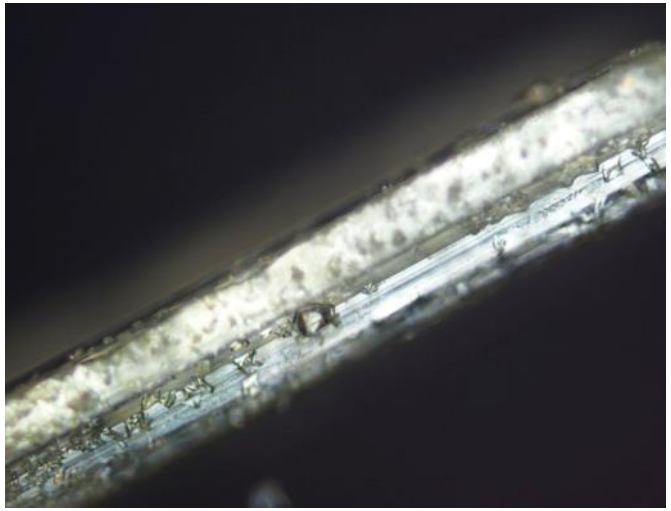
pubs.acs.org/crystal

Continuous Heterogeneous Crystallization on Excipient Surfaces

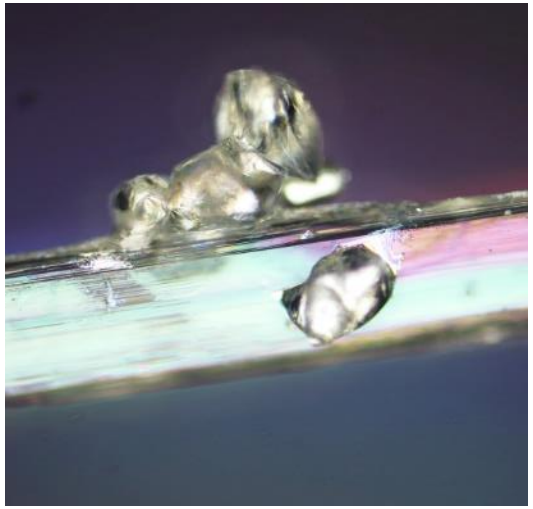
Nima Yazdanpanah, Christopher J. Testa, Siva R. K. Perala, Keith D. Jensen, Richard D. Braatz, Allan S. Myerson, and Bernhardt L. Trout*

DOI: 10.1021/acs.cgd.7b00297

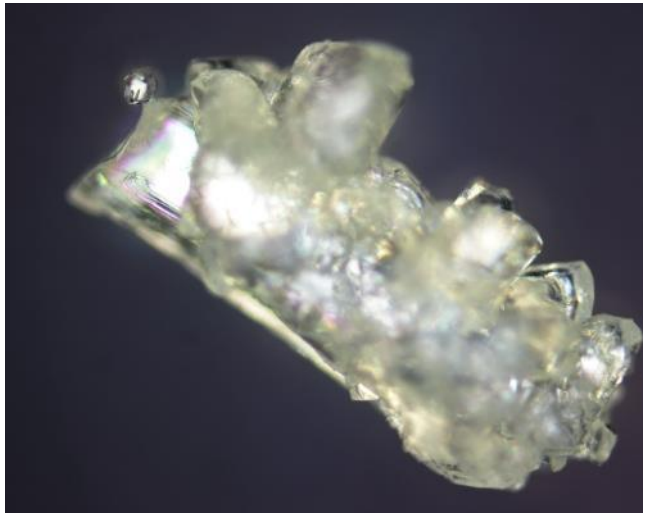
Cryst. Growth Des. 2017, 17, 3321−3330



Nucleation on surface of excipient

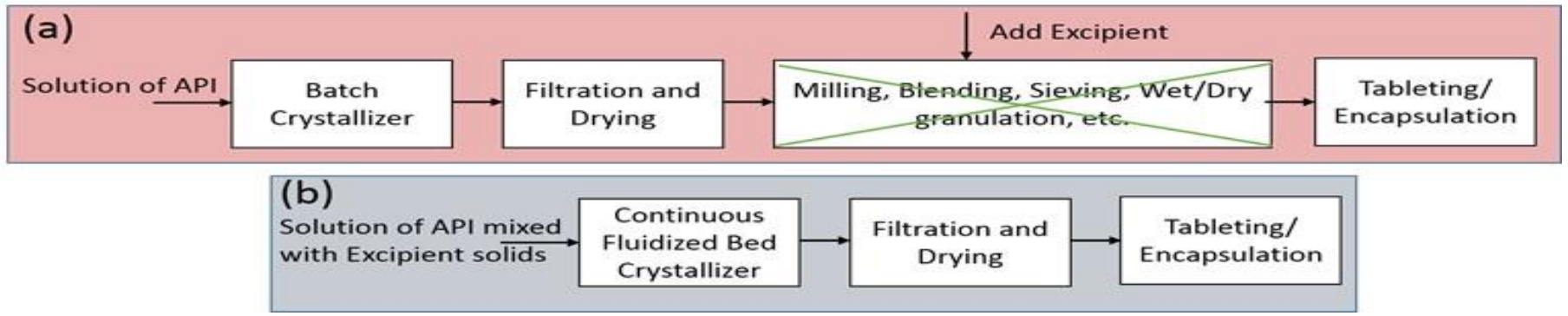


Growth

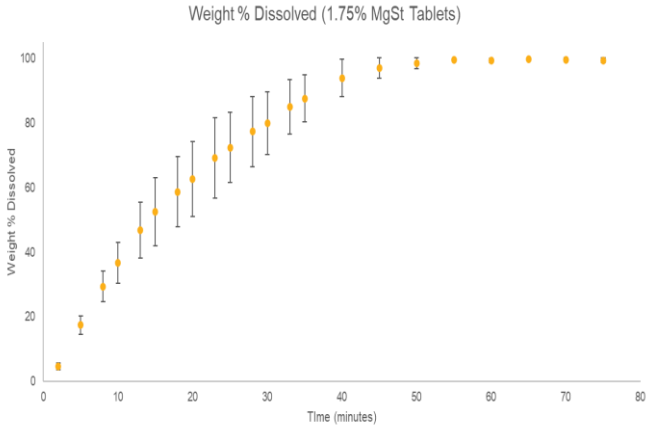


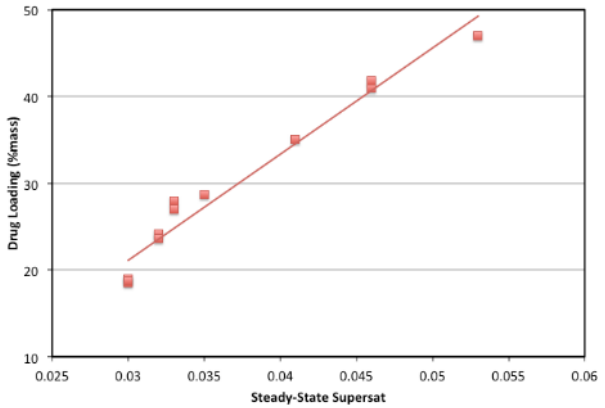
Final

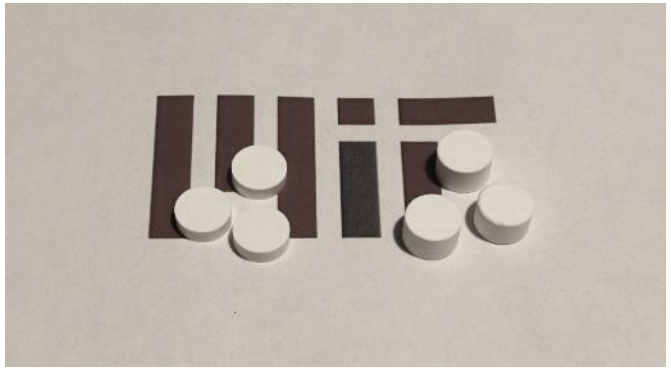
Case 1: Benefit



Co-processed API reduced the downstream steps, prevented segregation, tuned dosage, and release

