IS A BLENDER NEEDED IN A CONTINUOUS DIRECT COMPRESSION MANUFACTURING LINE?

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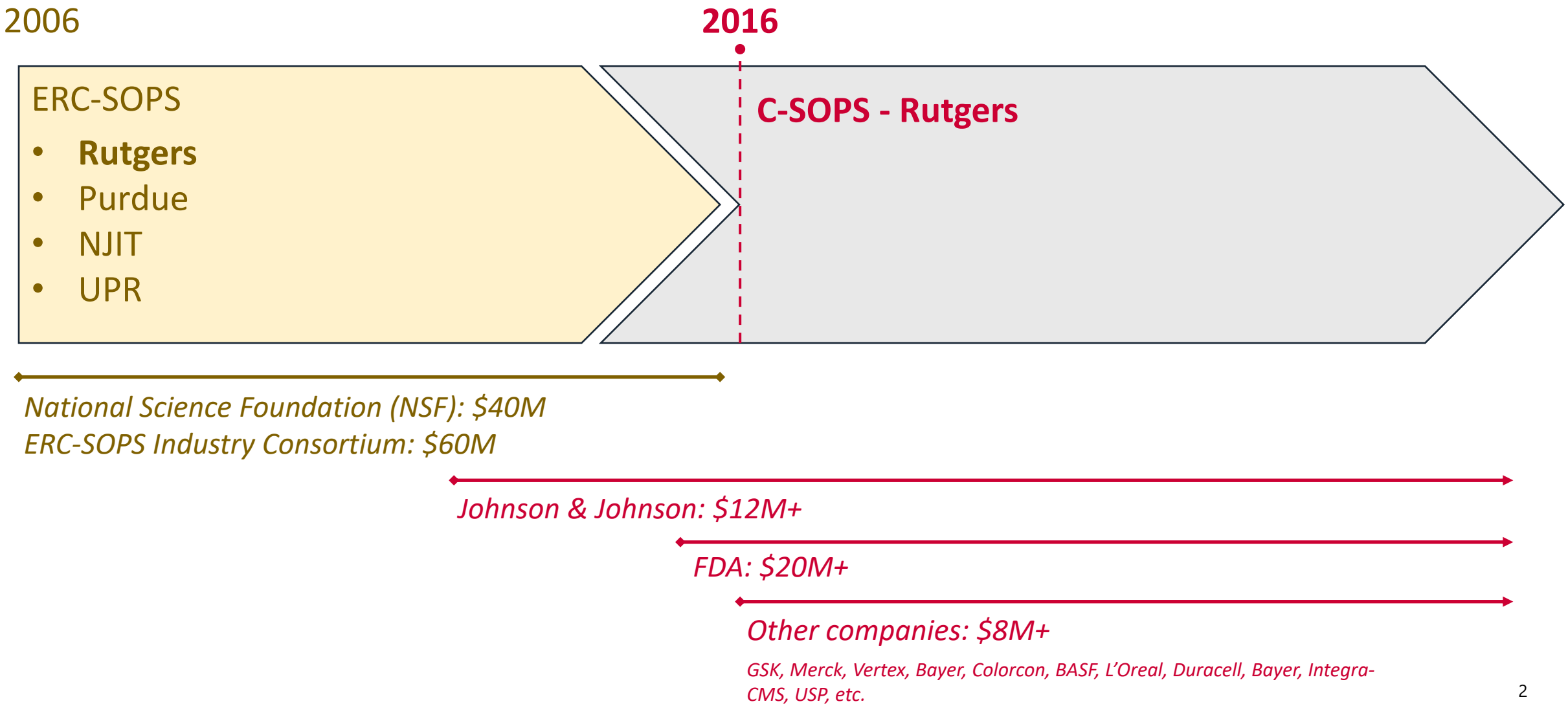
C-SOPS

Rutgers, The State University of New Jersey

Advantages of continuous manufacturing

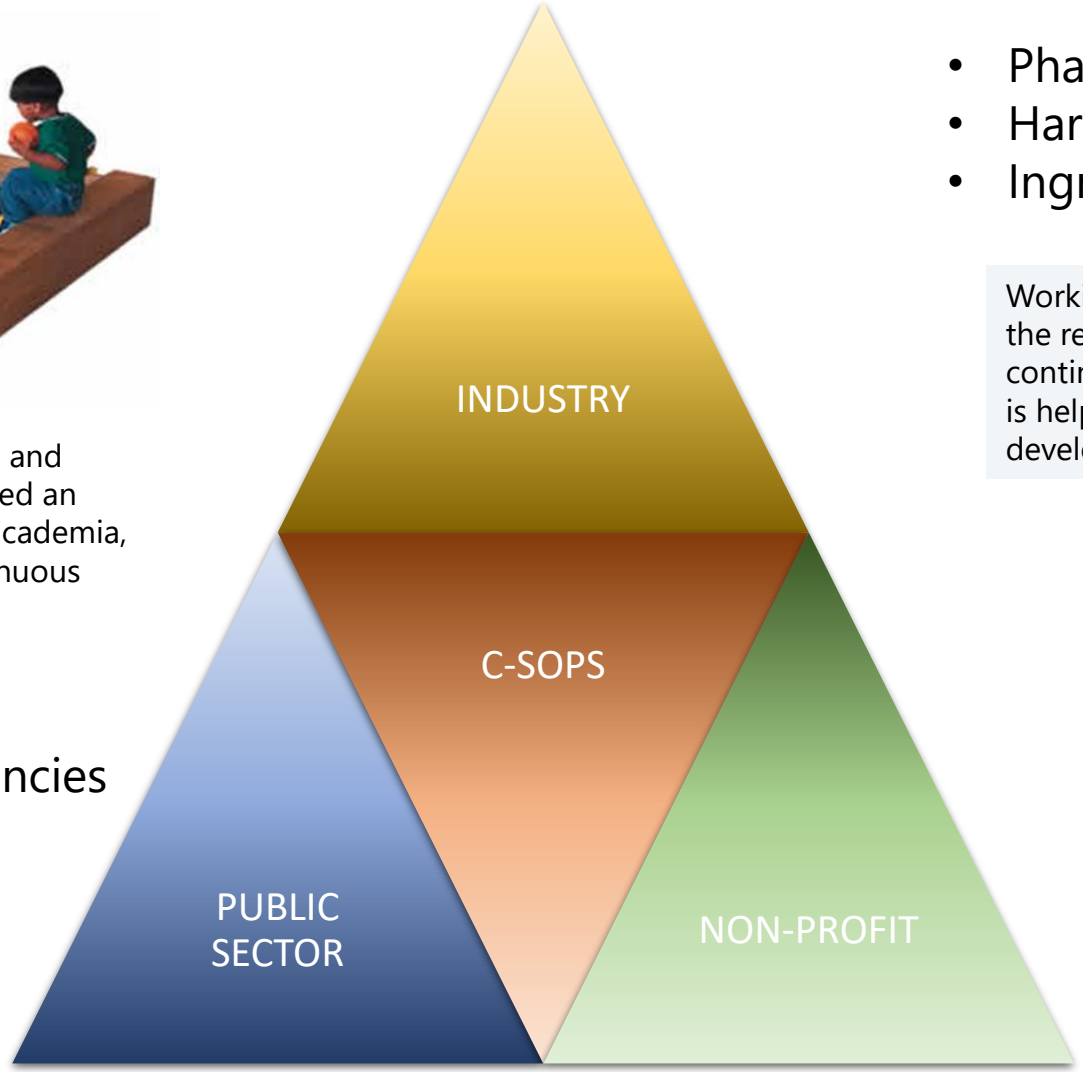
History & funding



Advantages of continuous manufacturing

Network & ecosystem

Rutgers/C-SOPS' engineering approach and industrial engagement model has created an engagement sandbox where industry, academia, and regulators come together on continuous pharmaceutical manufacturing.



