# Future of Continuous Manufacturing in Drug Products Containing Nanomaterials

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# Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

# Outline

- Continuous manufacturing
- Opportunities for nanomaterials
- A research example
- Regulatory considerations

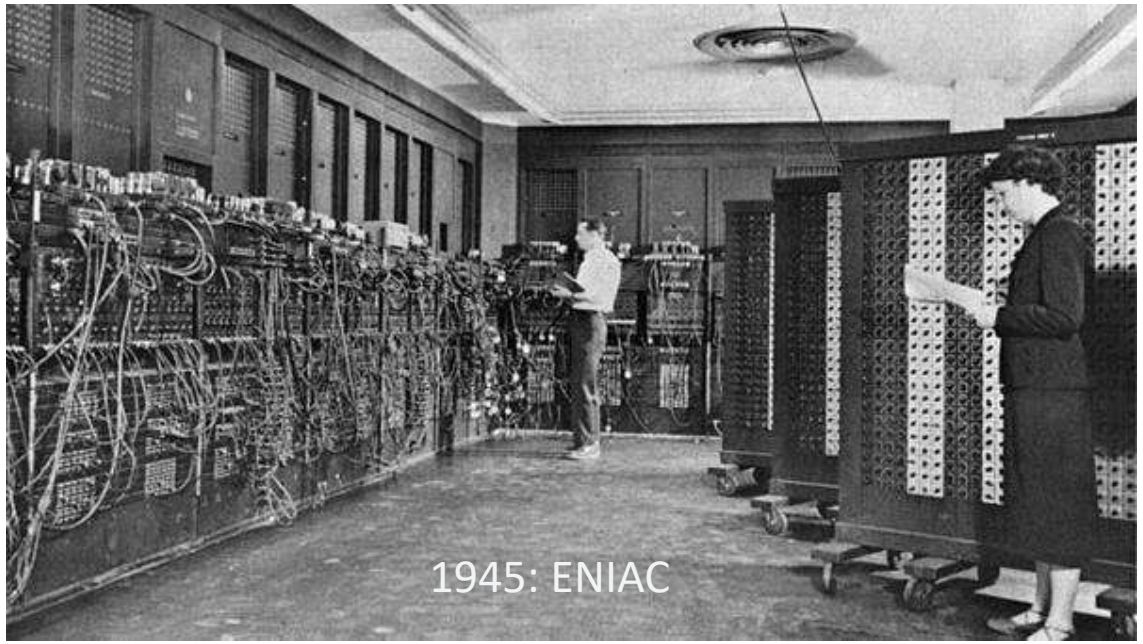
# Innovation in Manufacturing

THEN

NOW

# Another Example…

THEN



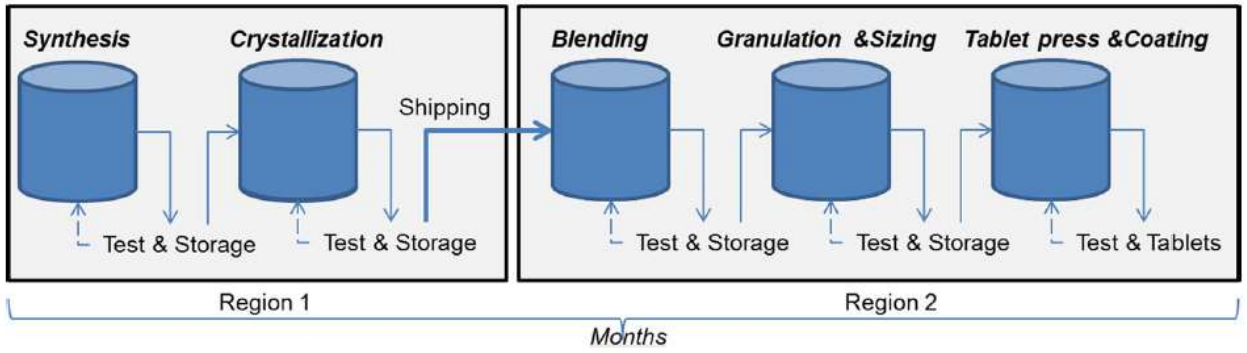

NOW

Pharmaceutical industry is also evolving…

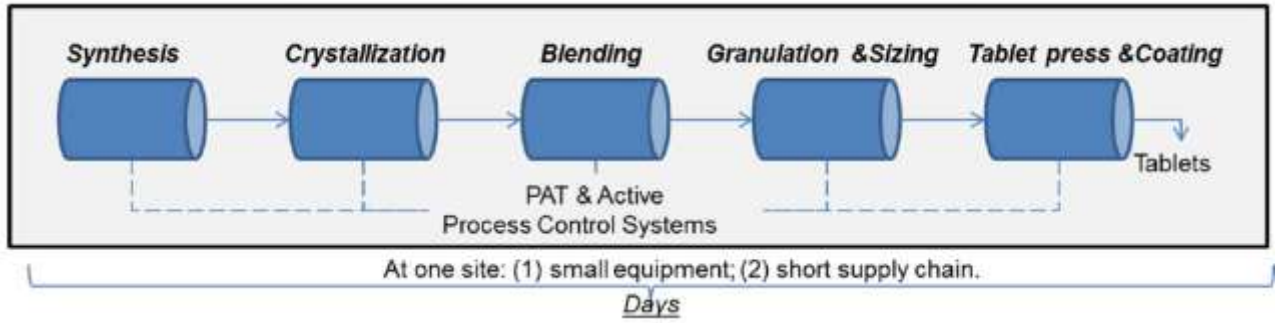
# What is Continuous Manufacturing (CM)?

- CM is an integrated process
- Consists of two or more steps
- Continuous flow of material
- Intensified process

**A typical batch manufacturing process**



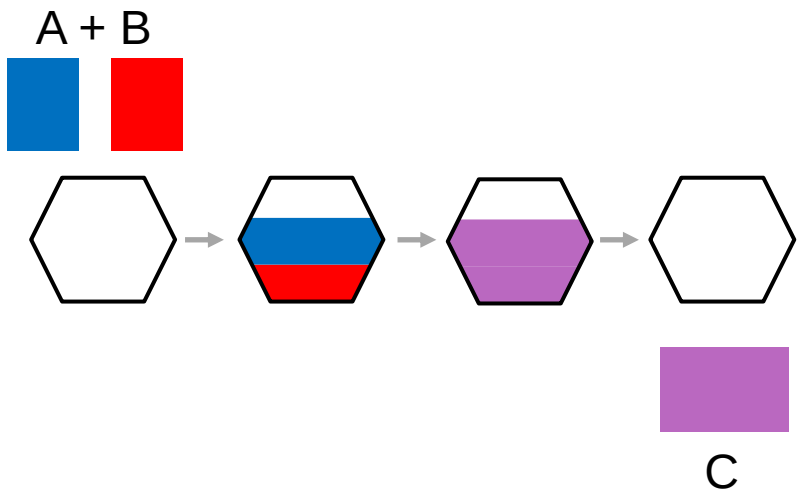

**A conceptual integrated continuous manufacturing process**




S. Lee, et al. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production, J Pharm Innov (2015) 10: 191-199

# Continuous Manufacturing: A Blending Example

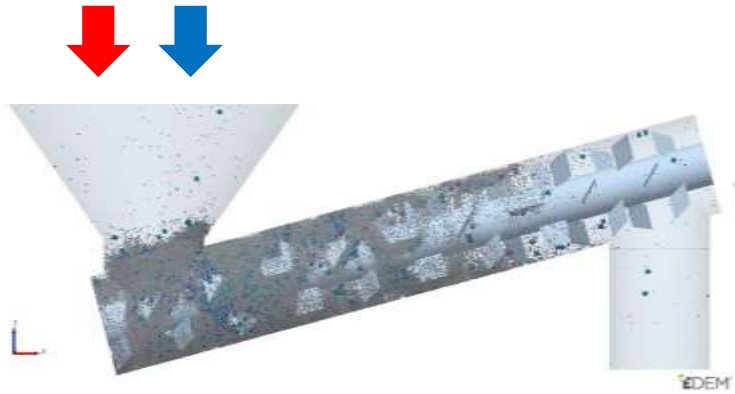
## Batch Process




Input: Fixed amount of **A** + **B**
Output: Fixed amount of **C**
Variables: Speed, time, fill level
**Keywords: Endpoint, Scale**

## Continuous Process

Continuous feeding of materials at A + B = C rate



Continuous output of blend at C rate

Input: Feeding **A** and **B** at a defined **rate**
Output: **C rate**
Variable: Feed rate and speed
**Keywords: Time, line rate**