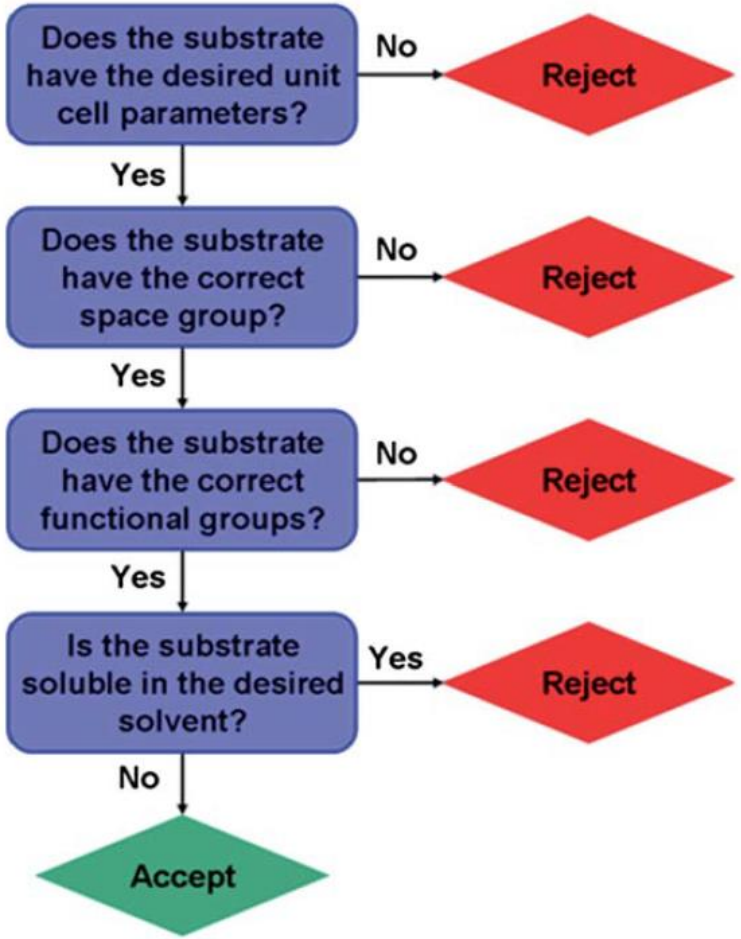


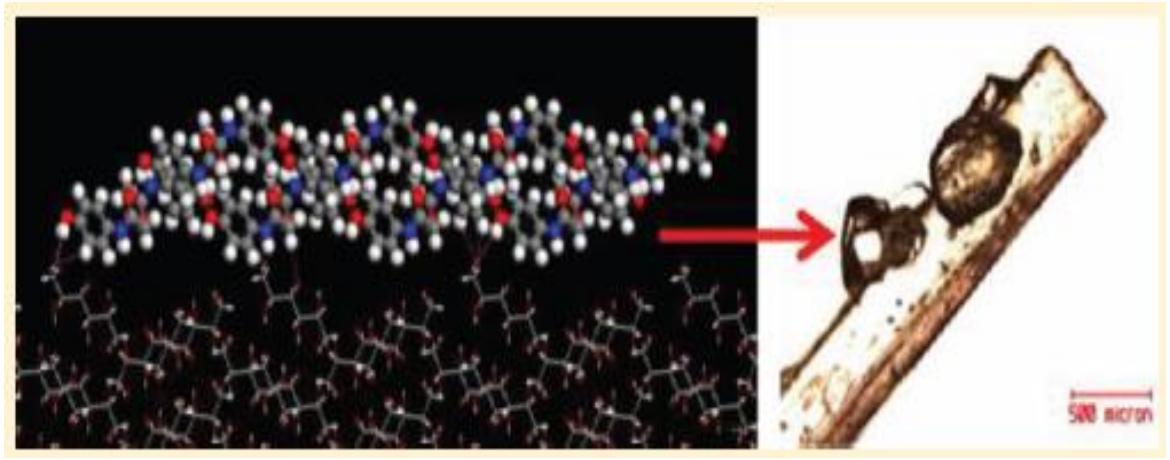


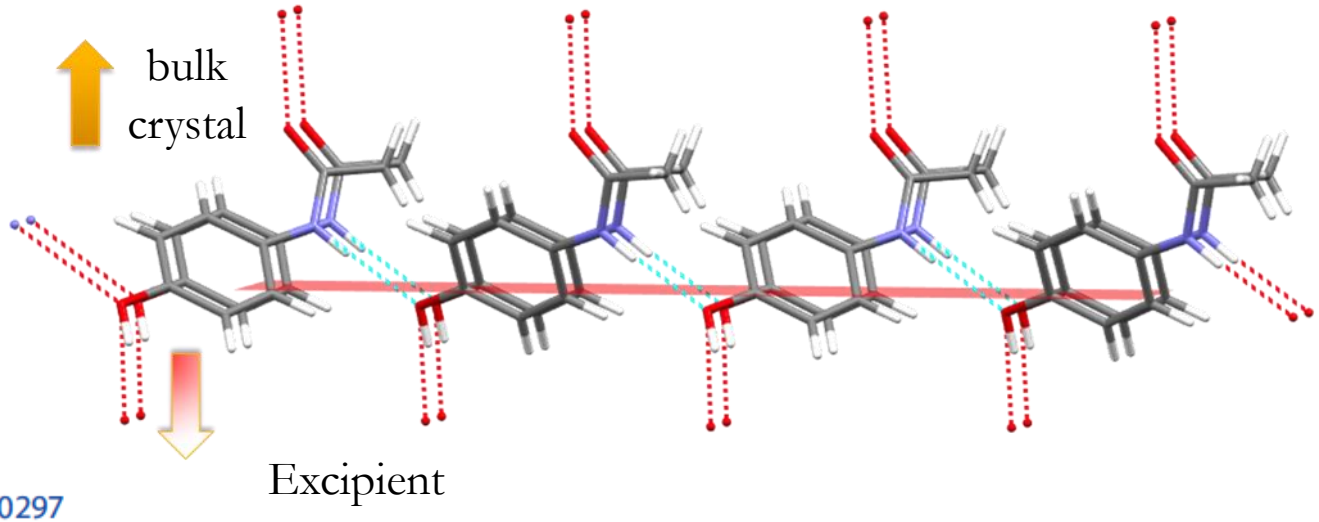


All conventional properties, formulation, and CMA-CPP-CQA were demonstrated

Case 1: How to: Excipient Selection







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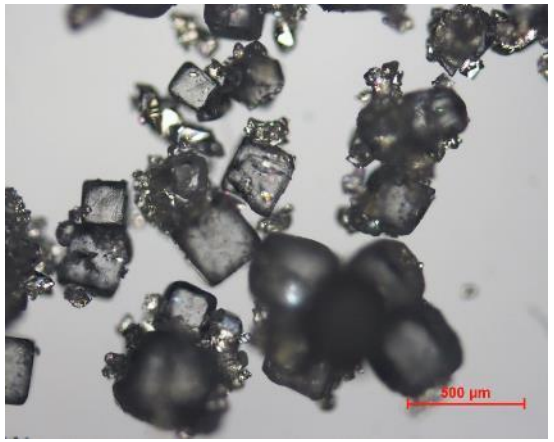
Experimental Induction Time Matrix

Validation of MD models

	No excipient	α-lactose Monohydrate	D-Mannitol	Glycine	L-Histidine	Calcium Carbonate	Micro Crystalline Cellulose	Sodium Chloride
Acetaminophen σ = 0.36	1930 ± 85	410 ± 11	390 ± 8	1860 ± 72	1910 ± 95	720 ± 13	530 ± 9	905 ± 19
Sulfathiazole σ = 0.52	*	486 ± 14	459 ± 12	3089 ± 280	*	1233 ± 97	350 ± 15	857 ± 24
Mefenamic acid σ = 0.14	300 ± 10	215 ± 9	216 ± 7	414 ± 9	263 ± 9	200 ± 8	251 ± 8	236 ± 9
Chloramphenicol σ = 0.86	4890 ± 370	219 ± 7	247 ± 13	202 ± 6	133 ± 4	649 ± 11	301 ± 7	859 ± 49
Indomethacin σ = 0.8	4410 ± 220	2600 ± 120	*	*	*	4270 ± 310	3780 ± 230	312 ± 12