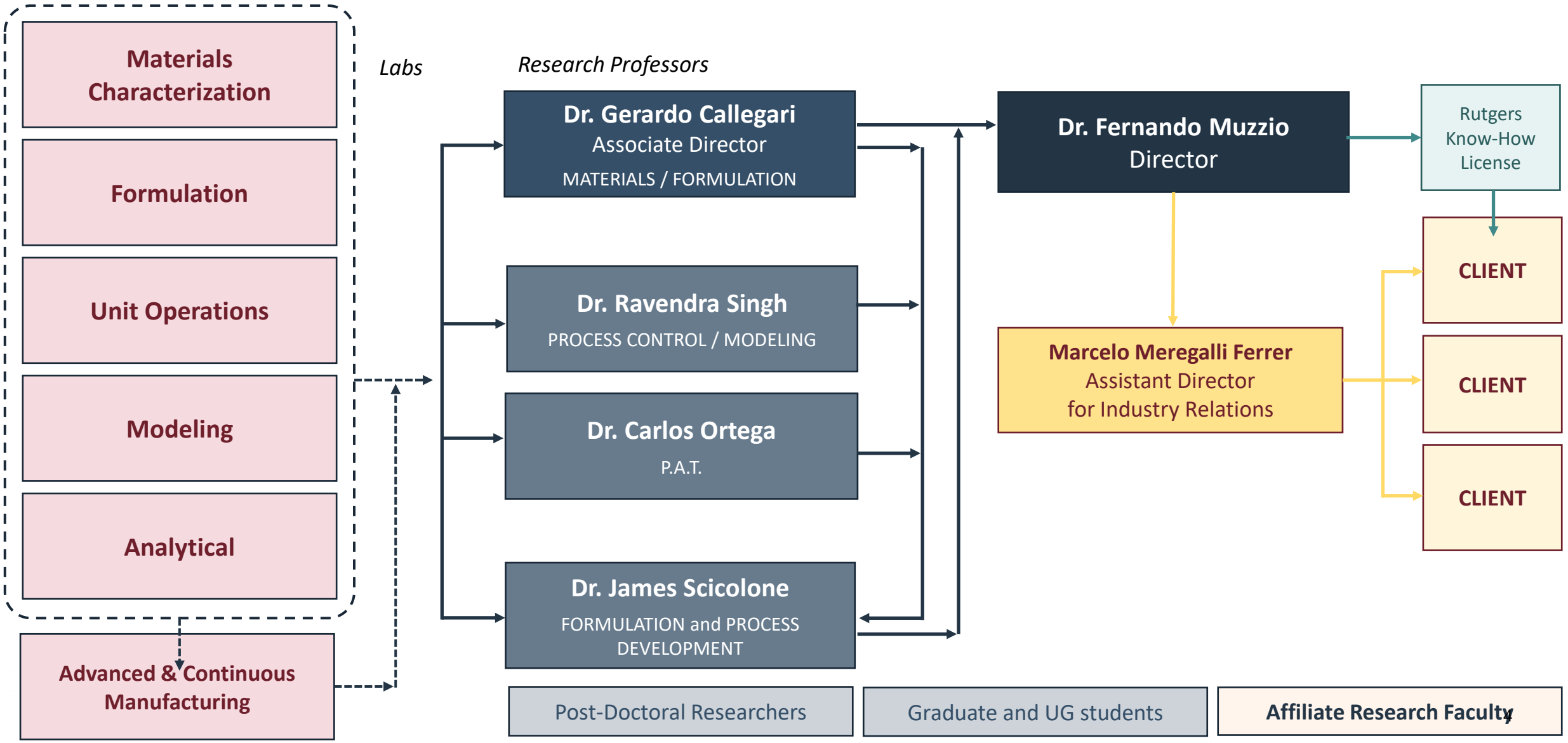
- Pharma companies
- Hardware & Software Vendors
- Ingredients Suppliers, etc.

Working with industry, C-SOPS has been involved in the regulatory approval of some of the first continuously manufactured solid dose products and is helping to shape the future of solid dose process development.

Federal & state agencies
e.g. FDA

- USP
- Trade Organizations

Physical & human infrastructure



Applied research areas

- **Continuous manufacturing for Oral Solid Dose (tablets, capsules…)**
- **Advanced batch processing Oral Solid Dose**
- **Continuous systems for liquid dosage forms (injectables and inhalable products)**
- **Manufacturing of active pharmaceutical ingredients**

Capabilities & technologies (i)

- **Materials properties, processability, and product performance**
  - Material characterization lab (flow, cohesiveness, bulk density, powder interactions with fluids, compressibility, etc.), an analytical lab for comprehensive testing, as well as a data base for materials and product performance
- **Powder processing**
  - Feeders, continuous and batch blenders, roller compaction, dry granulation, wet granulation (high shear and twin screw) with continuous drying, hotmelt extrusion, hotmelt granulation, fluid bed, etc.
- **Formulation and process development and optimization, and technology transfer**
  - Integrated method for accelerated product, analytical, and process development (6-8 weeks).
- **Technologies for poorly soluble APIs and high-dosage products**
  - Rutgers has developed two methods to enhance solubility and increase API loading, reducing the use of solvents and improving stability (bench-top and manufacturing scale).

Capabilities & technologies (ii)

- **Process Analytical Technology**
  - Blend monitoring (batch and continuous processing), process monitoring (tablet press, capsule filling, fluid bed systems, etc.), development and optimization of PAT instruments, Real-Time Dissolution Testing and models (API content and dissolution profile), PAT for API synthesis, API monitoring in fill-finish systems.
- **Process modeling, control, automation, and Digital Twins**
- **Continuous API manufacturing processes and API Synthesis**
  - Modelling toolbox development, reaction kinetic determination, PAT. Unit operation model library including digital model, RTD, and CFD models. Monitoring and mitigation methods for impurities and residual catalysts.
- **Capacity building**
  - Development and delivery of and hands-on training (industry and FDA)

Federal Initiative to reshore and promote distributive manufacturing

- FDA's Pharmaceutical Quality for the 21st Century Initiative promotes an efficient, agile, and flexible pharmaceutical manufacturing sector that reliably produces quality drugs without excessive regulatory oversight

- The FDA's Center for Drug Evaluation and Research published a discussion paper in October 2022 focusing on Distributive Manufacturing and Point-of-Care Manufacturing of Drugs

- Defined as: A decentralized manufacturing strategy consisting of a manufacturing platform comprising manufacturing units deployed to multiple locations. Possible use scenarios include:

- **Units located within manufacturing facilities operating within the host's pharmaceutical quality system (PQS).**

- **Units manufactured and installed to the same specifications at multiple manufacturing facilities, networked and operated by a central remote PQS.**

- **Units as independent manufacturing facilities, each with its own PQS.**

Reasons for distributive manufacturing

- Due to the 2019 Pandemic, shortages in critical supplies alarmed Washington, and others, to the vulnerabilities of the US Pharmaceutical Supply Chain

- 2023: The Bipartisan Domestic Pharmaceutical Manufacturing Caucus with the aim to "incentivizes more domestic production for essential medicines to reduce American reliance on foreign adversaries, head off potential supply chain disruptions, and ensure a steady supply of pharmaceuticals in the event of public health emergencies or natural disasters."

- Rep. Cartwright: According to the Food and Drug Administration, approximately 72 percent of active pharmaceutical ingredients (API) used in the U.S. drug supply are manufactured in more than 150 countries, with 13 percent coming from China alone. The U.S. is also dependent on other countries for personal protective equipment (PPE), with approximately 95 percent of surgical masks and 70 percent of tighter-fitting respirators, such as N95 masks, being made overseas"

Reasons for distributive manufacturing

- The ideas pertaining to DM can also play a significant role in product transfer and during times of critically short supplies
- **In the last month over a dozen OSD have been listed in short supply including Adderall, cancer medications, and blood pressure medications**
- **2022 baby formula supply shortage was caused by the shut down of one manufacturing plant int Sturgis, MI**

- A faster method of product transfer is needed
- **An accepted and proven method of transfer from bench to production, and from one production line to another**
- **Incorporate advanced manufacturing knowledge, such as PAT and controls**

CDER area of discussion for DM

- **Each new location of a DM unit may cause the applicant to be required to generate analytical comparability, method transfer and validation, and stability data.**

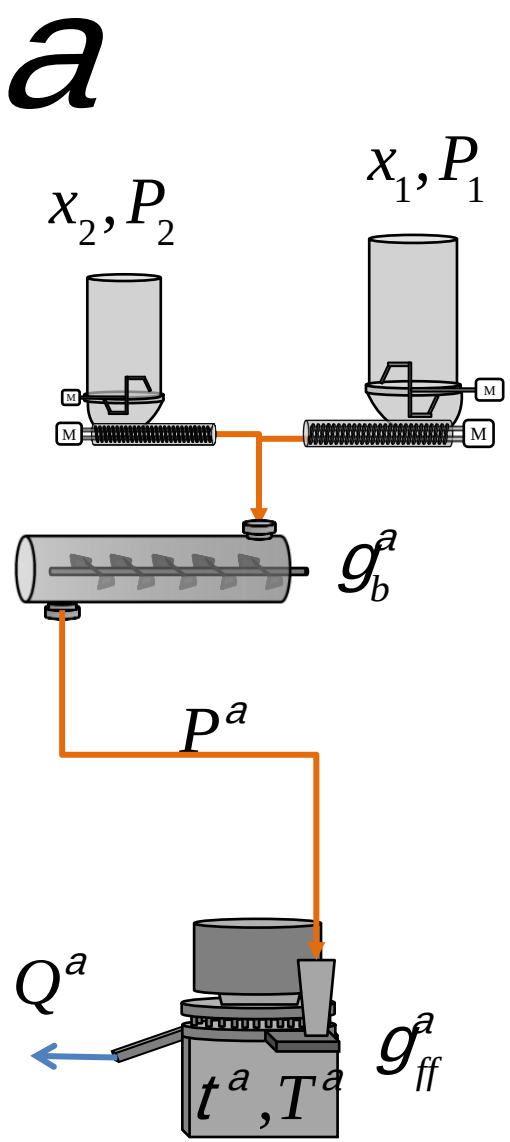
- Using Extensive DOEs on the manufacturing lines will not be cost effective and would disincentivize companies to move towards DM

- A method will be necessary to quickly prove comparability and validation for both manufacturers and the FDA

Rapid process development

- Industry is currently using extensive DOEs each time a process is developed for a CM line
- This approach uses too much raw material and effort, and does not use efficiently the knowledge created already in the successful implementation of the CM process
- We proposed a greatly accelerated approach for product development and for product transfers, based on available, prior process knowledge, and a rational classification of formulations characteristics

Material properties and product CQA in a DCCM line



Will the materials feed?

