Opportunities in Continuous Manufacturing of Nanomaterials

Xiaoming Xu, Ph.D.
Director, Division of Product Quality Research
Office of Testing and Research, Office of Pharmaceutical Quality
CDER | U.S. FDA

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user – Drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their ***next*** dose of medicine.

Outline

- Regulatory considerations of nanotechnology
- Opportunities with continous manufacturing
- Research example

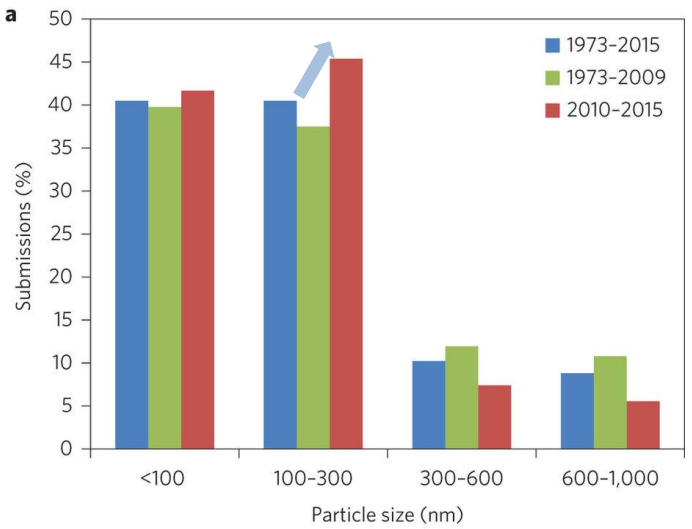
Considering Whether an FDA Regulated Product Involves the Application of Nanotechnology

Points to Consider:

1. *Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the **nanoscale** range (approximately 1 nm to 100 nm);*

2. *Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).*

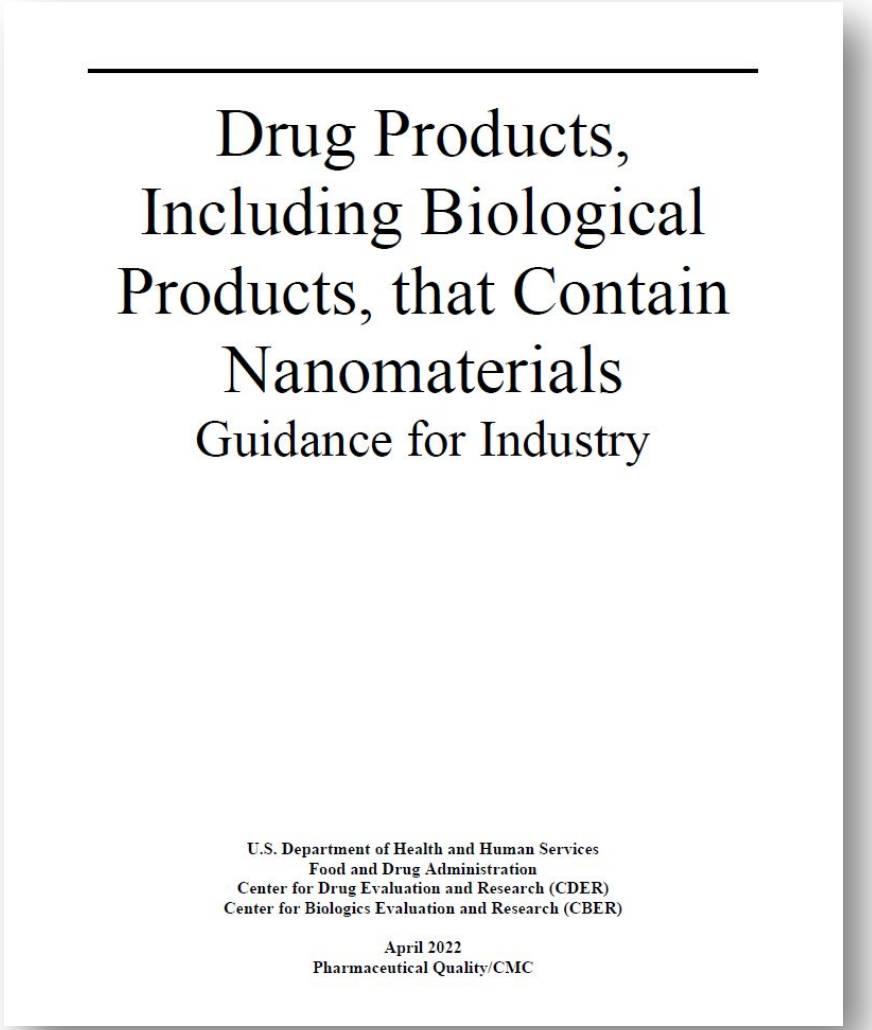
Particle sizes within drug products containing nanomaterials from 1973 to 2015.



- Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (2014)
- S. D'Mello, et al. The evolving landscape of drug products containing nanomaterials in the United States, Nature Nanotechnology, 2017, 12, p.523-529

CDER/CBER Nanotechnology Guidance

- Focuses on identifying and managing new risks,
  - FDA does not categorically judge nanomaterial products as intrinsically benign or harmful
  - Same standards of safety, efficacy, and quality
  - No new regulatory requirements
  - Risk-based approach
  - Characterization is key
  - Intent of nanomaterials
  - Bridging physical/chemical properties to clinical outcome
  - Lifecycle approach



Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

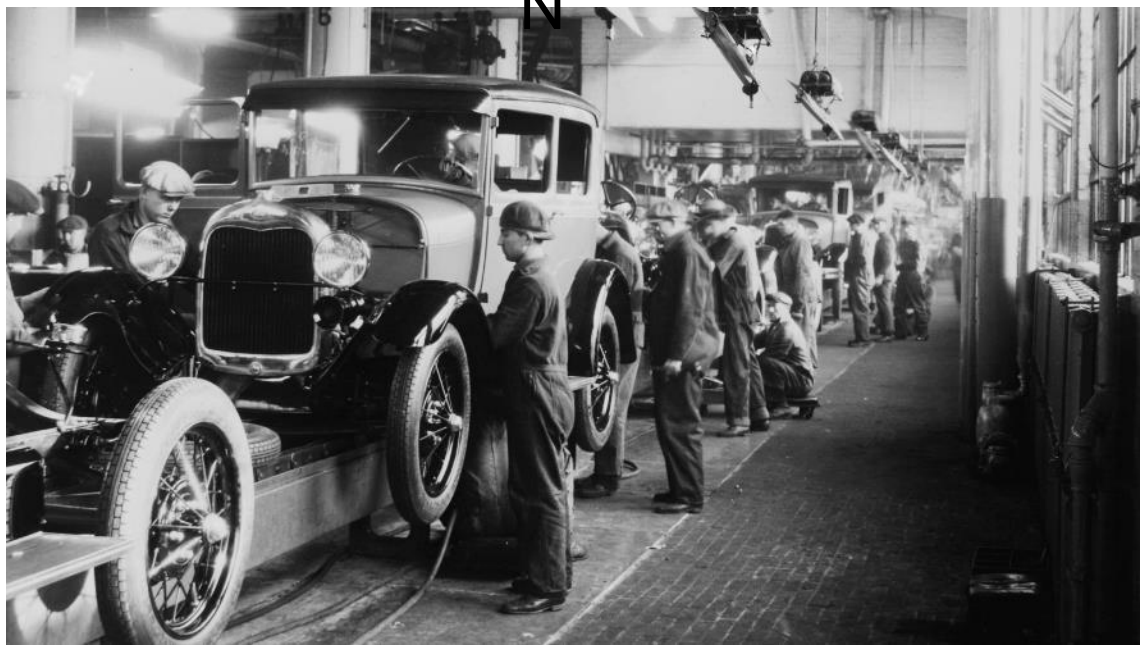
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
Pharmaceutical Quality/CMC

Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry (2022)
https://www.fda.gov/media/157812/download