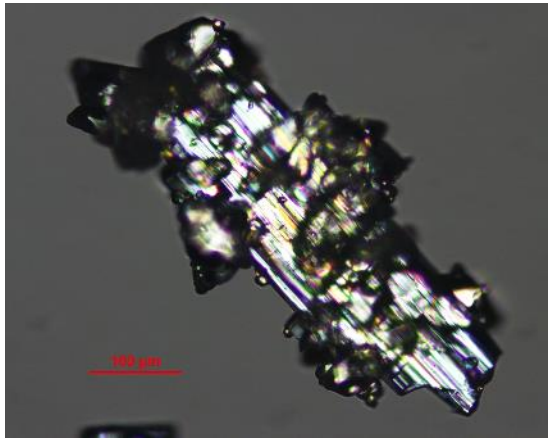
Yazdanpanah, N., et. Al.,(2016), *Continuous Heterogeneous Crystallization of Active Pharmaceutical Ingredients on Excipient Surfaces*, in 2016 *AIChE Annual Meeting.* San Francisco, USA.

Undesirable Cases (Effect of Substrate/Excipient)

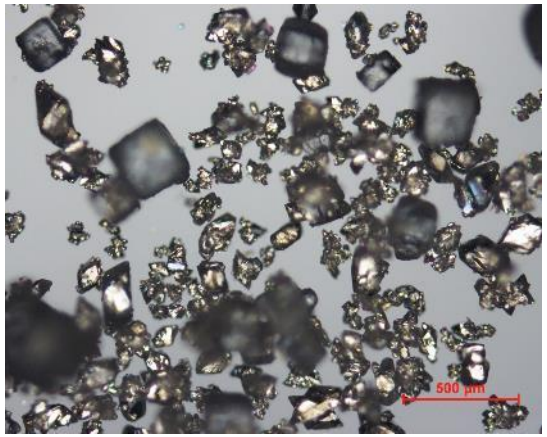


NaCl

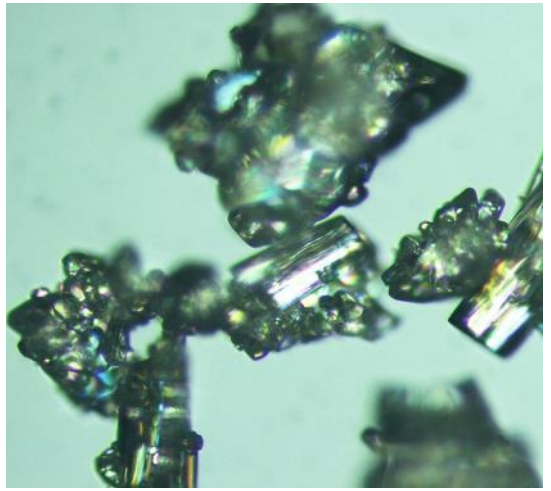
Correct substrate (Mannitol here) promotes controlled nucleation and growth on the surface



Mannitol



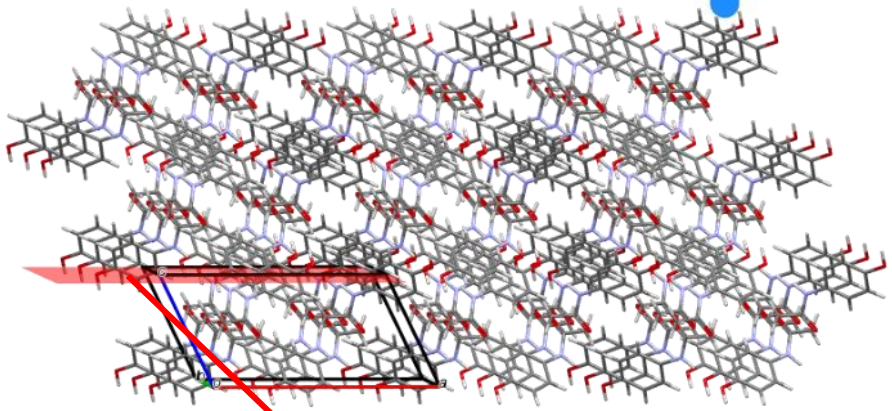
Random substrate (NaCl here) is not effective. Note “homogenous” nucleation and free API crystals floating in the solution. No epitaxy.

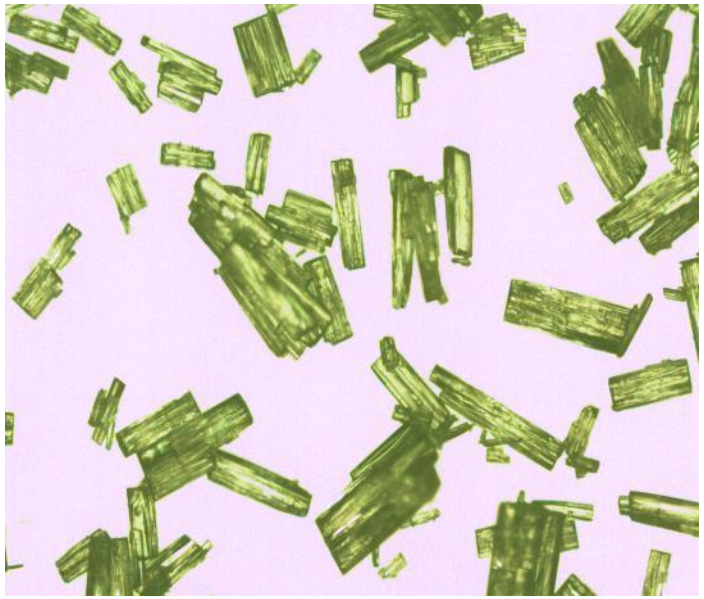


Take away: the substrate (co-processed agent) should be carefully selected.

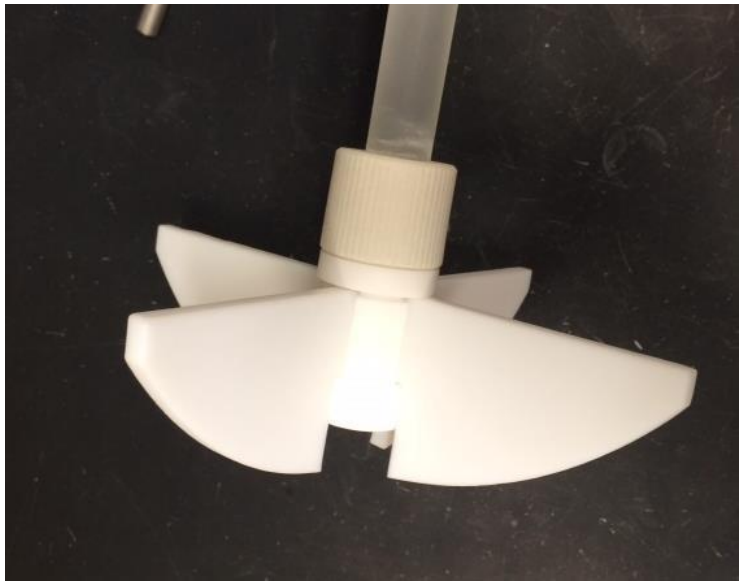
Some Process Challenges and Workaround

- Mixing and type of impeller, Lab scale and Manufacturing
  - P-P, P-I attrition
  - Not just heterogenous nucleation
  - Exposing new surface chemistry and bond propensity