Will the components reach a homogeneous state?

Will the compaction CPP be sufficient?

Continuous manufacturing of pharmaceutical product

The future of pharmaceutical manufacturing

- Superior quality of final products
  - Equivalent processing conditions for each portion of materials
  - Every portion can be monitored and tracked
- Faster product and process development
  - Process and formulation development can be done on the same equipment
- Can be manufactured more efficiently
  - Shorter cycle time and less solid handing
  - Less waste

Ramanadham, Mahesh.” An FDA Self-Audit of Continuous Manufacturing for Drug Products”. Last modified June 28, 2022. https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/fda-self-audit-continuous-manufacturing-drug-products

Continuous manufacturing of pharmaceutical product

The future of pharmaceutical manufacturing

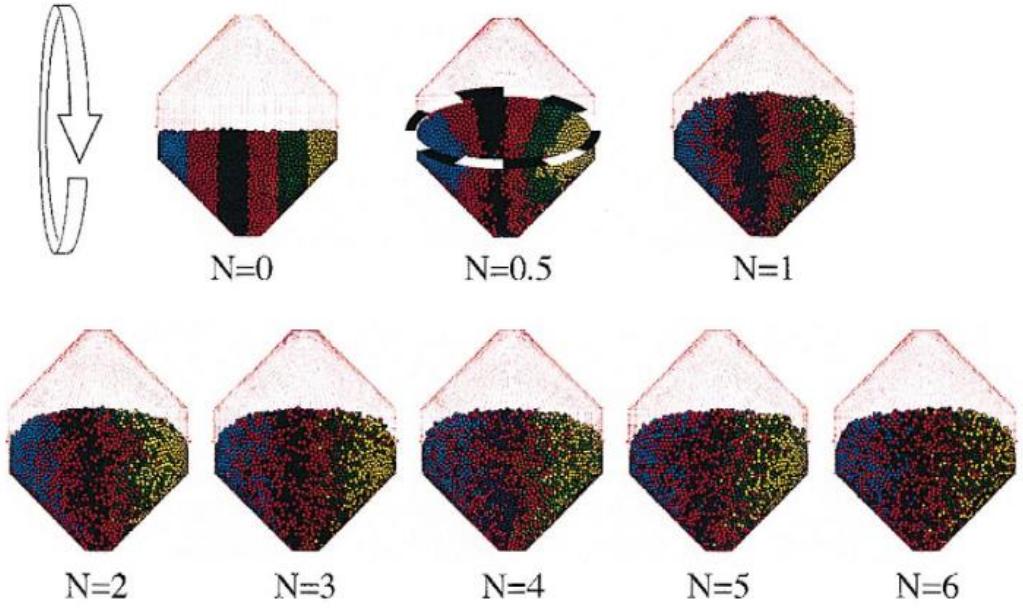
- Hurdles for CM
  - High upfront investment
  - Lack of trained professionals

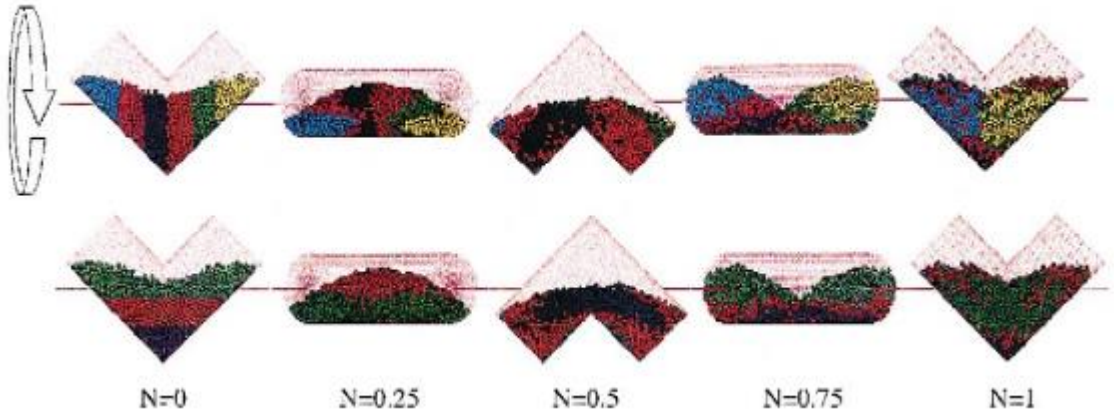
- What if we can reduce a unit operation to reduce some burden in upfront investment, while not negatively affecting product quality?

Ramanadham, Mahesh.” An FDA Self-Audit of Continuous Manufacturing for Drug Products”. Last modified June 28, 2022. https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/fda-self-audit-continuous-manufacturing-drug-products

Need of blending

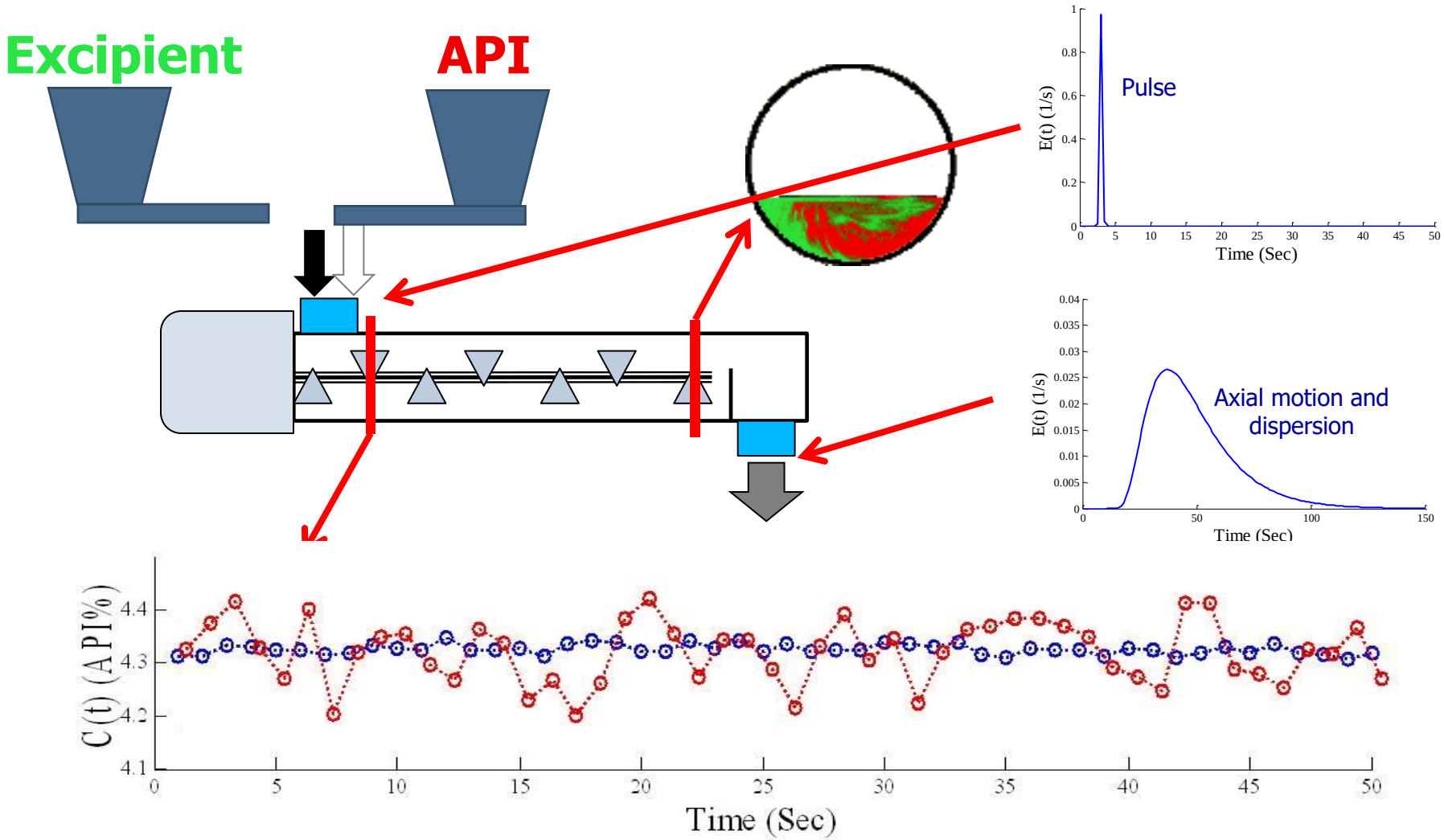
- Blending is required in many situations
- This idea was carried over to continuous direct compaction manufacturing





Moakher, Maher, Troy Shinbrot, and Fernando J. Muzzio. "Experimentally validated computations of flow, mixing and segregation of non-cohesive grains in 3D tumbling blenders." *Powder technology* 109.1-3 (2000): 58-71.