# Why CM?

- FDA has identified CM as an emerging technology
- FDA recognizes that CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
  - Integrated processing with fewer discrete steps
    - No manual handling, increased safety
    - Shorter processing times
  - Smaller equipment and facilities
    - More flexible operation
    - Lower capital costs, less work-in-progress materials
    - Reduced environmental footprint
    - Feasible to manufacture small batch sizes
  - On-line monitoring and control for increased product quality assurance in real-time
    - Amenable to Real Time Release Testing approaches
- Benefits to both patients and industry

# CDER Progress with CM

**6** Approved CM solid oral dosage forms

**1** Approved semi-CM small molecule API

**2** Approved semi-CM sterile products

**1** Approved semi-CM biotechnology product

CDER collaborated on research to support CM application assessment and policy development

For details regarding activities related to emerging technology including CM, please visit the Emerging Technology Program (ETP) Website

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm

# FDA's Regulatory Approach for CM

## Science & Research

- Foster innovation and development of CM (e.g., intramural and extramural research)
- Understand key CM concepts and identify CM specific risks to product quality
- Develop a framework for control strategy considerations

## Regulations & Guidance



- Existing regulations and ICH guidances are generally applicable to CM (e.g., Q7 through Q12)
- New ICH Q13 focuses on CM
- Emerging Technology Guidance and MAPP (establishment of Emerging Technology Team, ETT)

## Feedback & Assessment



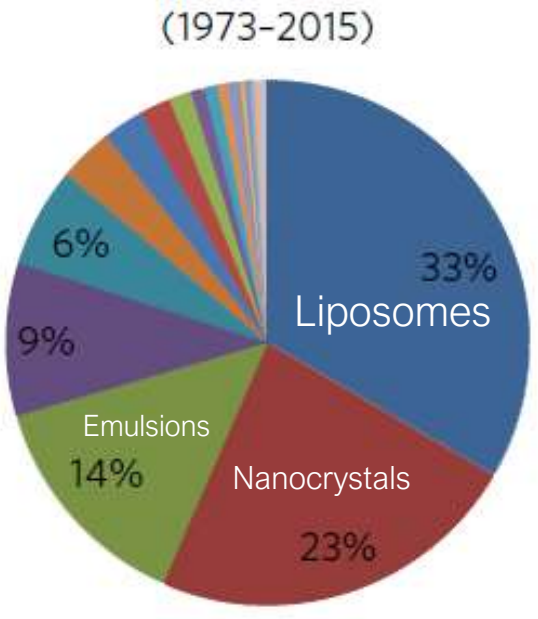
- Early engagement with ETT to address scientific and regulatory gaps
- Site visits
- Integrated review and facility assessments including pre-approval inspection

## Reg. Basis Maturation

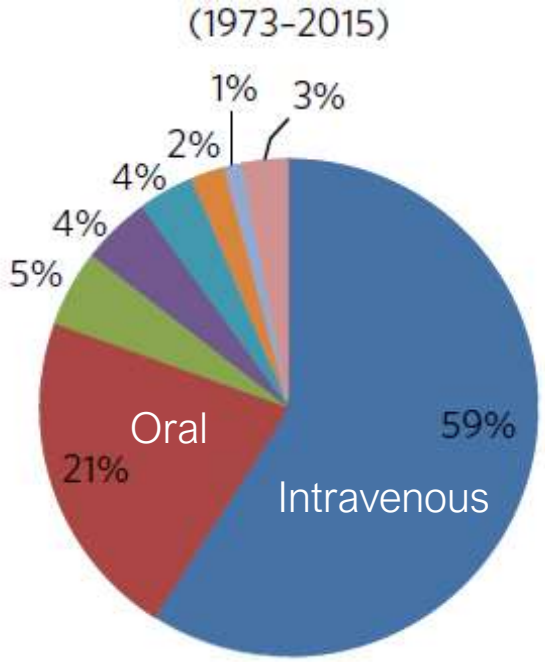


- Evolution of regulatory basis as experience gained with CM applications
- Knowledge management
- Regulatory guidance (e.g., FDA, ICH)

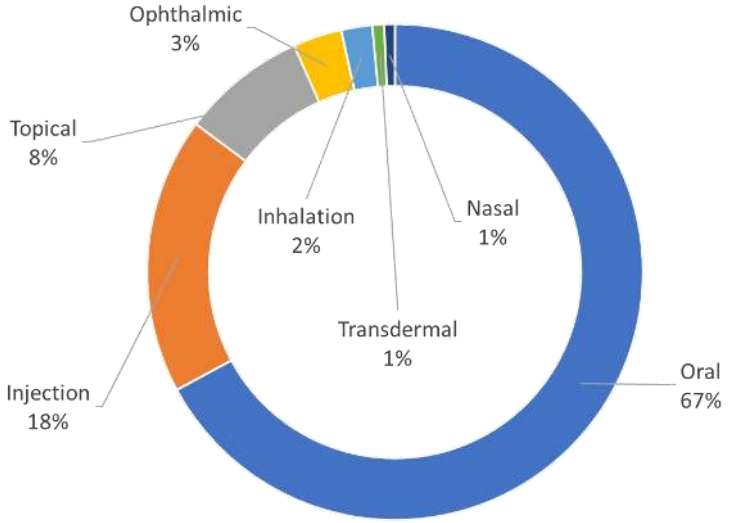
# Why CM for Nanomaterials?




Type of Formulation




Route of Administration for Nanomaterials

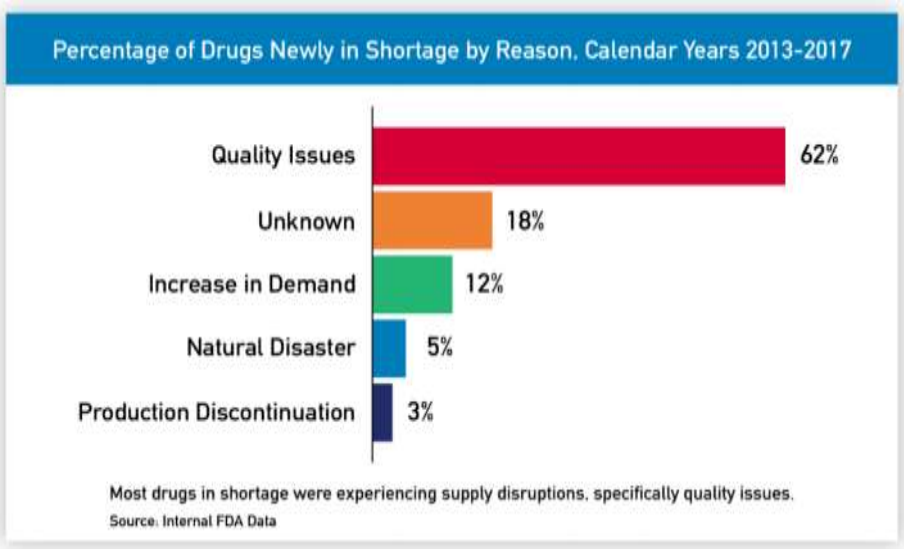



Route of Administration for All Approved Products
(data from Drugs@FDA)

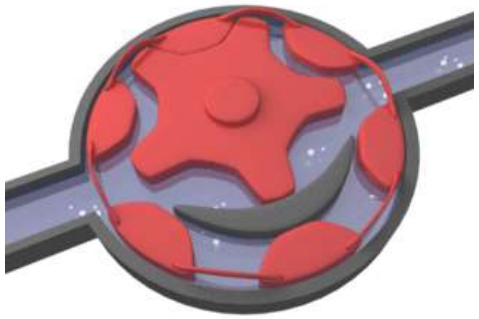
S. D'Mello et al. The evolving landscape of drug products containing nanomaterials in the United States, *Nature Nanotechnology*, 2017, 12, p.523-529

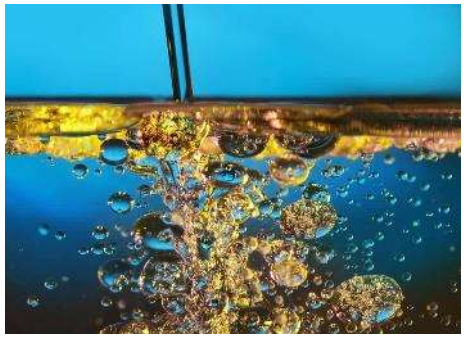
# CM for Nanomaterials: Two Sides of the Coin