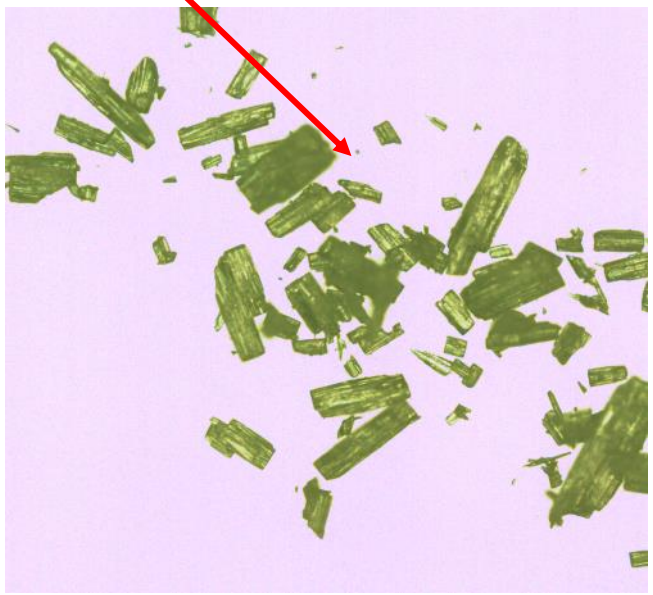




Starting excipient crystals



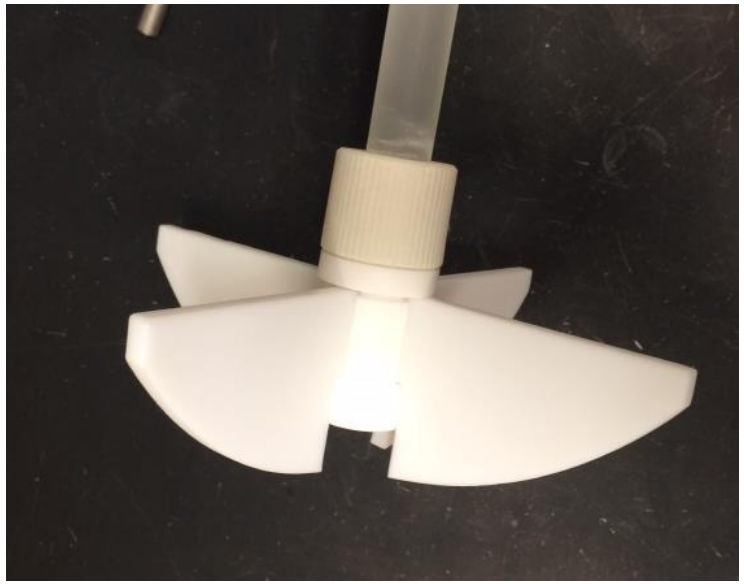
Few minute of mixing



Crushed crystals

Some Process Challenges and Workaround

- Mixing and type of impeller, Lab scale and Manufacturing
  - P-P, P-I attrition
  - Change type of impeller to avoid crushing (P-P, P-I). Keep crystals unaltered.



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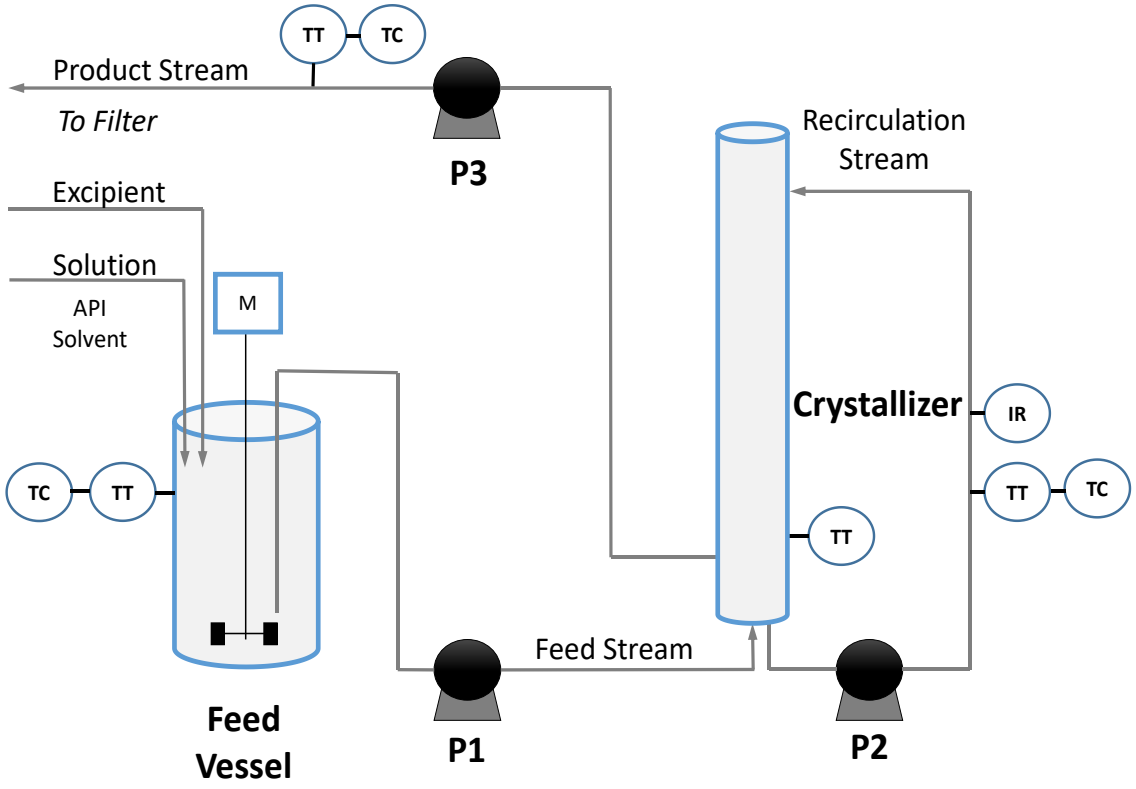
Shear Rate, Mixing and P-P attrition

Change process to impeller free

Fluidized bed crystallizer

Continuous

Movie



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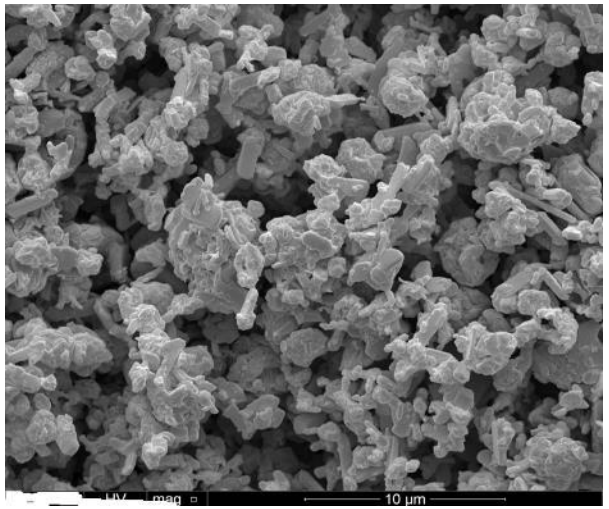
Case 2: Co-Processed API in Spray Drying - DPI

- in-situ Crystallization in Spray Drying (not amorphous dispersion)
- Co-processed API: L + API
- Formulation: L + API+ Water+ Ethanol+ Surfactant
- CQA: >95% crystallinity, perfect concentration uniformity (per particle), narrow PSD, aerodynamic properties, residual solvent

- Crystallinity and Uniformity: Stability and Quality issue
- PSD and MMAD: Drug delivery (and Pk)
- Formulation and particle microstructure: Bioavailability
- Challenge: Manufacturing scale, nonlinear system, complex formulation, expensive products



Case 2: in-situ Crystallization in Spray Drying- DPI

Project Objective:

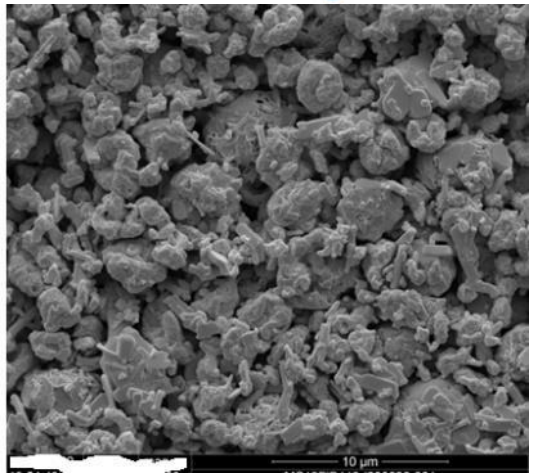
DPI by a complex formulation and >95% crystallinity
Product design and co-processed API
Define scale-up and tech-transfer to CMO
Define CMAs and CPPs to meet CQAs

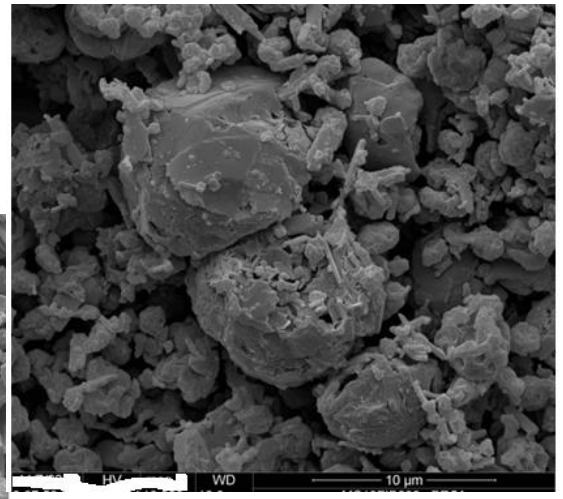
Problems:

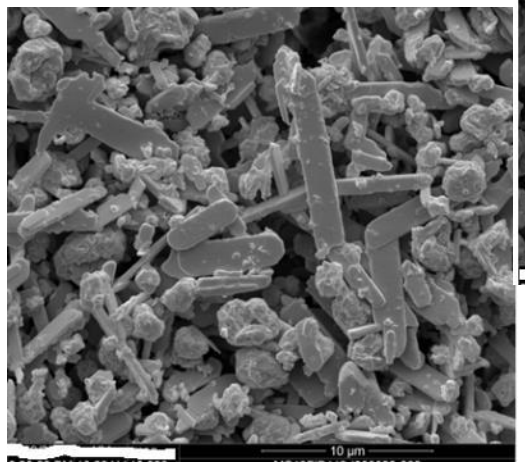
Client didn't know optimum formulation and CPP to achieve required CQA
Process development team and CMO couldn't meet CQA
Nonlinearities and complex formulation
In-situ crystallization in manufacturing scale SD for a narrow PSD

How We Helped:

Developed multiscale predictive simulations
Performed equipment and process characterization
Correlated CMA-CPP-CQA
Developed an optimized design space







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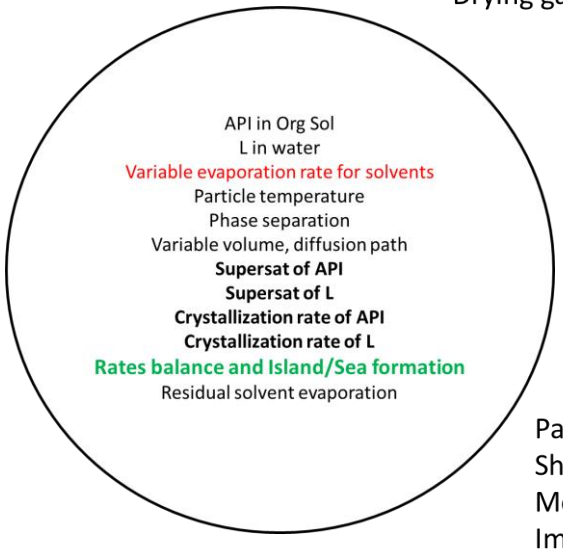
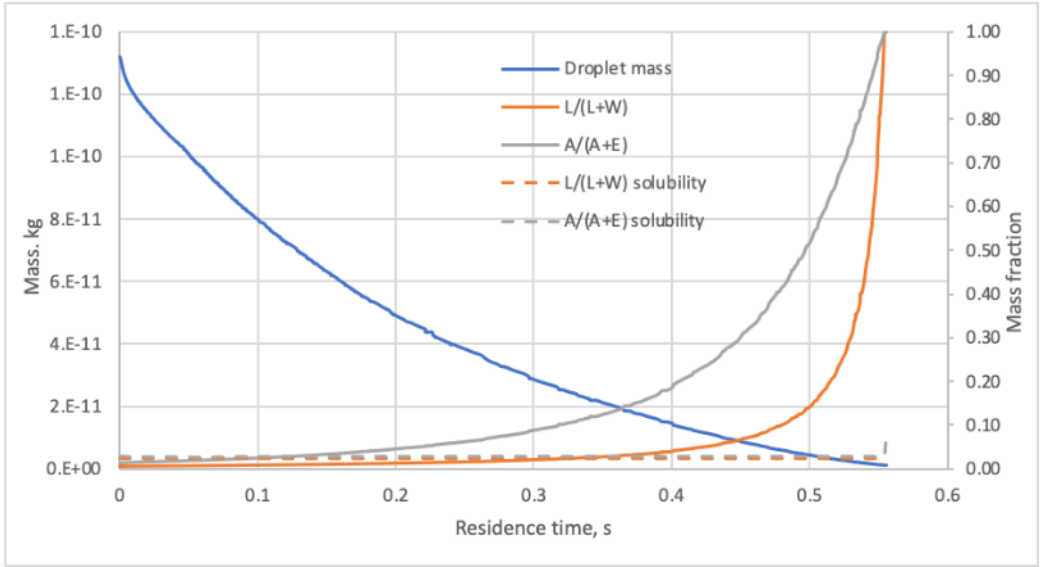
Process Challenge

- Impact of solvent system, Evaporation and supersaturation
- Impact of feed flowrate, saturation and enthalpy
- Impact of atomization, droplet size, diffusion rate, interfacial force
- Impact of gas T, Cond T, gas flow, evaporation, enthalpy, saturation
- ..



Drying gas:
Temperature
Vapor pressure of water
Vapor pressure of ethanol
Evaporation gradient

Particle residence time
Shape and surface area/volume
Motion, rotation, trajectory
Impacts to wall, p-p



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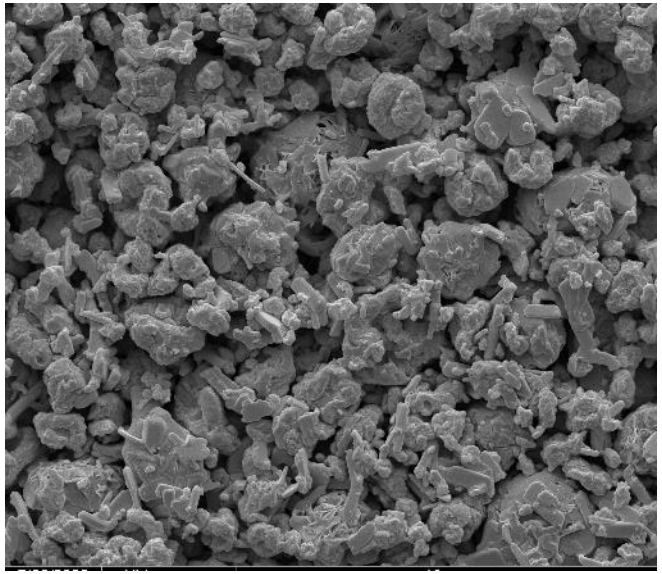
Manufacturing Process Scale-up