Feeder/blender interaction

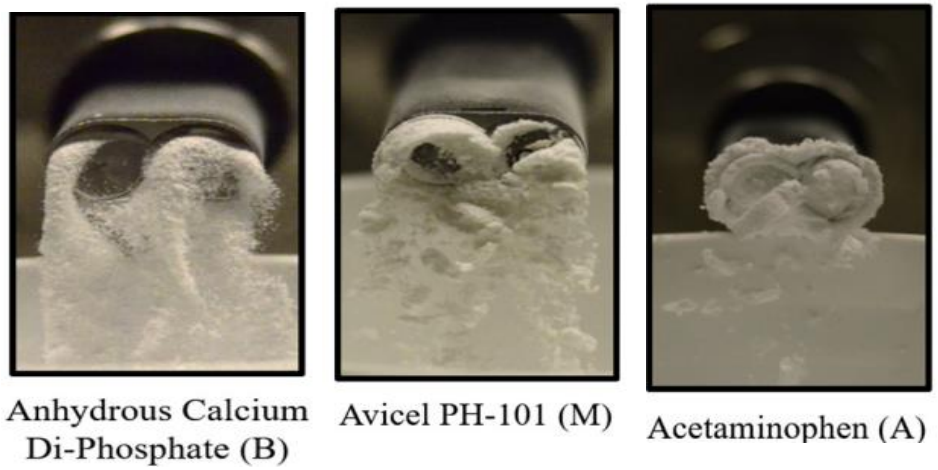


Need of blending?

- For continuous manufacturing, materials are dosed using gravimetric loss-in-weight feeders

- **Instead of kilograms of material being dispensed into a bin, only a few grams per second are in flux leaving the feeder**
  - Mixing happens during freefall and in unit operations
  - Plug flow through mass hold up in pipes

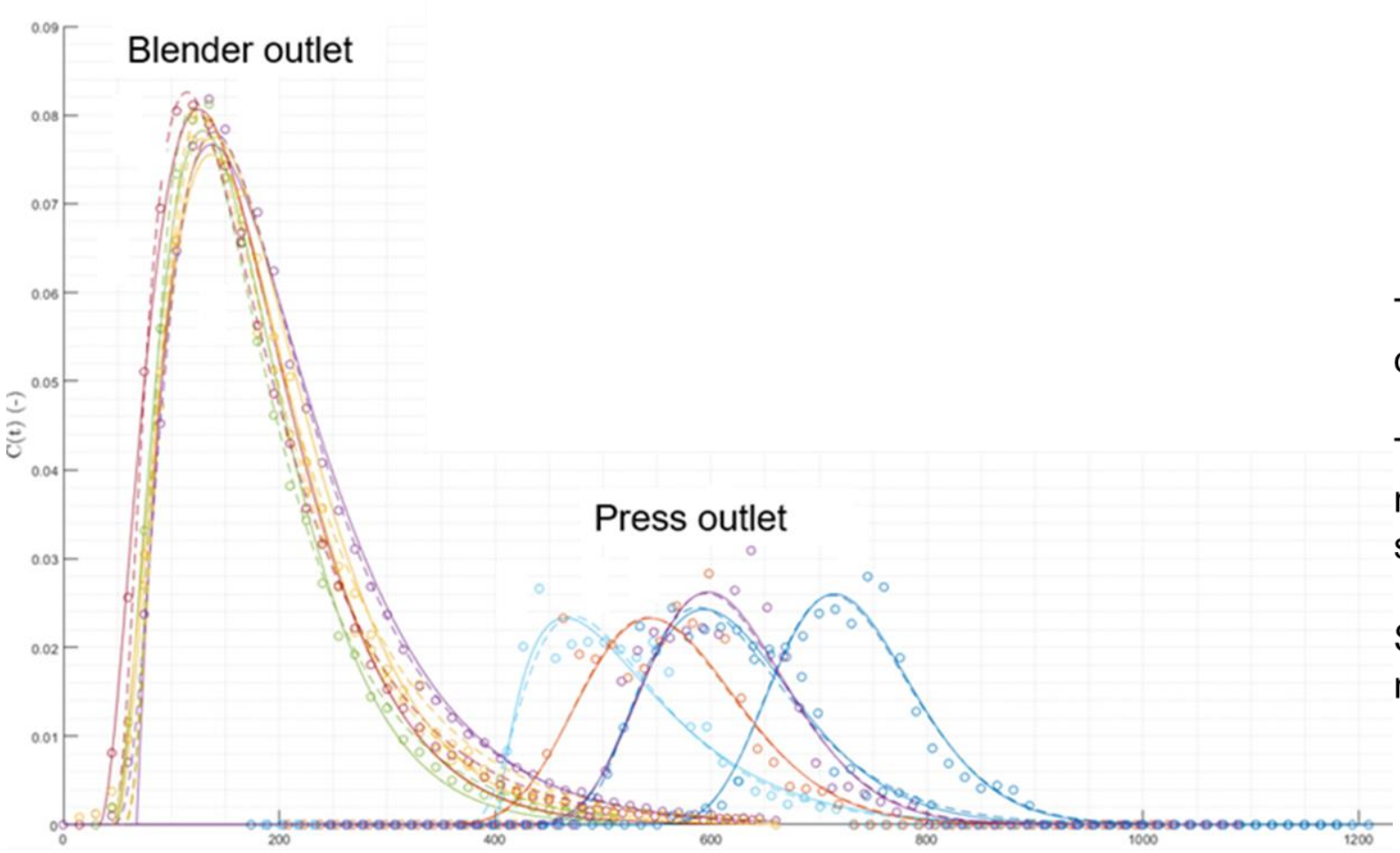
- **Example with 25kg/hr throughput (6.9 g/s):**
  - 50wt.% Excip A = 12.5 kg/hr = 3.5 g/s
  - 25wt.% Excip B = 6.25 kg/hr = 1.7 g/s
  - 10wt% API = 2.5 kg/hr = 0.7 g/s
  - 1wt.% Excip C = 0.25kg/hr = 0.07 g/s



Escotet-Espinoza, M. Sebastian, et al. "Using a material property library to find surrogate materials for pharmaceutical process development." *Powder technology* 339 (2018): 659-676.

Need of blending? RTD Study on CM lines

Rutgers C-SOPS CDC Line



These three results were performed all on unique manufacturing lines.