Innovation in Manufacturing

THEN



NOW

Another Example…

THE
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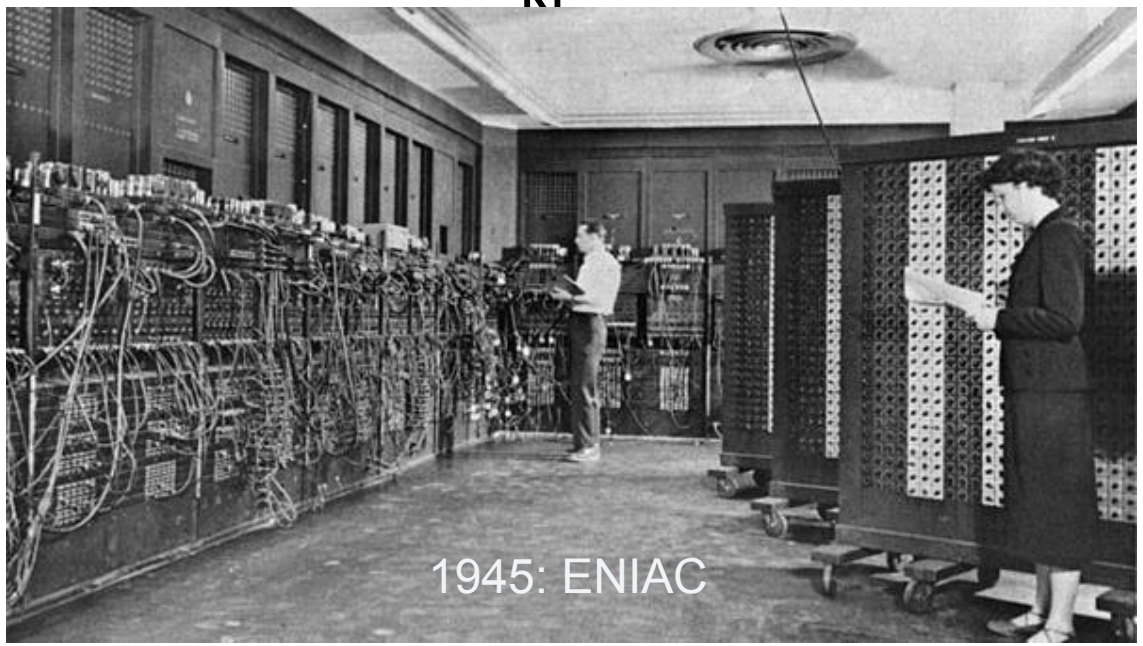


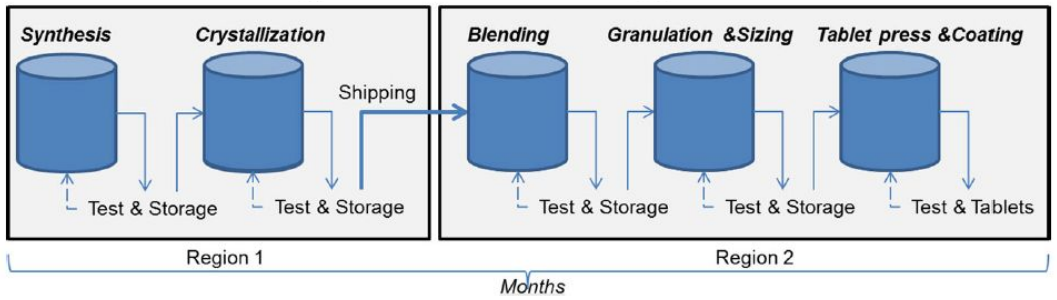
NO
W

Pharmaceutical industry is also evolving…

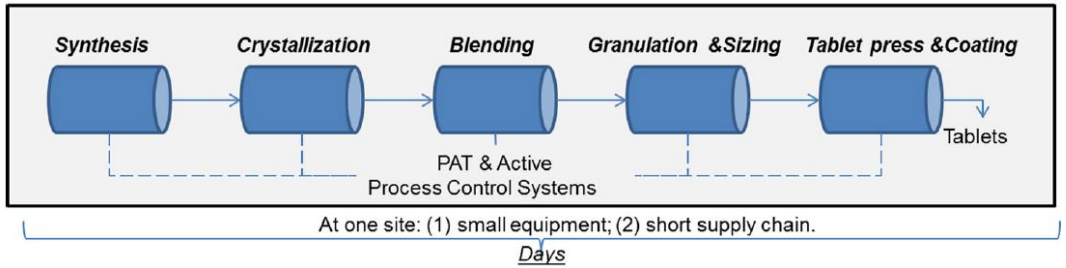
What is Continuous Manufacturing (CM)?