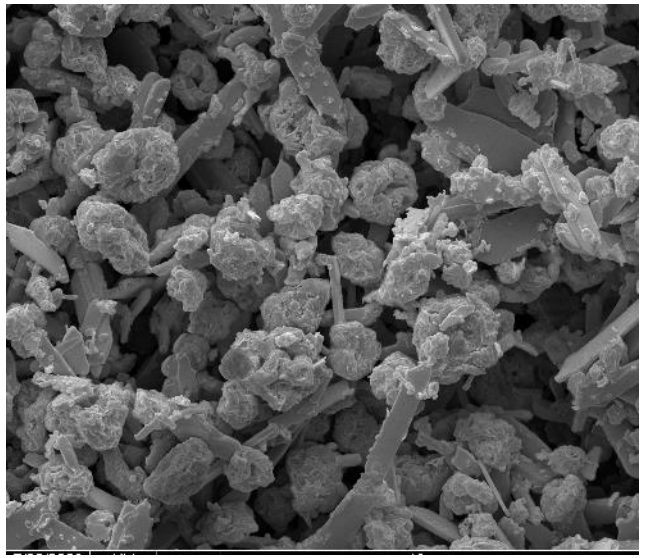
- Multiple intercorrelated parameters, nonlinear system -> Large scale Man.:
- Don’t waste your time, budget, and material

- Multidimensional virtual DoE for: (aka simulation)
  - Parametric study
  - Sensitivity analysis
  - Dynamic CMA~CPP~CQA correlation
  - Design space and optimization

Some CPP~CQA Correlations



100C



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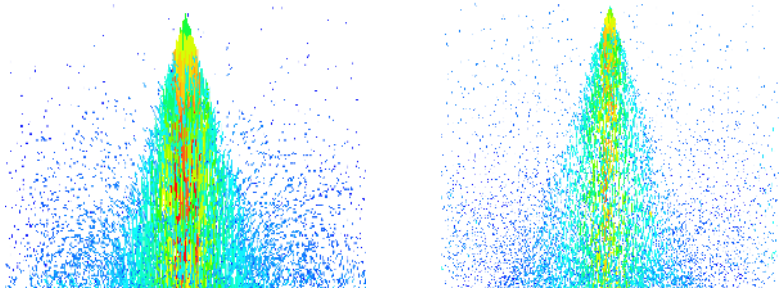
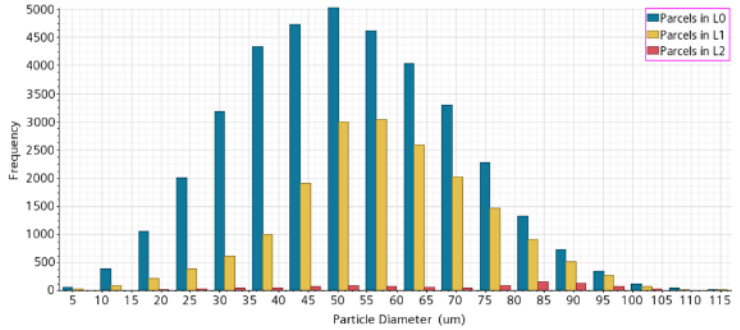


Effect of Solution/Feed Flowrate



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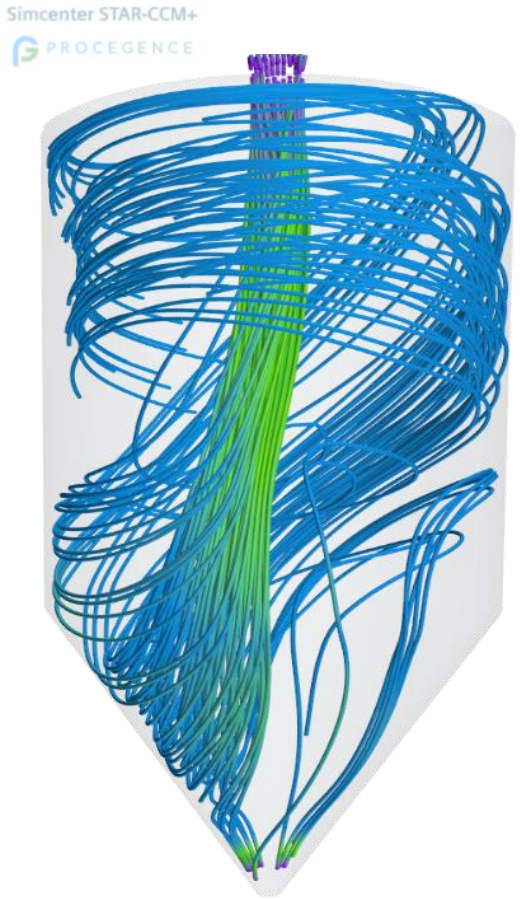
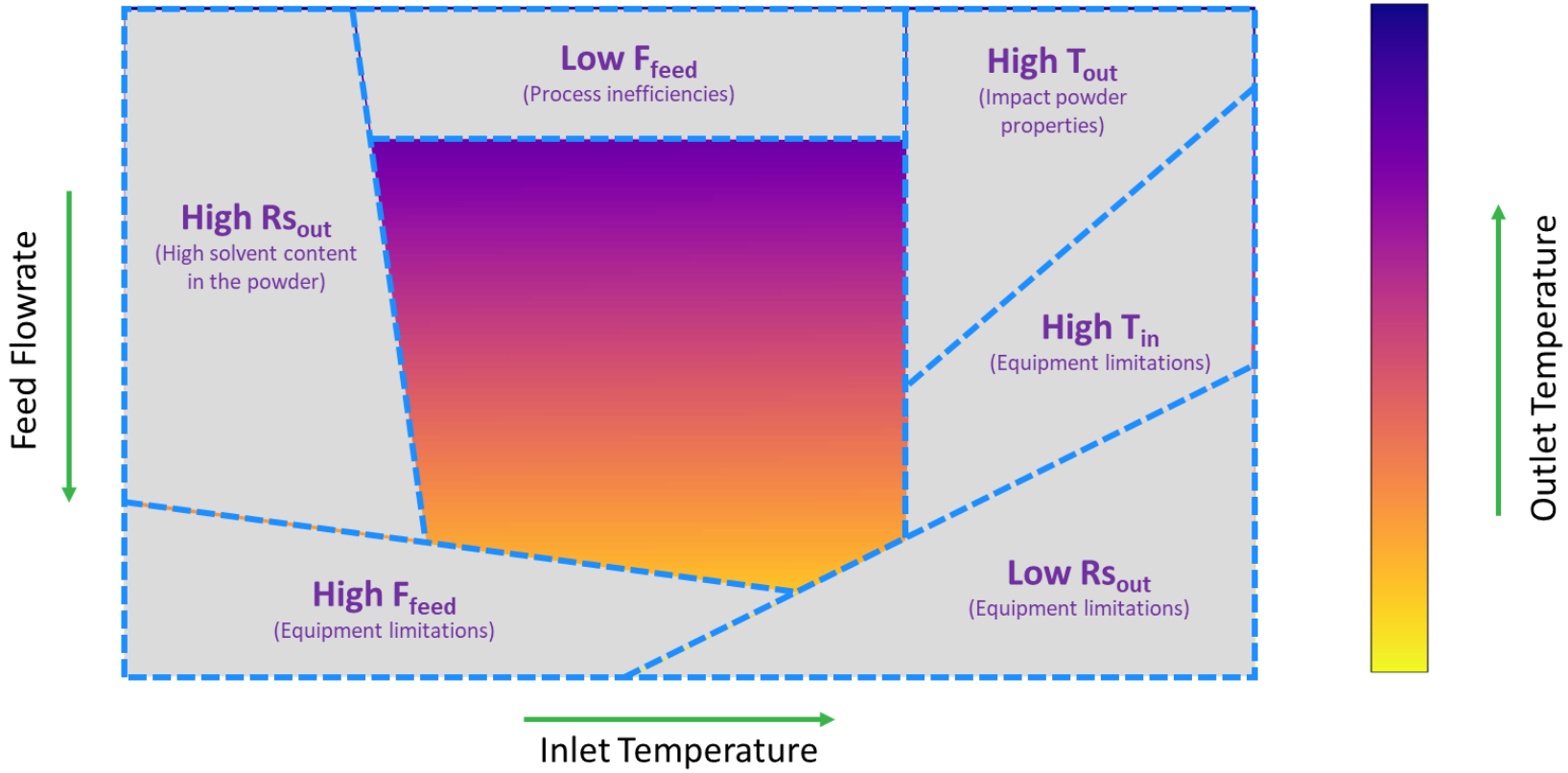
Design Space Development