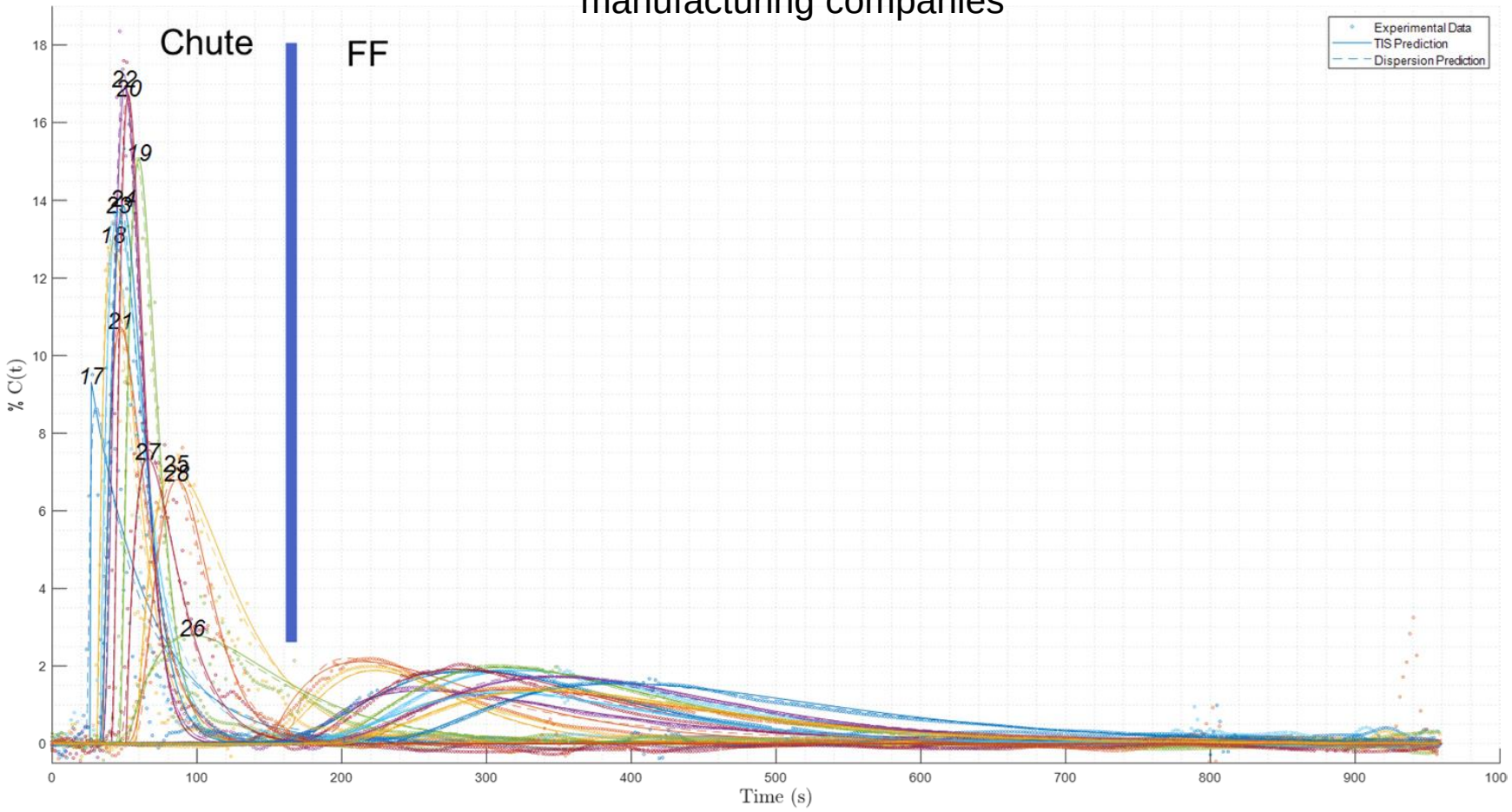
Two lines show a 66% decrease in max concentration while the third line shows a 85% decrease

Similar results have been published in many manuscripts

Need of blending? RTD Study on CM lines

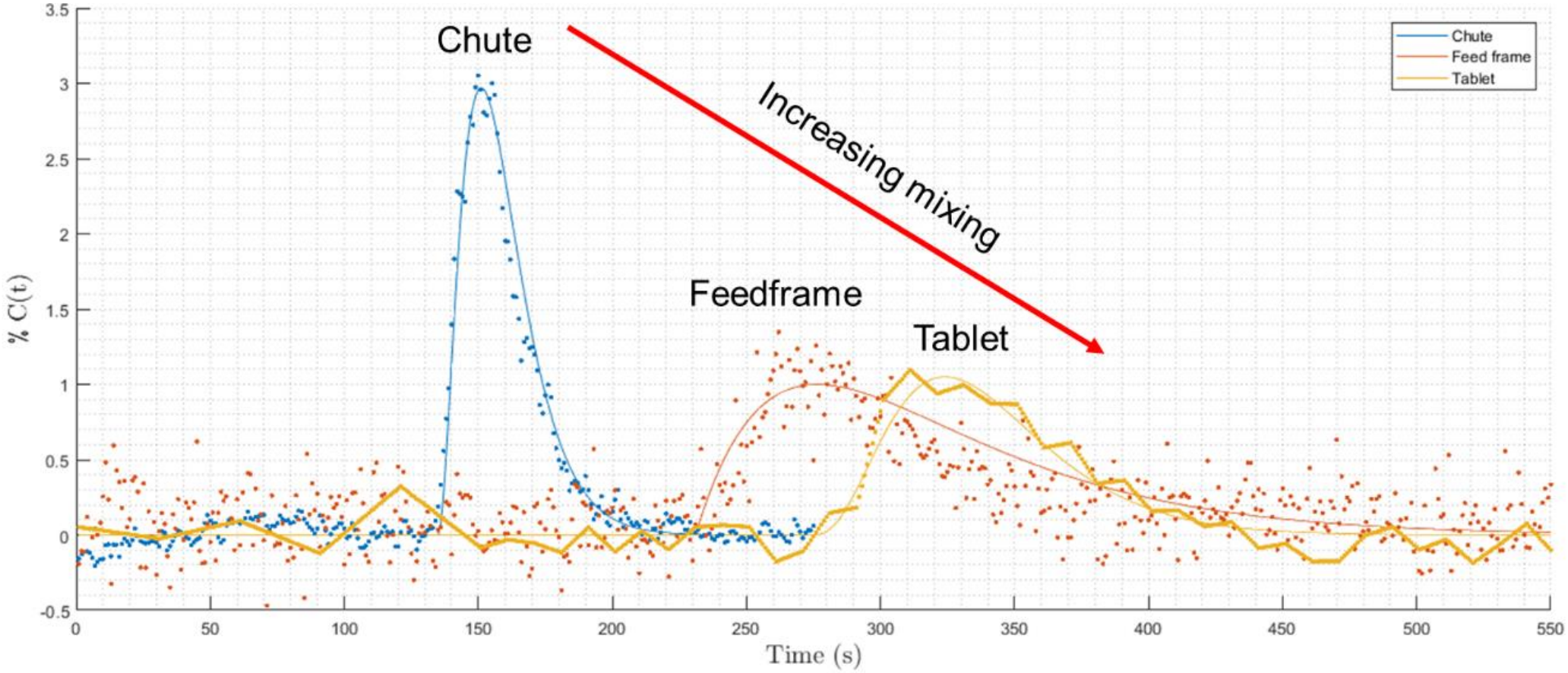
Round Robin Site 2

As part of an FDA funded BAA research project, a round robin RTD DOE was performed at various pharmaceutical and equipment manufacturing companies



Need of blending? RTD Study on CM lines

Round Robin Site 1



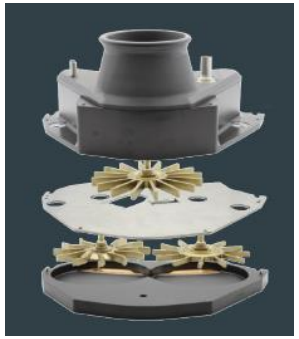
If we see such reduction of intensity in the FF, is a blender still required?

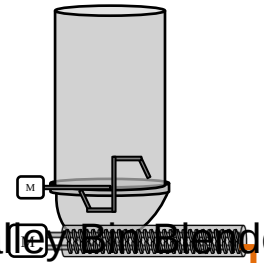
FDA BAA 75F40120C00125

We evaluated blend homogeneity in three blending

1

Bin blender



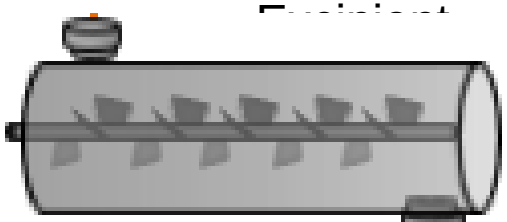


Galley Bin Blender 10RPM for 10 mins then 2mins.

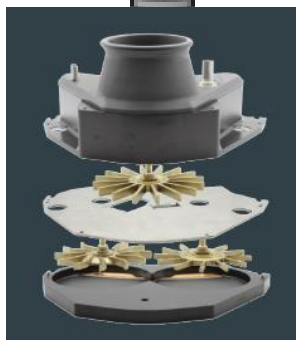
Dispensed by a Coperion K-Tron LIW feeder directly into the Fette tablet press, FF 60RPM.