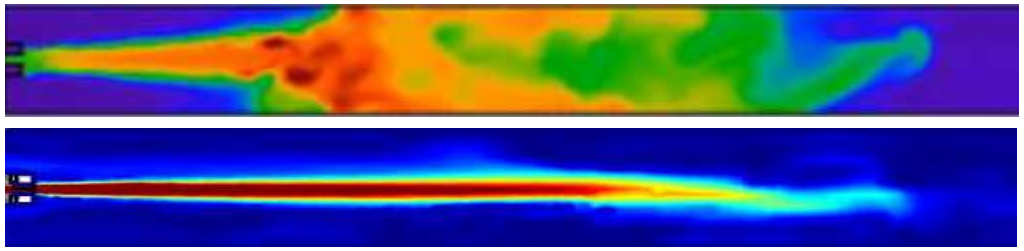
Quality issues were the most common reason for disruptions that became shortages




63% were Injectables





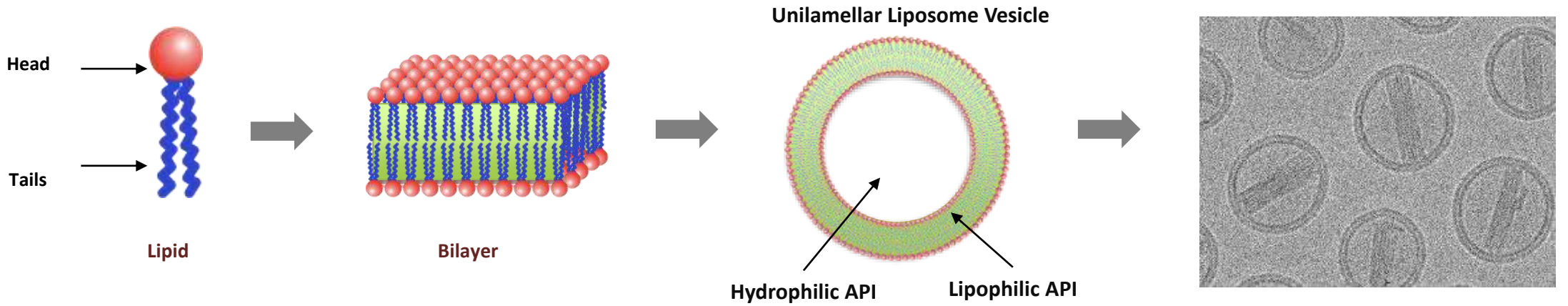


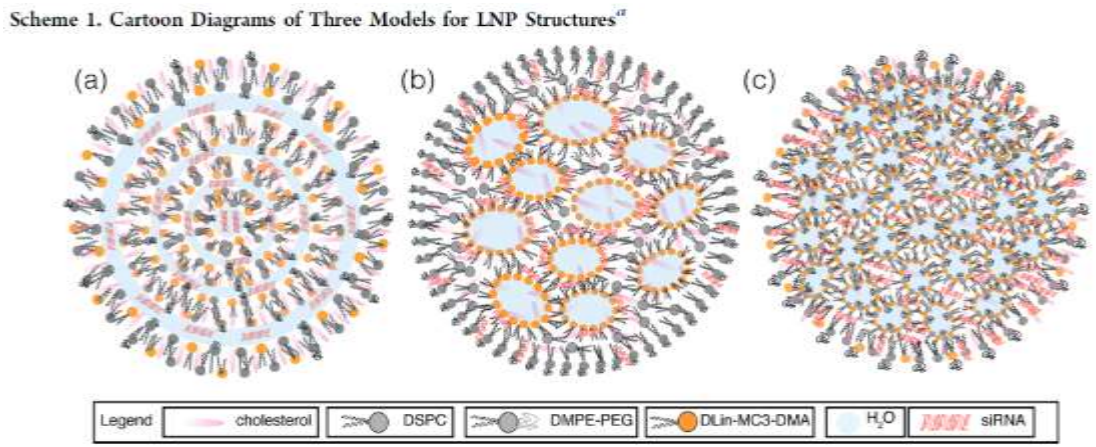
Drug Shortages: Root Causes and Potential Solutions. https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions

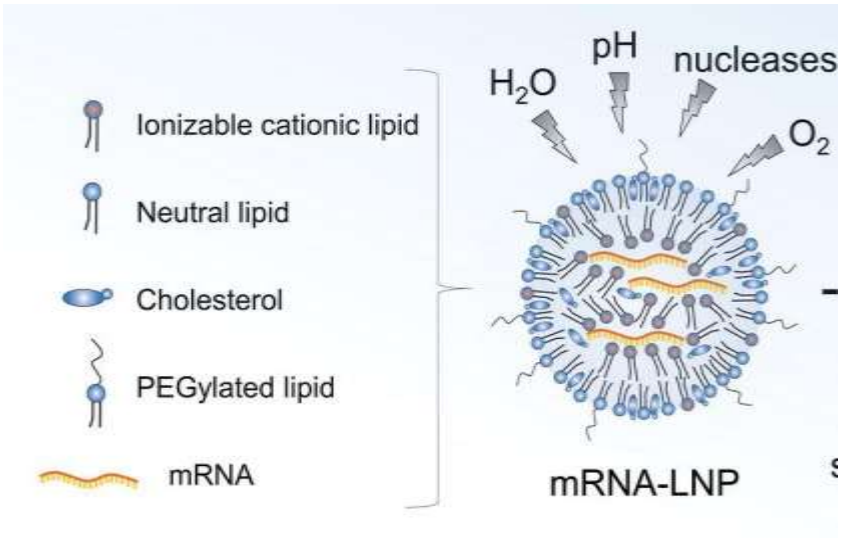
# RESEARCH EXAMPLE

Extramural Research

# Liposomes and Lipid Nanoparticles



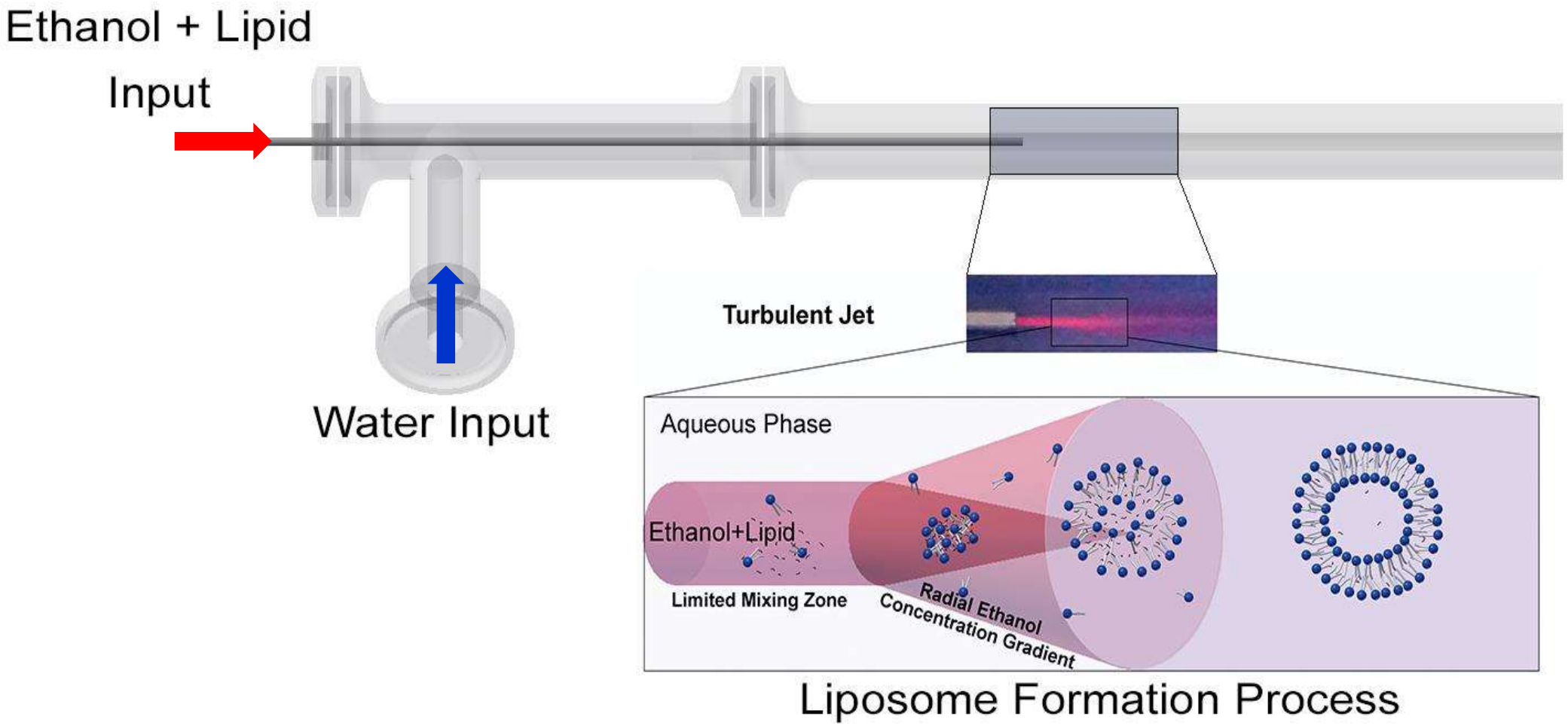

http://dx.doi.org/10.1021/acs.jpcb.7b10795

https://doi.org/10.1016/j.ijpharm.2021.120586

# Typical Batch Process of Liposome Manufacturing

1. Liposome (empty) formation (e.g., film hydration, **ethanol injection,** reverse phase evaporation)
2. **Down-sizing** (e.g., sonication, extrusion, microfluidization)
3. Drug encapsulation (e.g., passive-, active- loading)
4. Purification (diafiltration, dialysis)
5. Fill-finish

# CM Enables One-step Unilamellar Liposome Formation




A.P. Costa, X. Xu, M. Khan, D.J. Burgess. Liposome Formation using a Coaxial Turbulent Jet in Co-Flow. Pharmaceutical Research. (**2015**), 33 (2), pp. 404-416.