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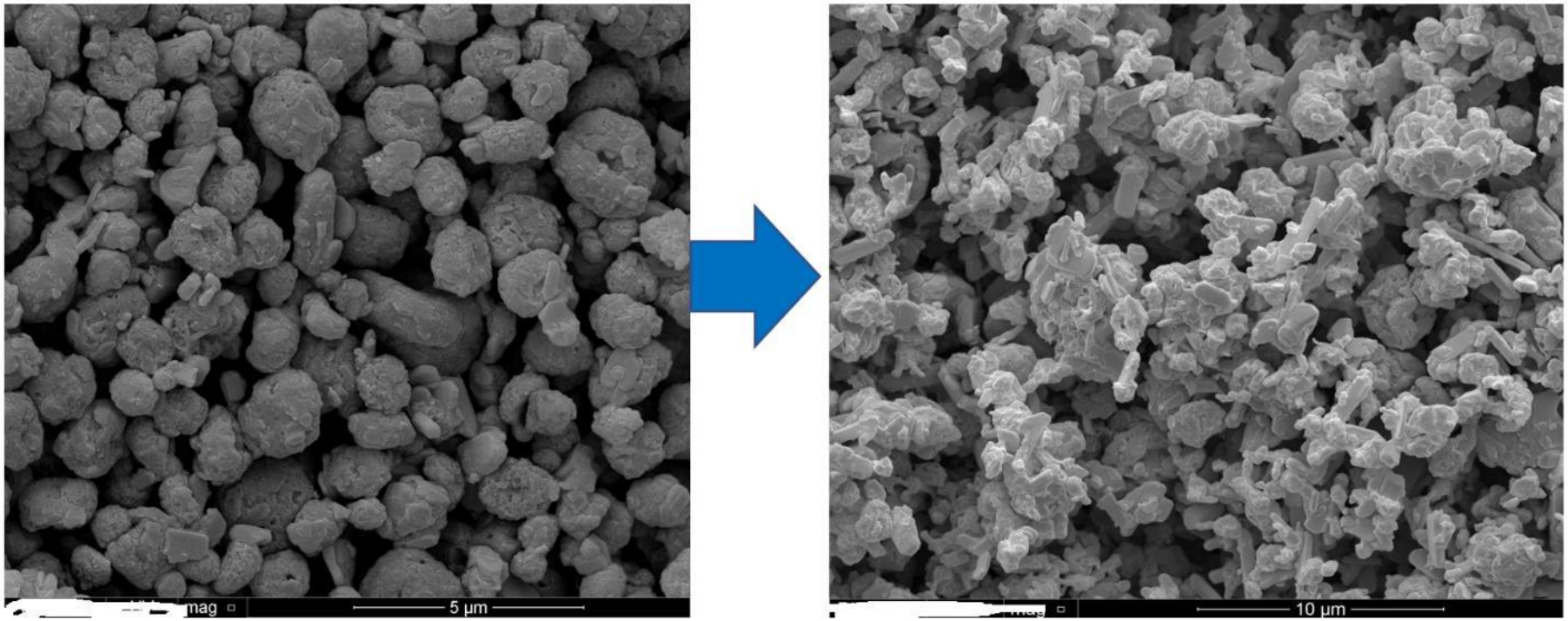
Process/product Optimization at Man Scale



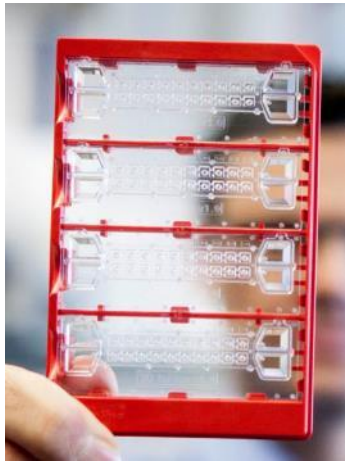
Case 3: mRNA, Exosome, Liposome, Lipid Nanoparticles

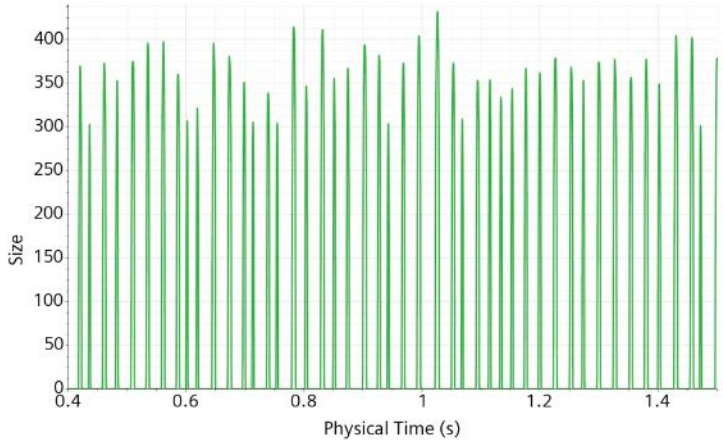
- Equipment design and optimization for a complex co-processed formulation
  - **Objective:** uniform encapsulation, size, payload.
    Optimized design, rapid, limited material
  - Problem: Complex system, Expensive API
    Crunched timeline, fabrication issues
  - How did we help

Sensitivity analysis, design optimization

Design space development

Optimization of equipment and CPP





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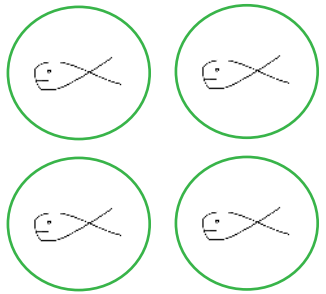
Challenge, Scope

- Scope: Co-processed components ratio (peptides, lipids, biologics, nanoparticles) changes the feed properties (CMA) and processability, and product design

  (such as viscosity, dispersion, surface tension, density, encapsulation,..)

Desired



Optimized by us

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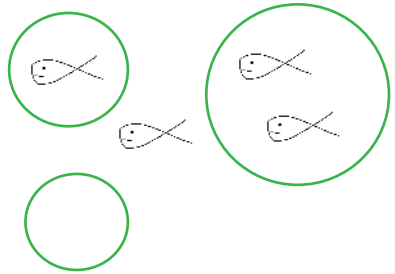
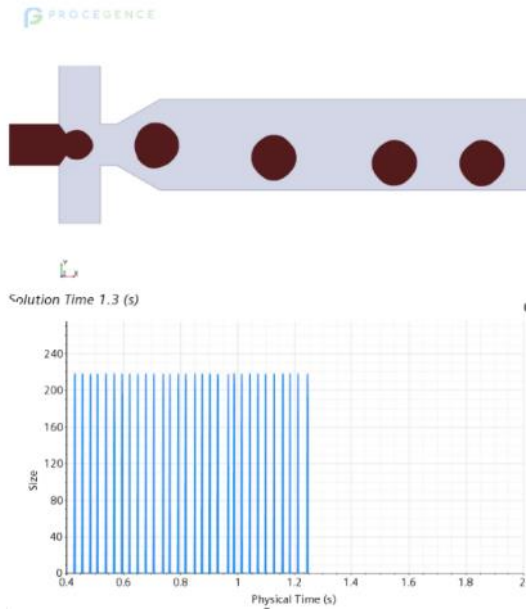
Undesired