2

Compap L



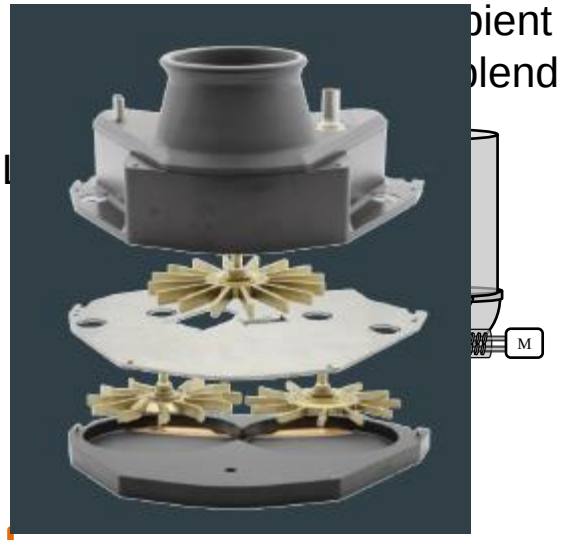
Continuous blender



Material dispensed by Coperion K-Tron LIW feeders into a Glatt continuous blender, 200 RPM. prior to reaching the Fette tablet press, ff 60RPM

3

Compap L



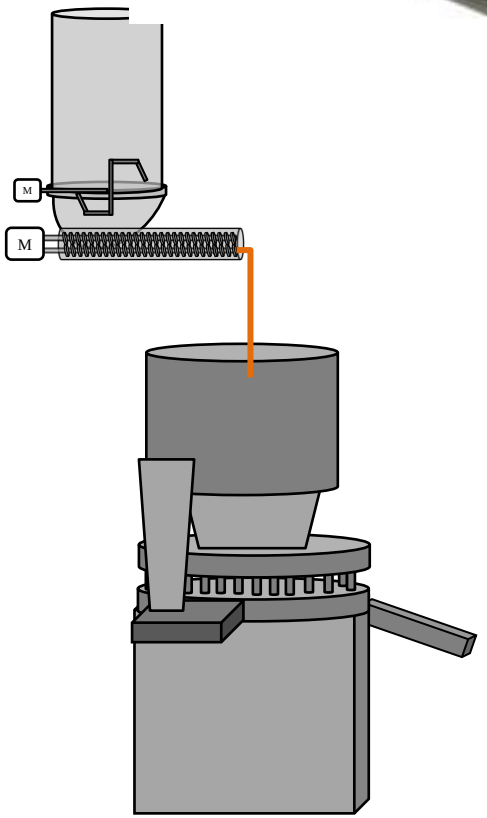
Material dispensed by Coperion K-Tron LIW feeders directly into the Fette tablet press, FF operated at 20, 40, 60, or 80 RPM

A Sentronic SentroProbe DLRS was installed in the feedframe of the press to obtain inline NIRS

We evaluated blend homogeneity in three blending

1

Bin blender

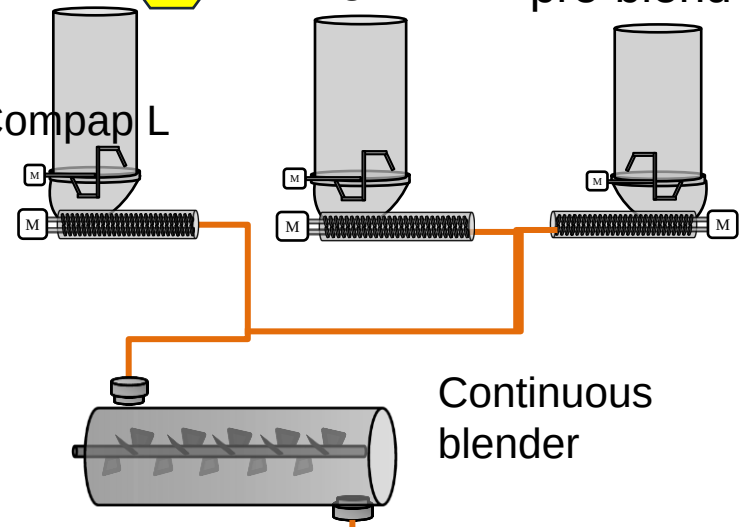


2

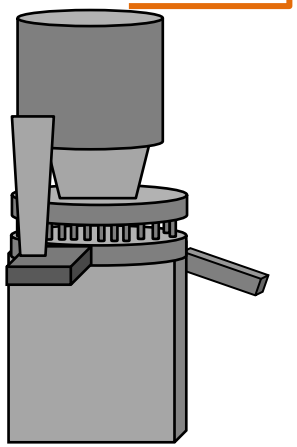
MgSt

Excipient pre-blend

Compap L



Continuous blender



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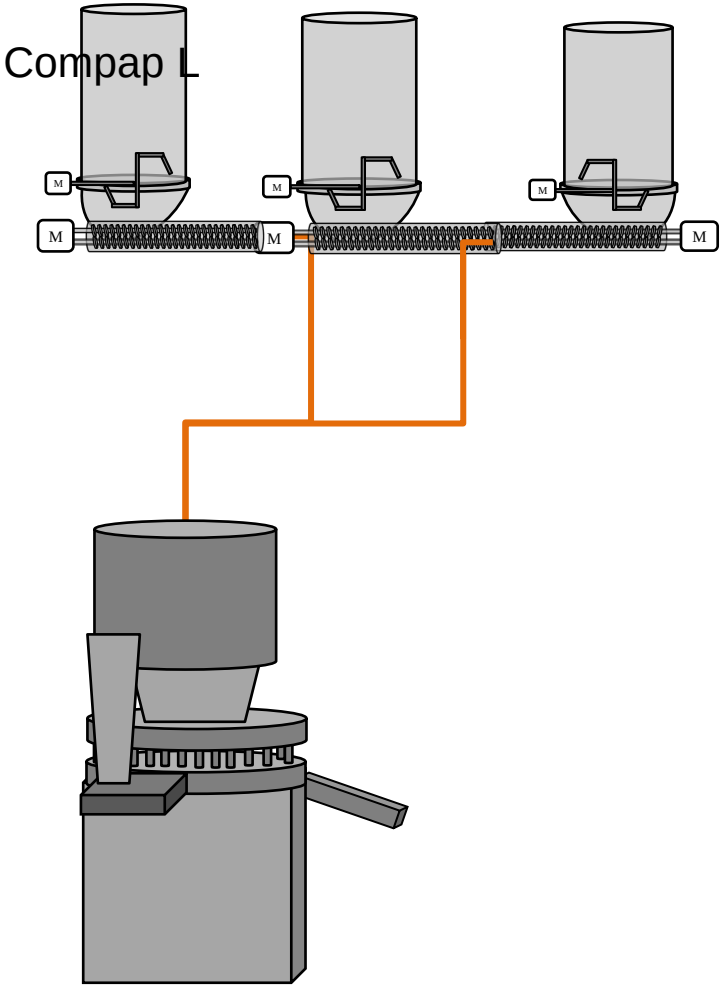
Compap L



We evaluated blend homogeneity in three blending

1

Galley Bin Blender 10RPM for 10 mins then 2mins.

Dispensed by a Coperion K-Tron LIW feeder directly into the Fette tablet press, FF 60RPM.

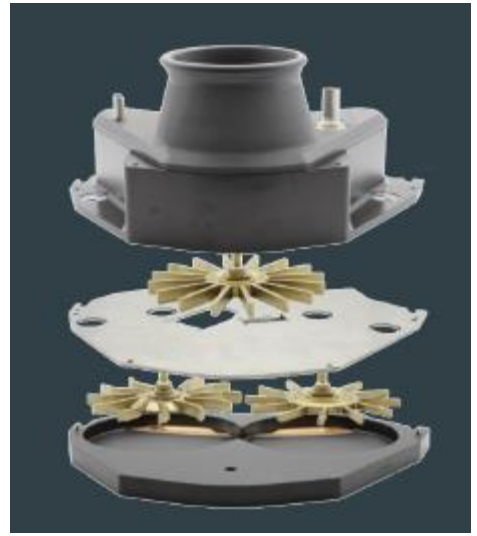
A Sentronic SentroProbe DLRS was installed in the feedframe of the press to obtain inline NIRS

2

Material dispensed by Coperion K-Tron LIW feeders into a Glatt continuous blender, 200 RPM. prior to reaching the Fette tablet press, ff 60RPM