# High-Speed Camera: Jet Formation

Entire 30 second video takes place in less than 1 second…

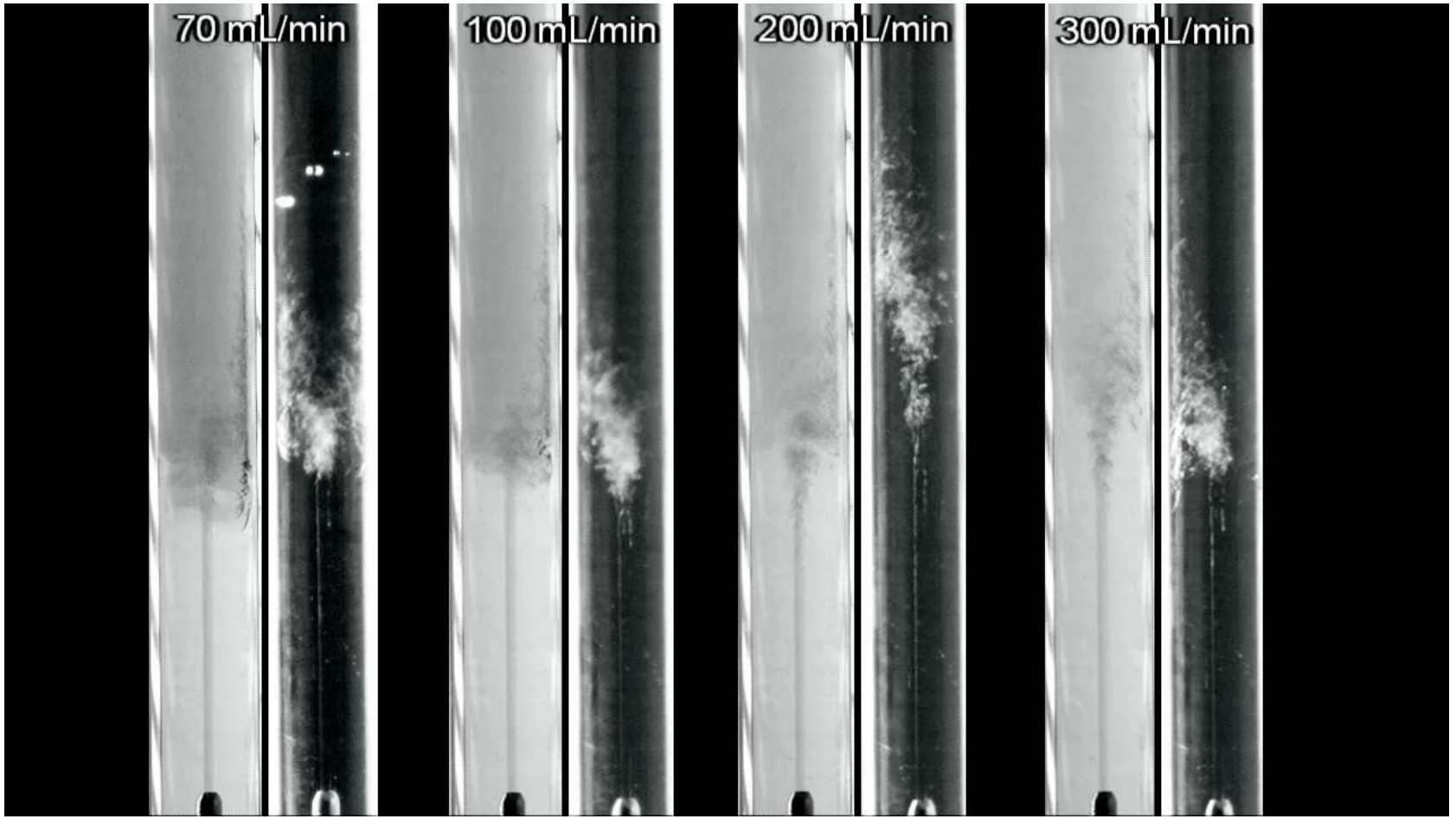
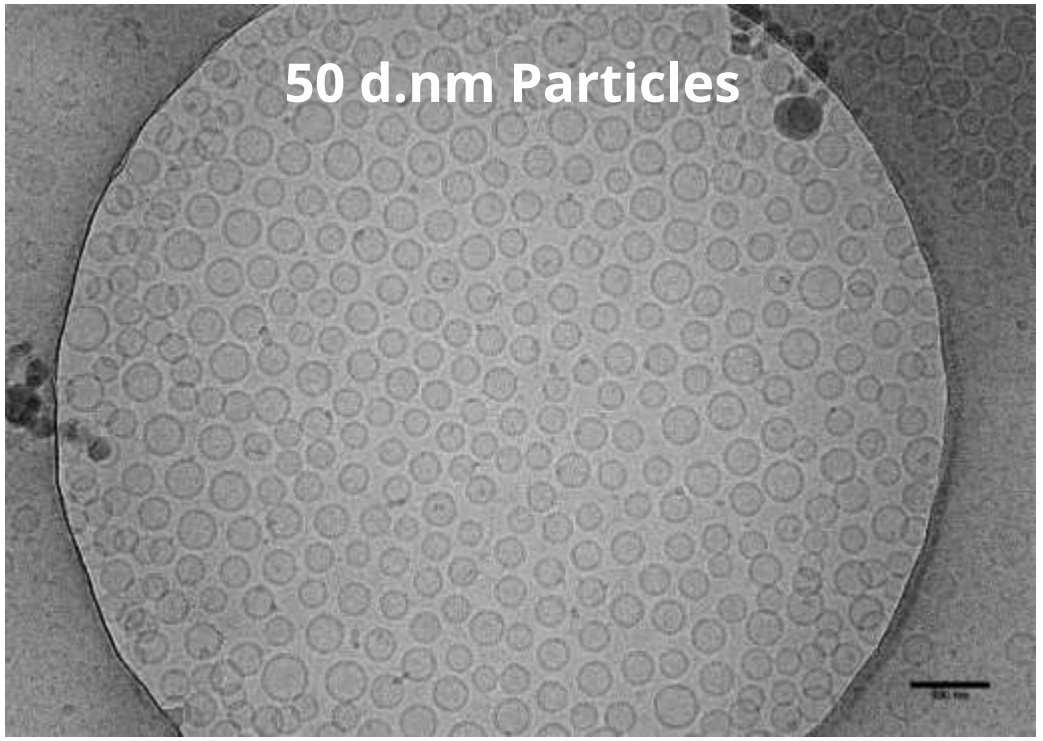
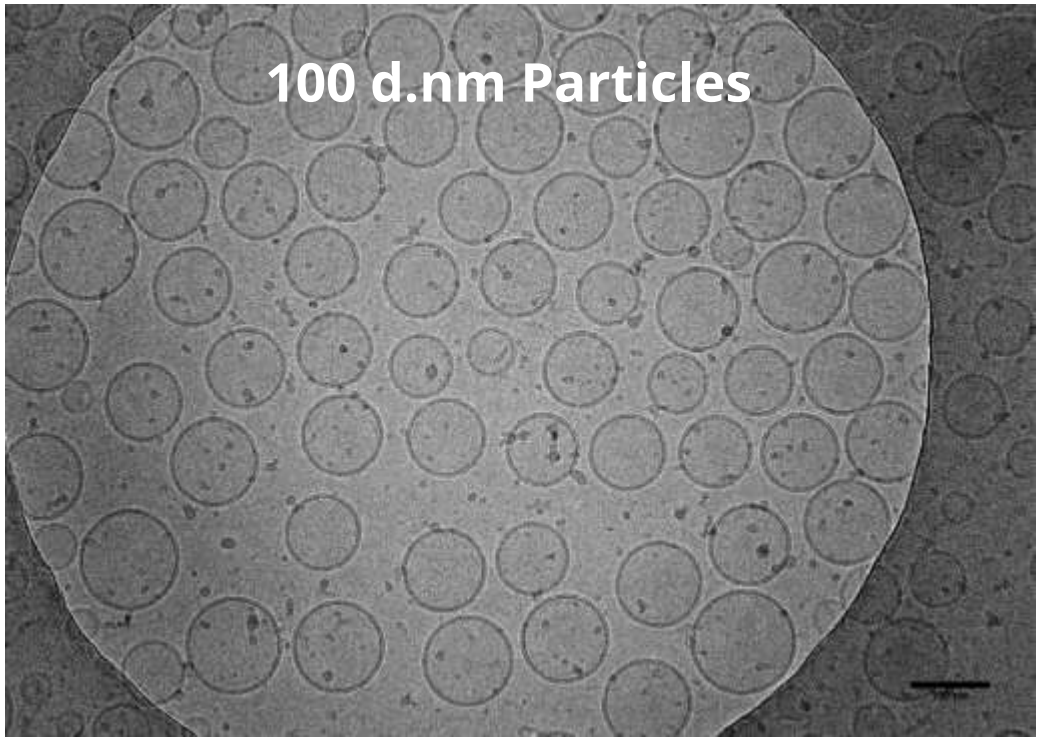