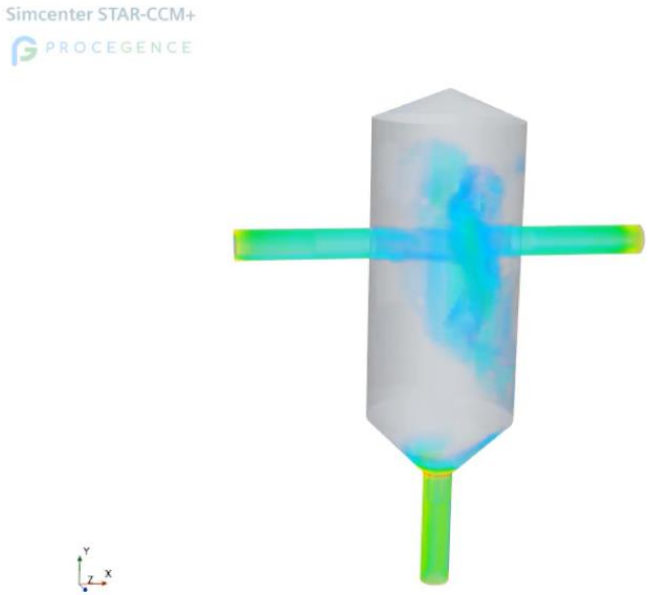


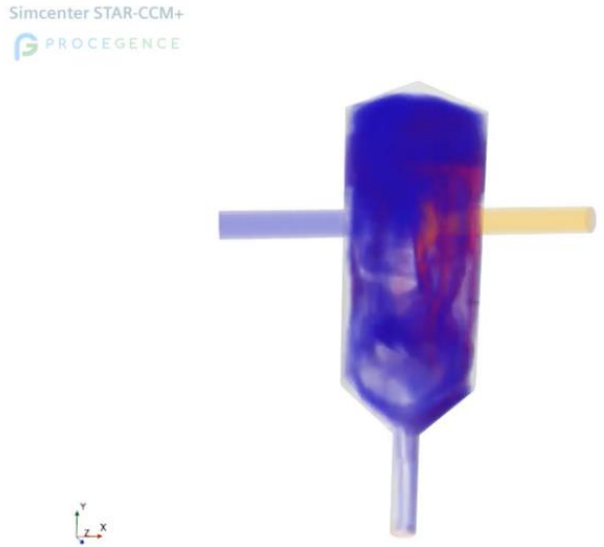
Many famous products in the market

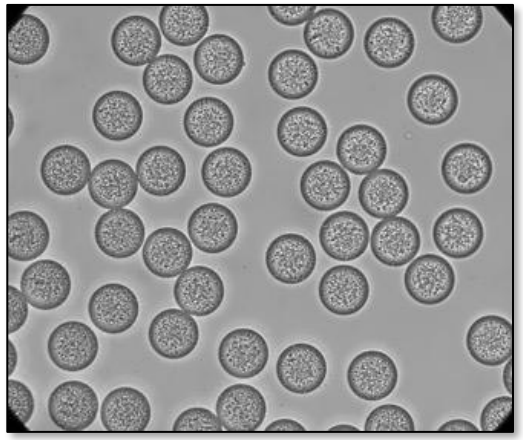
Stability, delivery, CQA issues

Product/Process Optimization



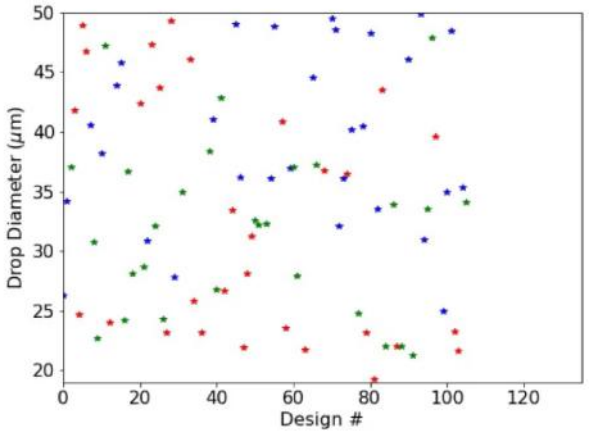


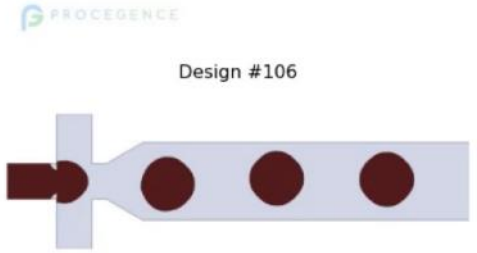


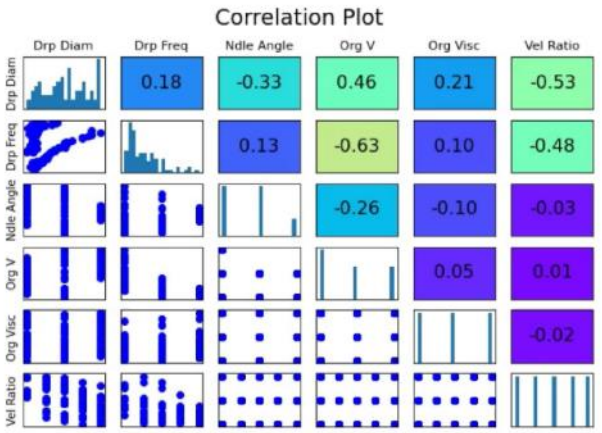


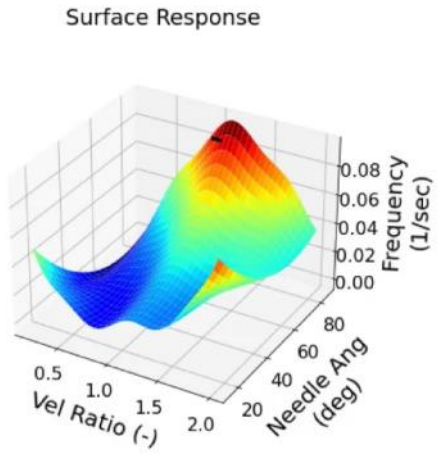
Design Exploration, Virtual Multidimensional DoE

- Global sensitivity analysis
- Rapid parametric study
- Multiparameter
- Response factors and dashboard
- Optimization
- Global optimum
- Design space development
- Device design and customization based on formulation CMA (co-processed)









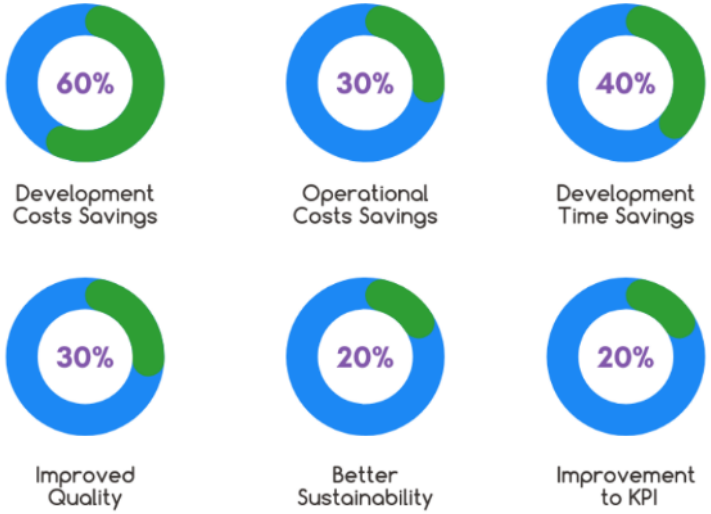
Summary

QbD (Knowledge-based product/process development); not a fitted line to some experimental data

How do you bring a product from lab to manufacturing scale?

Scale dependent phenomena impact on scale-up and Tech-transfer

Average Client Benefit of Working with Procegence



Case Studies

	Business Challenge	Procegence's Solution	Results Obtained
Client #1 New Drug	Time constraints Complex process	Reduced process development time by 12 months	Brought the product to the market 8 months ahead of the original schedule
Client #2 Fine Chemicals	Budget constraints (Capex) Costly manufacturing process (Opex)	Rapid scale-up and sensitivity analysis parametric study for a wide range of cases	Savings of over $1 million in capital; the yield, efficiency, and operation cost improved.
Client #3 Pharmaceutical	Material constraints Limited amount of HPAPI available	Developed design space Defined optimum manufacturing conditions	Eliminated the need for large amounts of expensive materials for process development
Client #4 Technology Vendor	Equipment customization Costly fabrication and testing for multiple prototypes	In-silico design of equipment and virtual testing	Reduced design and testing time by 9 months Significant cost savings

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