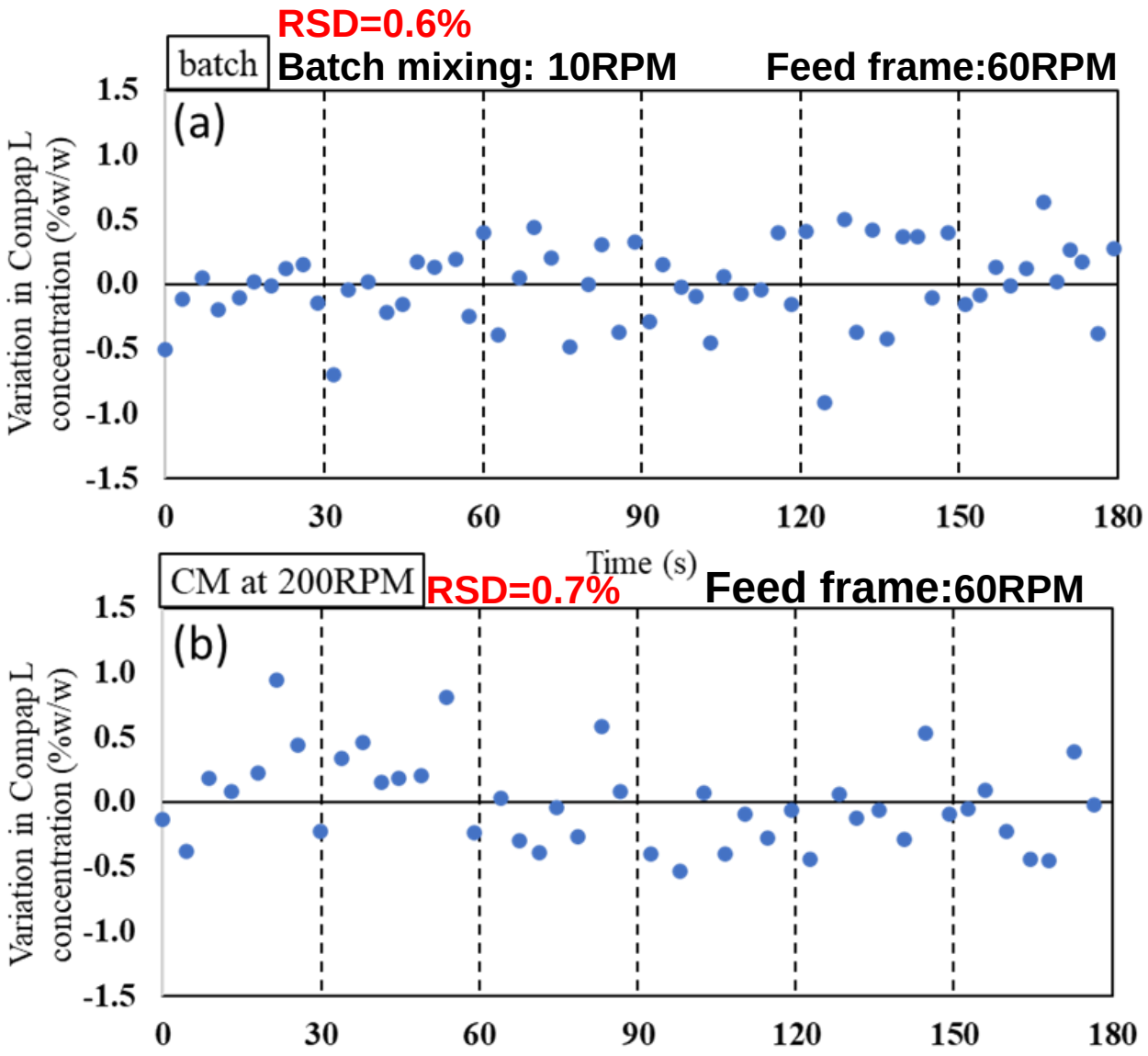
Material	Weight Percent
Compap L (API)	50
Prosolv HD90 (filler)	44
Pregel Starch (filler/disintegrant)	5
MgSt (compaction lubricant)	1

3



Material dispensed by Coperion K-Tron LIW feeders directly into the Fette tablet press, FF operated at 20, 40, 60, or 80 RPM

Results - batch and continuous mixing scenario

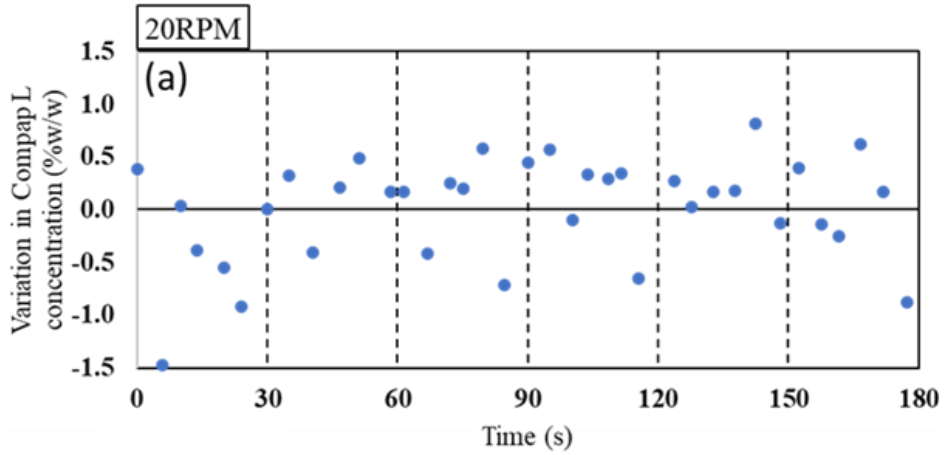


- Variation of Compap L %w/w, predicted using an NIR chemometric model, was graphed by mean centered method for all scenarios.
- It is not surprising to see RSDs are low for both cases, indicating the achievement of a homogeneous blend
- Content uniformity was performed on tablets, using UV/Vis to validate results from NIRS

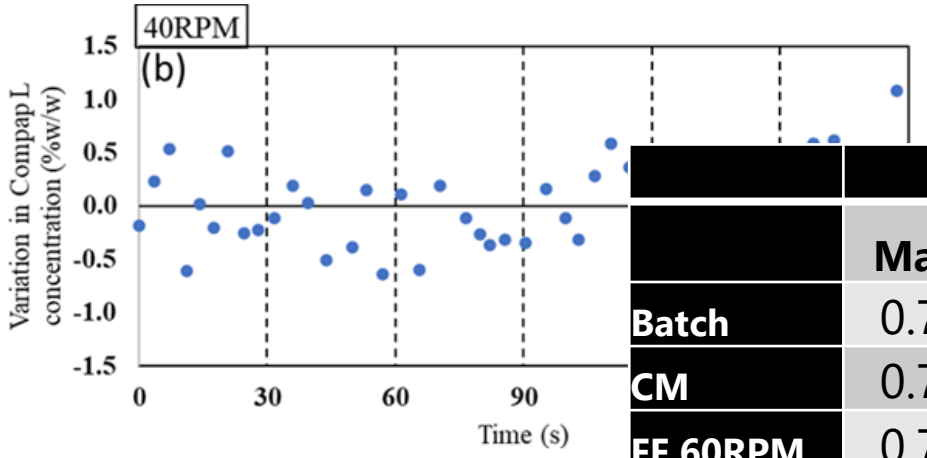
Results - feed frame mixing only scenario