Image credit: UConn team (D. Burgess, A. Costa)

# Improved Precision and Robustness



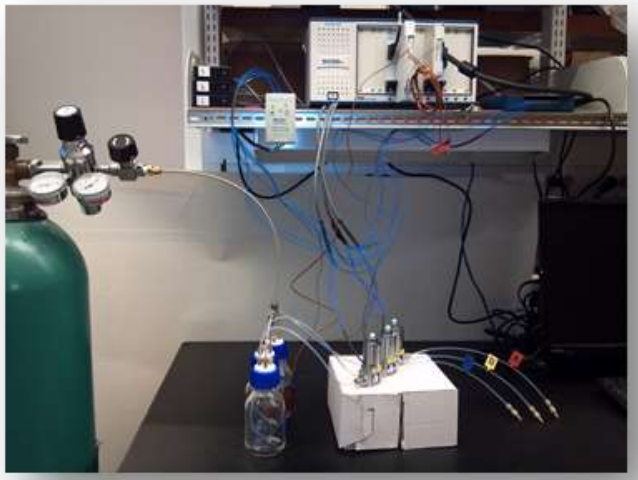

| Sample ID | Z-Average (d.nm) | ± | PDI | ± |
|---|---|---|---|---|
| 50 nm | 50.08 | 0.27 | 0.029 | 0.015 |
| 100 nm | 97.63 | 0.73 | 0.047 | 0.019 |

* Measured by Dynamic Light Scattering

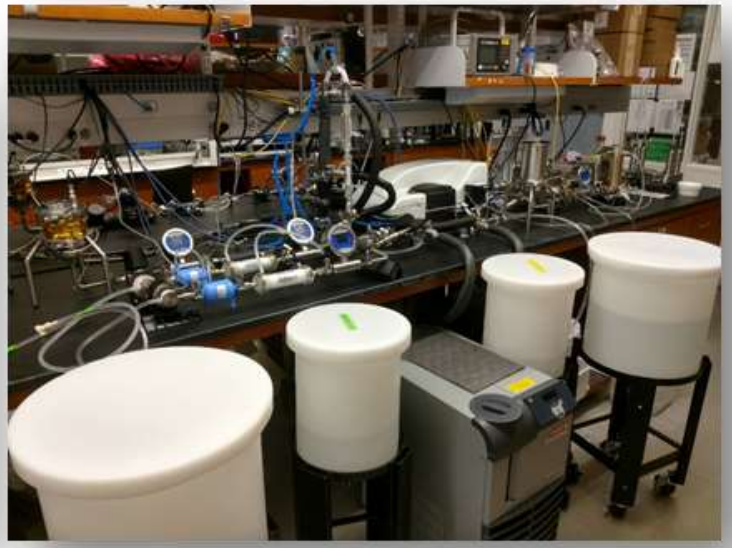
Yenduri, G., et al. "Impact of critical process parameters and critical material attributes on the critical quality attributes of liposomal formulations prepared using continuous processing." International Journal of Pharmaceutics, 619 (2022): 121700.

# Concept to Production: CM Development Journey

2014



2018

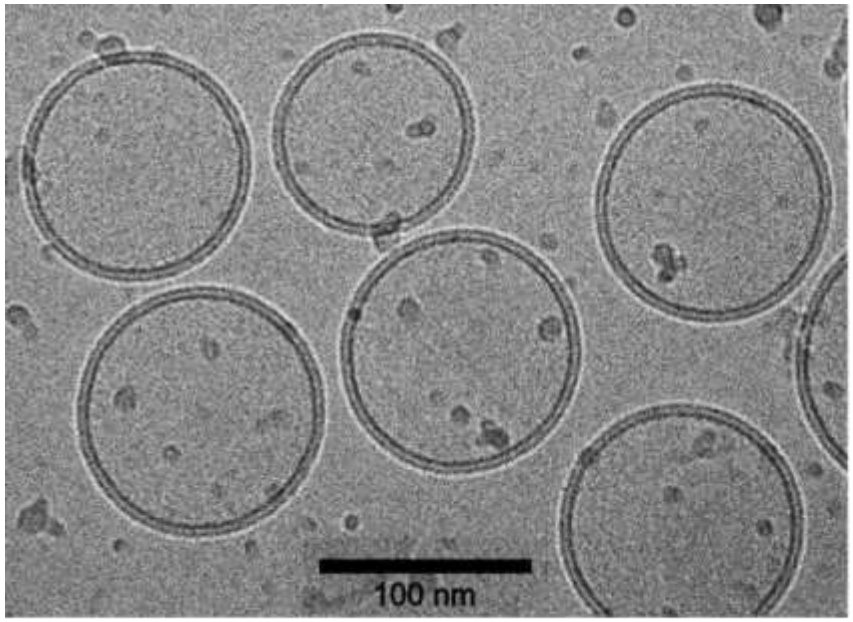


2022

Image credit: UConn team (D. Burgess, A. Costa)

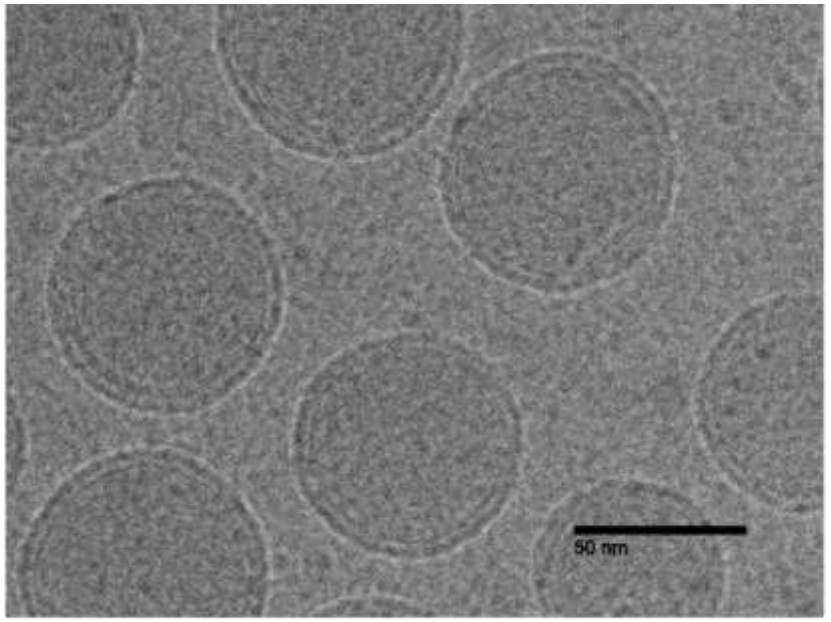
# One CM System, Multiple Nanoparticles

## Liposomes



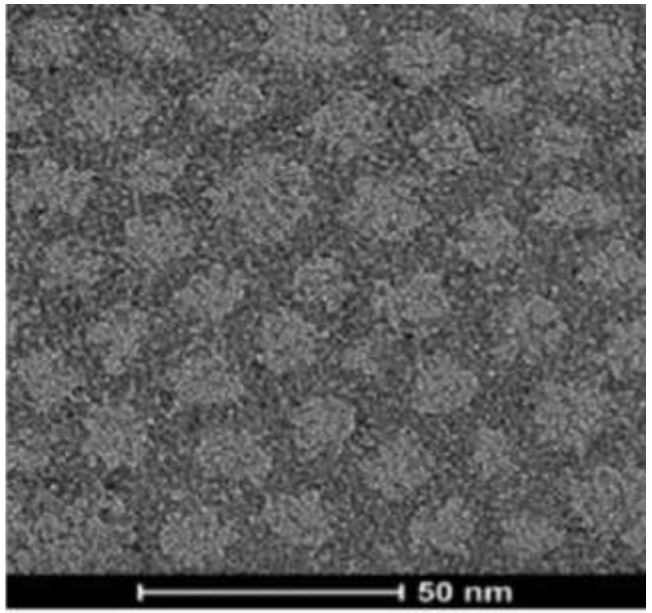

Bilayer Structure
Aqueous Core

## Lipid Nanoparticles




Outer Lipid Layer
Aqueous/Lipid/Nucleic Acid Core

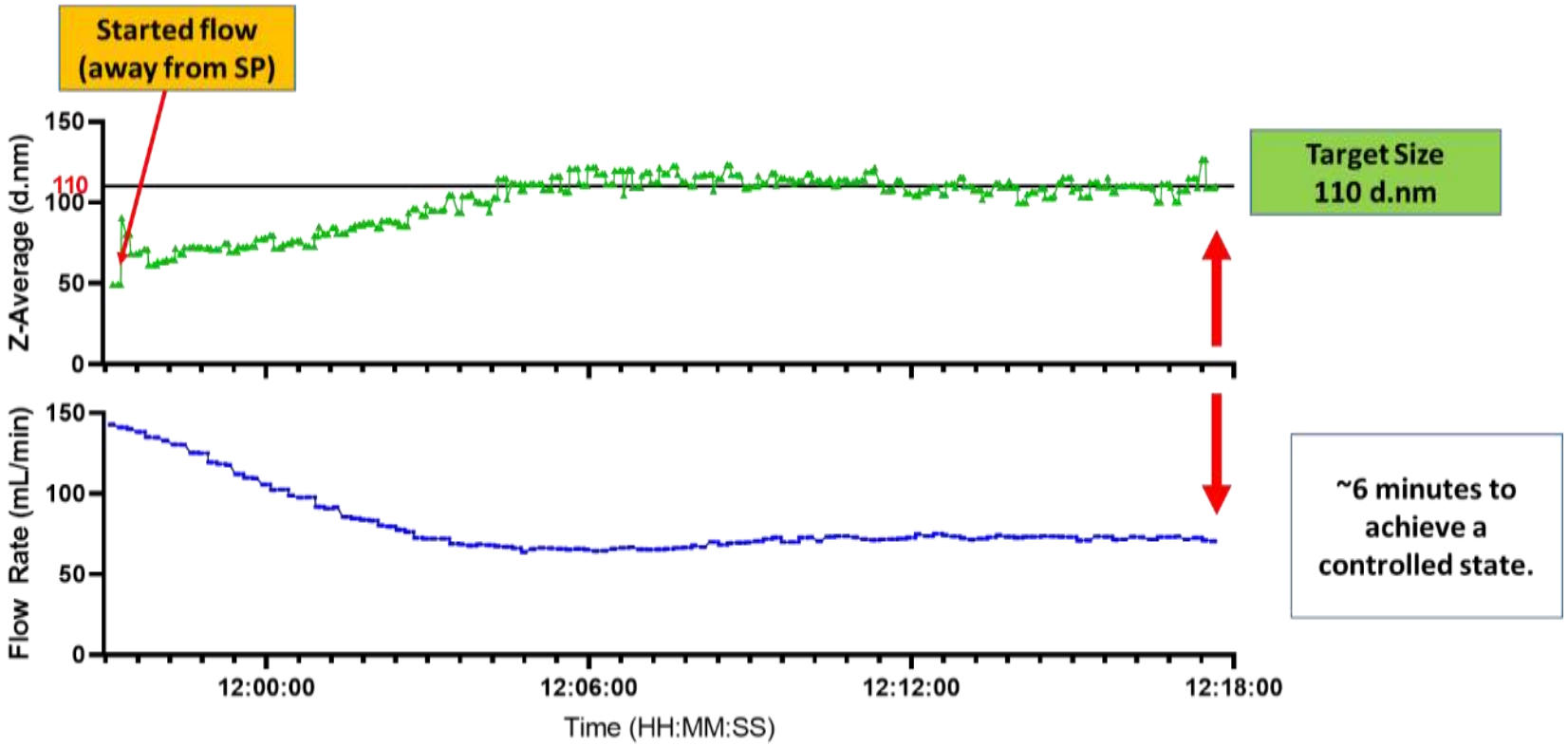
## Polymeric Micelles




Block copolymer
Hydrophobic Core

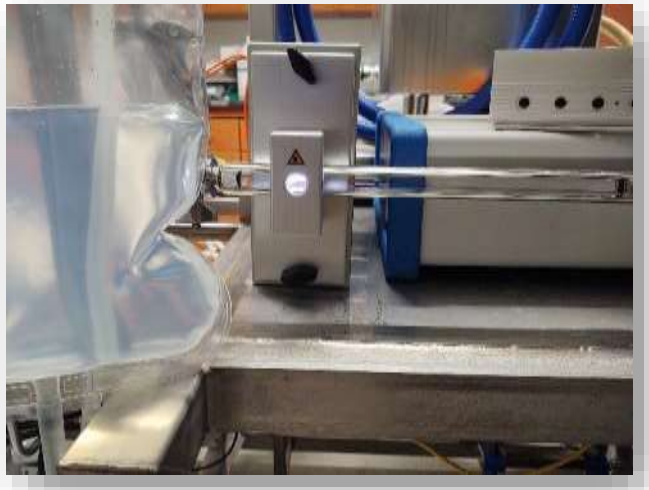

- Yenduri, G., et al. "Impact of critical process parameters and critical material attributes on the critical quality attributes of liposomal formulations prepared using continuous processing." International Journal of Pharmaceutics, 619 (2022): 121700.
- Gupta, A., et al. “Continuous processing of paclitaxel polymeric micelles” International Journal of Pharmaceutics, 607 (2021): 120946.