Feed frame mixing: 20, 40, 60, 80RPM

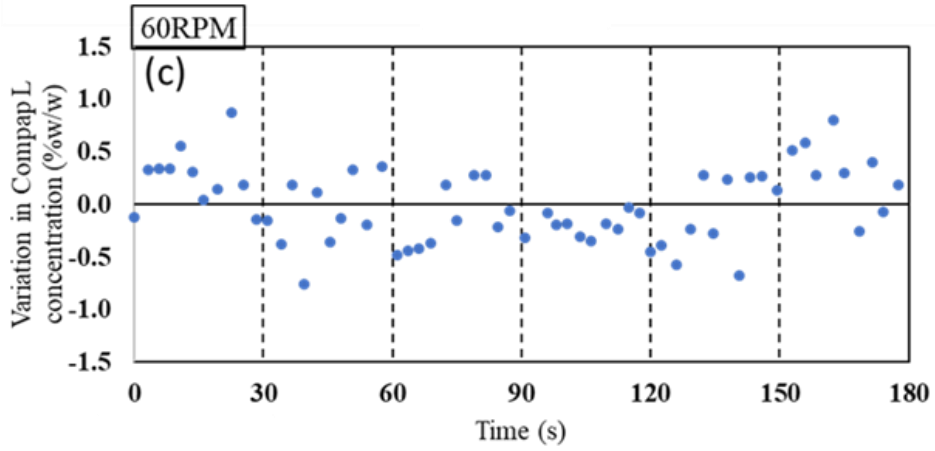
RSD (blends): 1% RSD (tablets): 0.7%



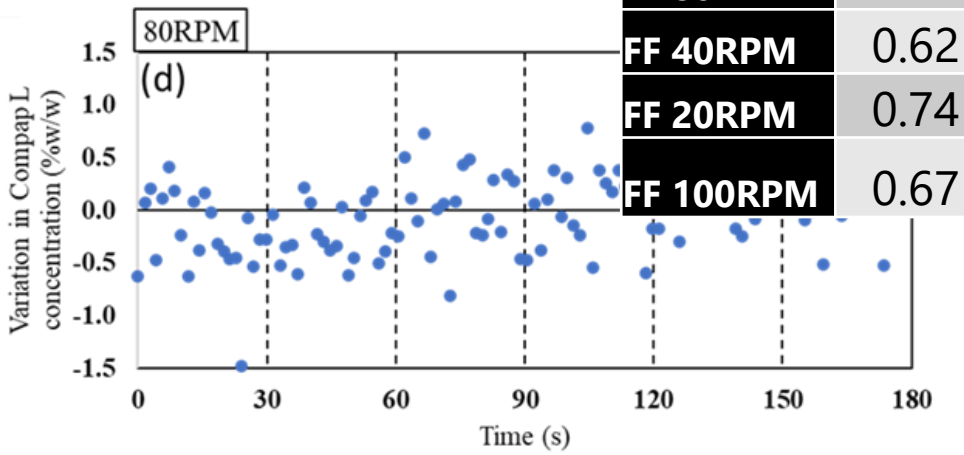
RSD (blends): 0.8% RSD (tablets): 0.8%



RSD (blends): 0.6% RSD (tablets) : 0.7%



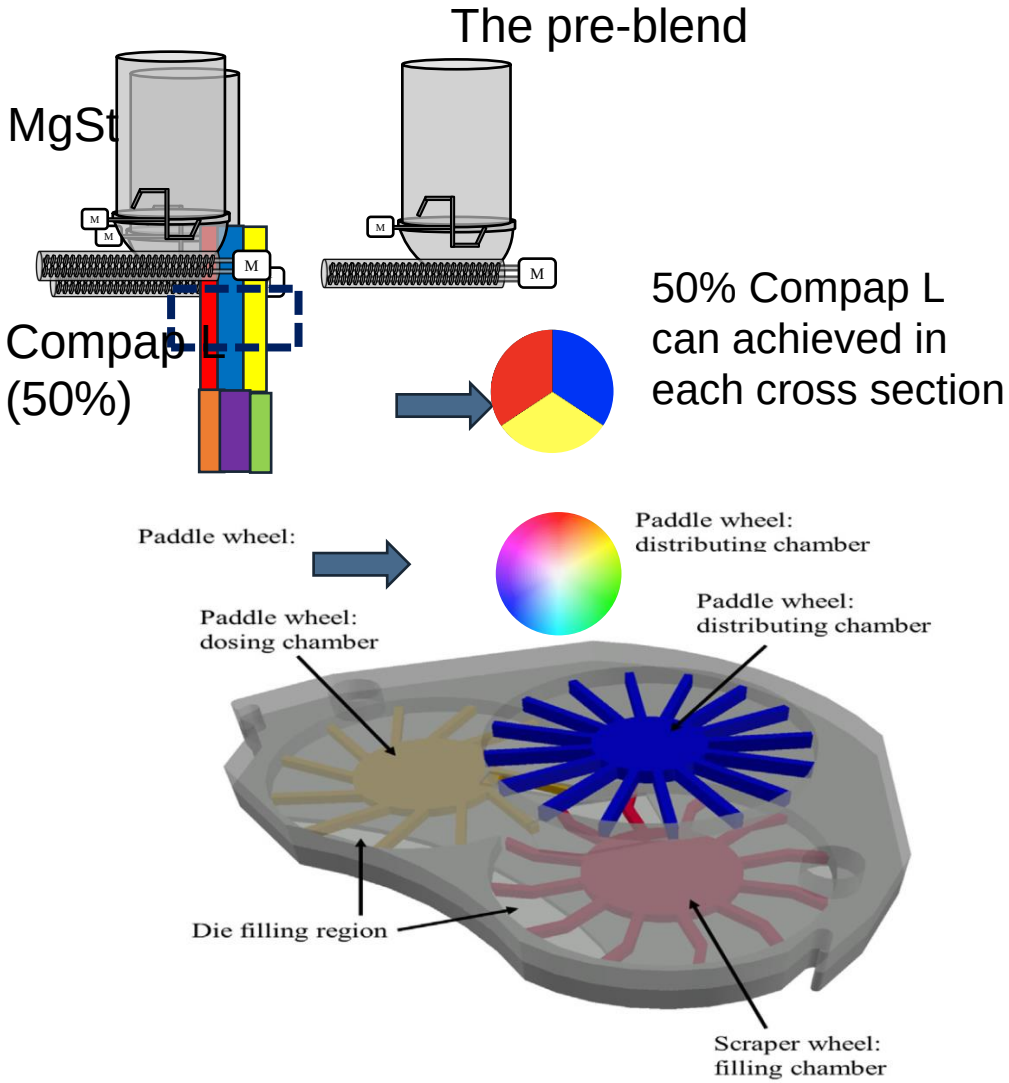
RSD (blends): 0.8% RSD



	RSD	
	Mass	Hardness
Batch	0.72	4.3
CM	0.77	4.4
FF 60RPM	0.74	3.6
FF 80RPM	0.93	4.5
FF 40RPM	0.62	3.5
FF 20RPM	0.74	3.9
FF 100RPM	0.67	3.8

- The variations are all within ±1.5%, corresponding to ±3% of the target (i.e., 50%)
- Precision and accuracy of API has been achieved in all routes

Why?



- Blend homogeneity is attained through a synergy of accurate feeding, the feed frame design and material properties.
- Feeding of each ingredient accurately ensures macro-mixing before mixing
- Feed frame design creates space for large holdup mass and sufficient shear mixing
- Less shear required to homogenize blends with easy-flowing properties

Can this method actually work?

A well flowing formulation with 50 wt.% API is one thing, what about a more challenging formulation?

- After the initial success, to test the process with a less ideal formulation, a second formulation was chosen, utilizing a low dose API

- Ibuprofen was impregnated into a mesoporous carrier Parteck® SLC 500, at a loading of 30wt.%, provided by EMD (Merck KGaA)

- The same three manufacturing routes were investigated

Material	Weight Percent
Parteck® SLC 500 with 30%IBU	10 (3% API)
Prosolv HD90 (filler/binder)	67
Parteck® Mannitol M100 (filler/binder)	22
Parteck® LUB (compaction lubricant)	1

Case study 2: Low dose API

Batch blending (3.00 %w/w)			
ID	**10 RPM**	**15 RPM**	**25 RPM**
%RSD	4.97	2.26	1.43
Difference (mg) Nominal – Avg	1.44	0.09	0.32

eed

Continuous blending (3.00 %w/w)			
ID	**114 RPM**	**200 RPM**	**286 RPM**
%RSD	3.71	1.05	3.19
Difference (mg) Nominal – Avg	1.03	1.32	0.13

Batch blending shows a decreased RSD when the blend underwent higher shear
Content uniformity is below 5% in all studies, with precision

UV/Vis Tablet Content Uniformity

Batch blending (3.00 %w/w)			
ID	**10 RPM**	**15 RPM**	**25 RPM**
%RSD	4.97	2.26	1.43
Difference (mg) Nominal - Avg	1.44	0.09	0.32

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ID	**114 RPM**	**200 RPM**	**286 RPM**
%RSD	3.71	1.05	3.19
Difference (mg) Nominal - Avg	1.03	1.32	0.13

Route 3: LIW feeders dispensed the components directly into a tablet press, at a throughput of 25kg/hr
The feedframe speed was varied between 20 to 100 RPM

Feed Frame blending (3.00 %w/w)					
ID	**20 RPM**	**40 RPM**	**55 RPM**	**65 RPM**	**80 RPM**
API mg nominal	16.35	16.35	16.35	16.35	16.35
Average	17.33	15.55	15.80	15.62	15.80
%RSD	1.14	3.15	2.09	1.41	2.71
Difference (mg) Nominal – Avg	0.98	0.80	0.55	0.73	0.55

	RSD	
	Mass	**Hardness**
Batch 10RPM	1.06	9.2
Batch 15RPM	0.76	5.9
Batch 25RPM	0.74	6.9
FF 20RPM	0.51	5.5
FF 40RPM	0.59	5.3
FF 55RPM	0.77	5.8
FF 65RPM	0.68	5.5
FF 80RPM	0.66	5.3

We have achieved low RSD in CU and low RSD in weight and hardness variability

Conclusion

- The work here demonstrates that equivalent blend homogeneity and tablet uniformity can be achieved via batch blending, traditional continuous manufacturing, and continuous feeding directly into a tablet press
- This has been demonstrated with a high dose granulated API and a low dose impregnated API
- The future of CM could be a flexible and portable feeder platform that can be placed above any tablet press

Thank you

Thank You

Group references

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- Tian, Huayu, et al. "Characterization and propagation of RTD uncertainty for continuous powder blending processes." *International Journal of Pharmaceutics* 628 (2022): 122326.
- Razavi, Sonia M., Atul Dubey, and Fernando J. Muzzio. "Residence Time Distribution in Continuous Manufacturing." *Continuous Pharmaceutical Processing and Process Analytical Technology*. CRC Press, 2023. 111-124.
- Continuous Blenders are Not Necessary for All Continuous Direct Compaction - Submission
- Understanding Shear Dynamics to Promote Rapid Product Transfer Between Manufacturing Routes - Submission

Case Study 2: Low dose API

- The bin blender was operated at three speeds, until each reached a total of 200revs, the blend was placed in a LIW feeder and dispensed into a tablet press, FF 60RPM
- The CM line was operated at 25kg/hr with three blender speeds and a tablet press FF speed of 60RPM
- Tablets were collected at two points during steady state and evaluated by UV/Vis

Batch blending (3.00 %w/w), 545 mg tablet			
ID	**10 RPM**	**15 RPM**	**25 RPM**
API mg nominal	16.35	16.35	16.35
Average	14.91	16.26	16.67
%RSD	4.97	2.26	1.43
Difference Nominal - Avg	1.44	0.09	0.32

Continuous blending (3.00 %w/w), 255 mg tablet			
ID	**114 RPM**	**200 RPM**	**286 RPM**
API mg nominal	7.65	7.65	7.65
Average	6.62	6.33	7.78
%RSD	3.71	1.05	3.19
Nominal - Avg	1.03	1.32	0.13