# Enables Automated Process Control




**NanoFlowSizer**

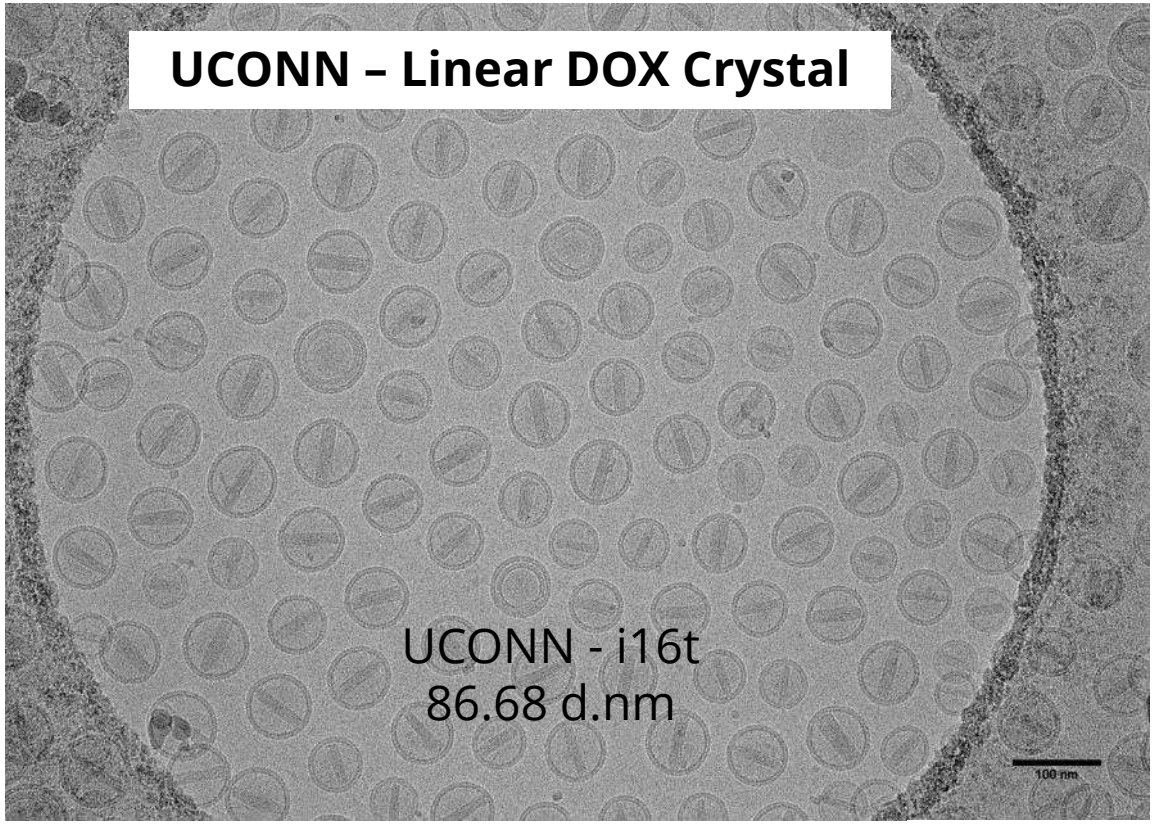
Spatially-Resolved DLS

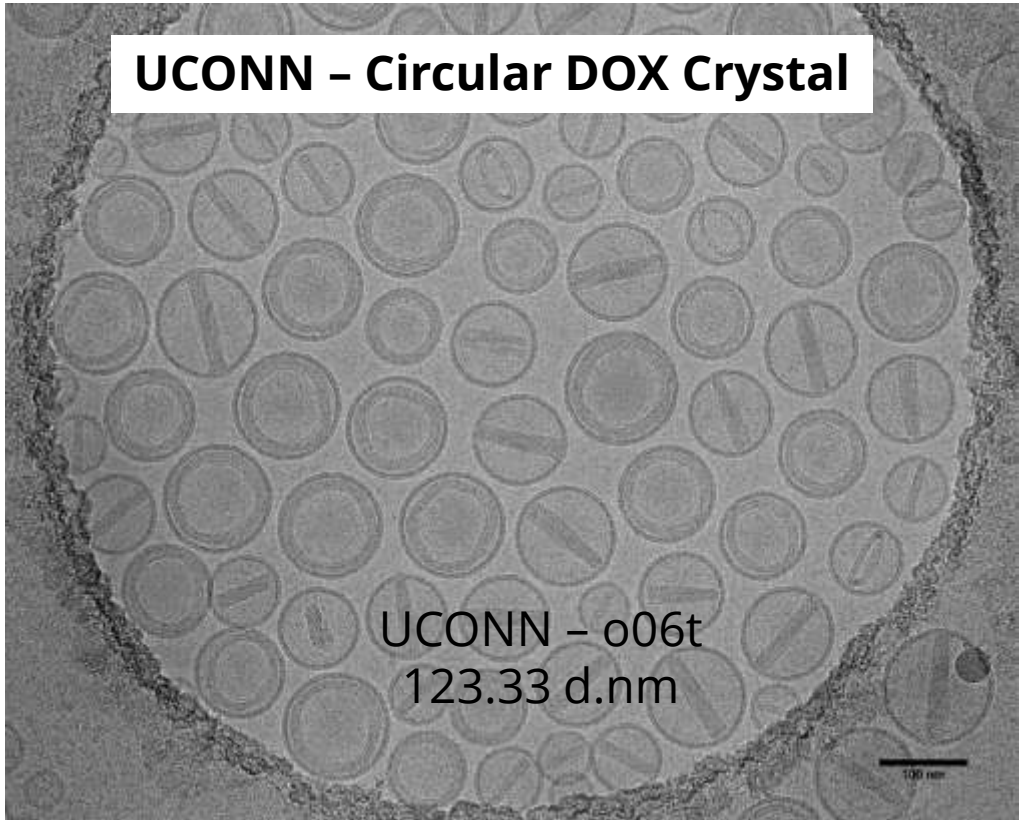


Example 20 Liters of Liposomes at 20 mM lipid conc. (about 3 hrs run)

"Product output change" is time dependent. Consistent quality can be maintained via appropriate PAT tools

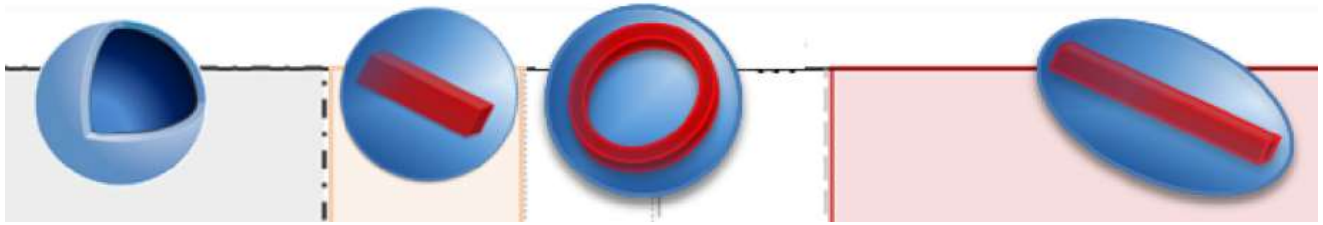
# Does Shape Matter?




Two types:

- Liposome (spherical vs. elongated)
- Crystal (linear vs. circular)



# Modeling and Simulation to Enhance Process Understanding

## Coarse-Grained Molecular Dynamics Simulation

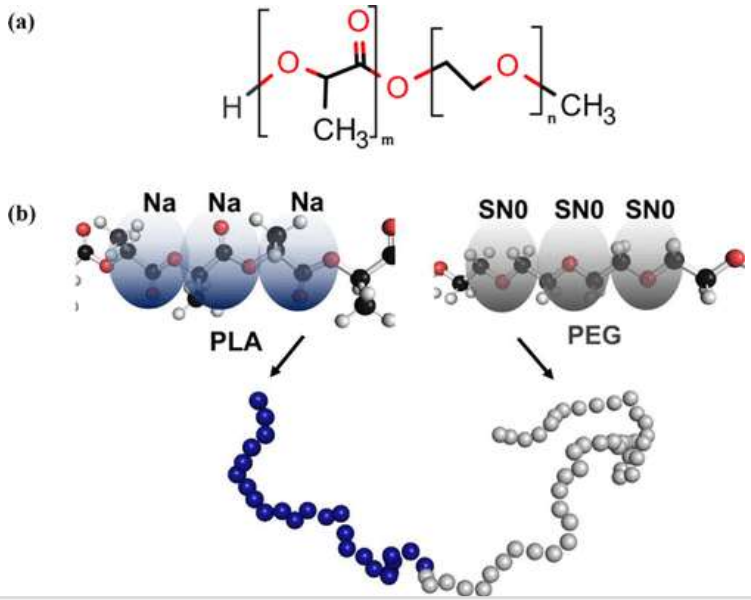



Figure 1. (a) Chemical structure of PEG–PLA and (b) correspondence between the AA and CG (MARTINI) models of PEG–PLA.

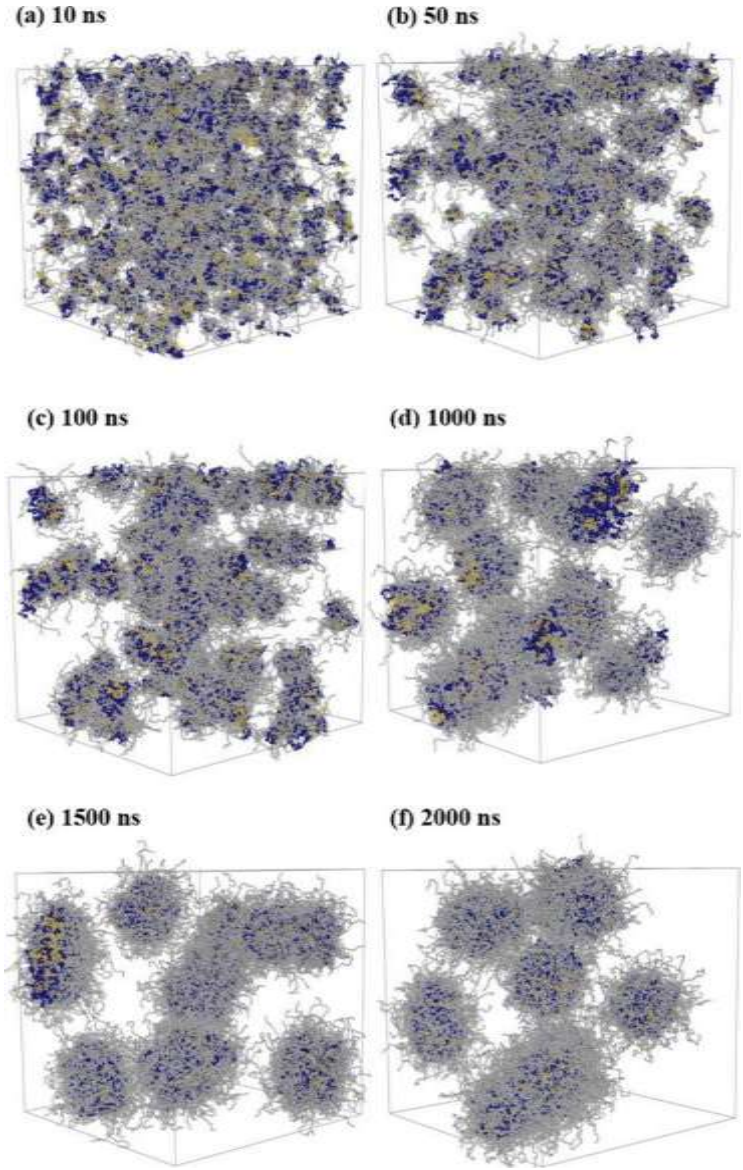



Figure 2. CG-MD simulation results of loading of the drug (paclitaxel) into PEG-PLA polymeric micelles over the course of 2000 nanoseconds

Modeling and simulation tools like discrete element method (DEM), computational fluid dynamics (CFD), molecular dynamics (MD), artificial intelligence and machine learning (AI/ML), and digital twins can enhance the product and process understanding, enabling the design of advanced process controls

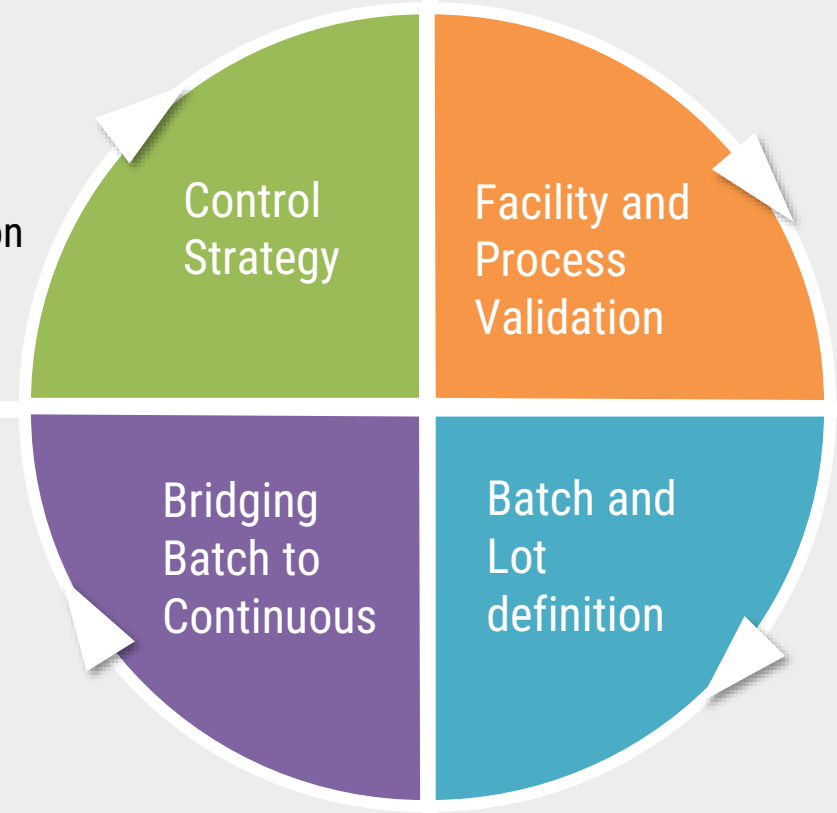
T. Duran et al. Molecular Pharmaceutics (2022), 19(4):1117-1134

Lesson learned

# REGULATORY CONSIDERATIONS

# CM Elements Discussed Between CDER and Industry

- System dynamics, RTD and transient disturbances
- Raw material control
- Sampling strategy
- Material traceability
- Start up and shut down
- PATs, models and RTRT
- Product collection and material diversion
- Process monitoring and control




- Model maintenance and update
- System integration, data processing and management
- Equipment qualification, maintenance and cleaning
- Process performance qualification
- Continued process verification

- Minor formulation changes
- Comparability and bioequivalence
- Stability data package

- Batch size – flow rate and run time
- Scale up – run time increase
- Primary stability batch size
- Mass balance or yield

# Quality Assessment Focus

- Characterization of process dynamics for critical steps and integrated system
  - Residence time distribution for a proposed mass flow rate
  - Understanding of the system response to transient disturbances
- Evaluation of the proposed attributes and specifications of raw materials
  - Impact of variations in material properties on the performance of CM and product quality
- Process monitoring and control strategy
  - Monitor and detect transient disturbances and process deviation
  - Frequency of PAT measurements
  - Active process controls
- Material collection and diversion
  - Start up and shutdown
  - Strategy to identify, isolate and divert non-conforming materials
- Real-time release testing
  - PAT tools for assay and content uniformity
  - Dissolution models

# Characterization of Residence Time Distribution (RTD) during Continuous Manufacturing (CM)

**Problem statement:**

- Understanding CM process dynamics as a function of material properties, process conditions and equipment design through characterization of RTD

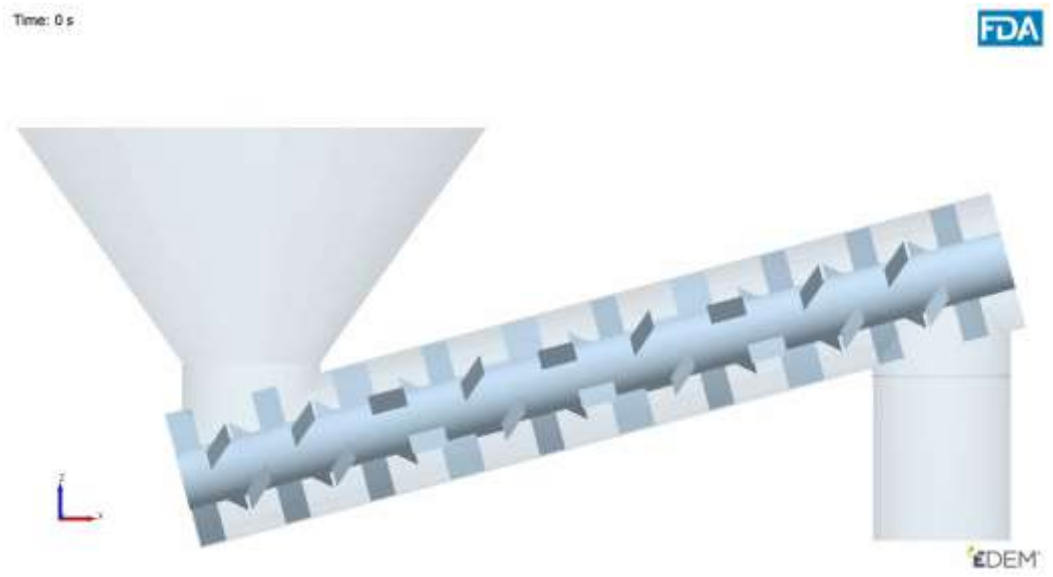
**Approaches:**

- Experimental RTD studies and *in silico* RTD modeling

**Outcomes:**

- Comprehensive Design of Experiment (DoE) for investigating the effects of material properties, process parameters, and equipment configuration on RTD in a continuous powder blending process at the commercial scale
- A modeling framework for assessment of RTD-based control strategy using Discrete Element Method (DEM)

***In Silico* RTD Modeling via DEM**




**Impact: RTD model provides insight into CM process and supports quality assessment, policy development and reviewer training**


- W. Yang., et al. "Assessing Residence Time Distributions and Hold-up Mass in Continuous Powder Blending using Discrete Element Method", Under Peer-review.

# Impact of Continuous Manufacturing

International Journal of Pharmaceutics 622 (2022) 121778

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journal homepage: www.elsevier.com/locate/ijpharm

## An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

Adam C. Fisher, William Liu, Andreas Schick, Mahesh Ramanadham, Sharmista Chatterjee, Raphael Brykman, Sau L. Lee, Steven Kozlowski, Ashley B. Boam, Stelios C. Tsinontides*, Michael Kopcha

*Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States*

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ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (3 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171–537 M in early revenue benefit.

- **CM applicants had <u>shorter</u> times to approval and marketing compared to batch applicants**
  - 3 months faster to approval (median)
  - 4 months faster to marketing
  - ~$171-537M in early revenue benefit
- **No substantial regulatory barriers for CM related to:**
  - Manufacturing process changes
  - Pre-approval inspections

https://doi.org/10.1016/j.ijpharm.2022.121778

# Closing thoughts

- FDA and CDER continue to foster innovation and the responsible development of drug products containing nanomaterials.
- Research to better understand product quality is crucial.
- Innovation in manufacturing and characterization is needed.
- Further development and utilization of continuous manufacturing in nanomaterials can be valuable to enhance the agility and quality of the products, benefiting the patient and society.

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- Gowtham Yenduri
- Tibo Duran


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