- 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



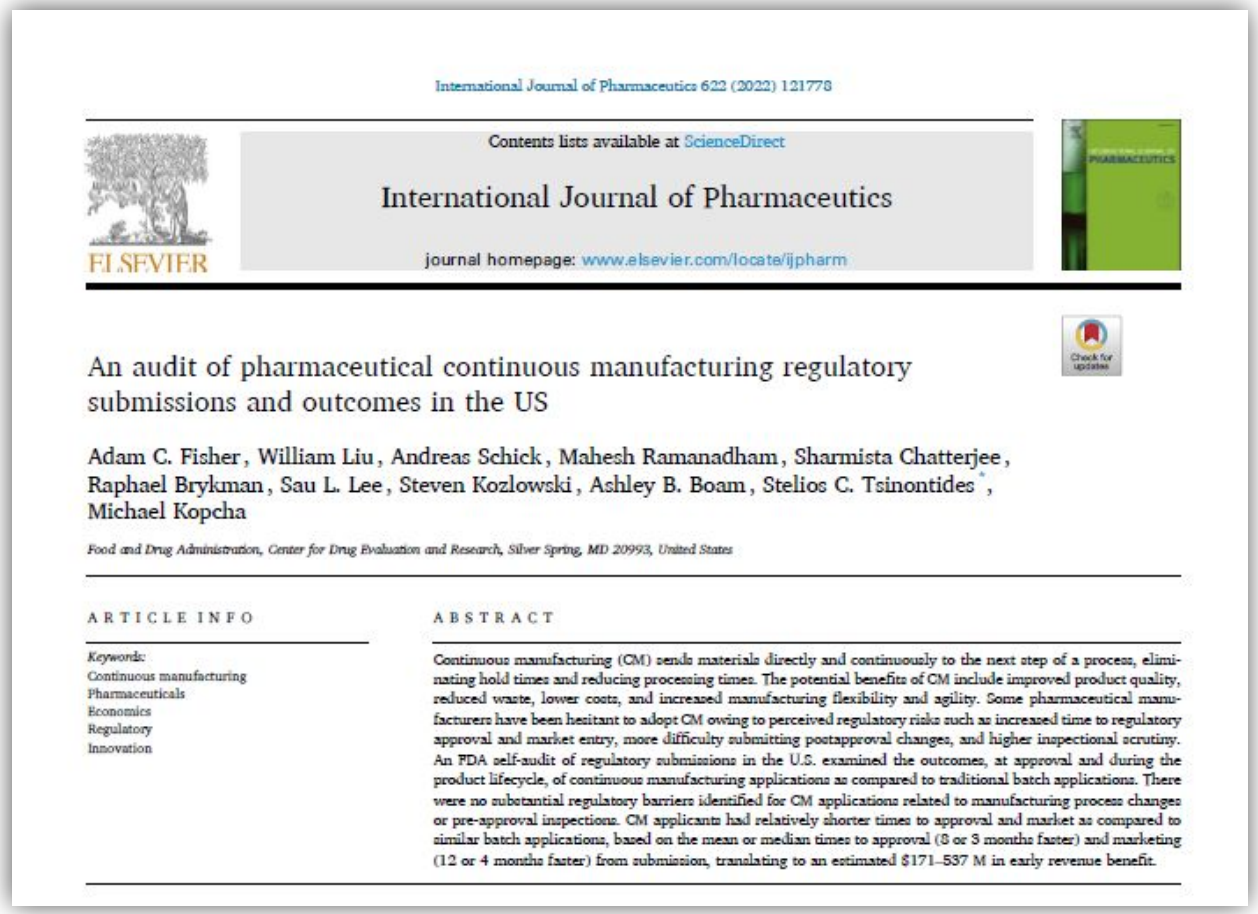
Advantage:

- Reduce processing time
- Reduce manufacturing footprint
- Increase efficiency, flexibility, agility, and robustness in manufacturing
- *Enable rapid response to drug shortages, emergencies, and patient demand*

To date, CDER has approved 15 drug products utilizing CM technology (all small molecules drugs). <u>No approved application utilizing CM of nanomaterials yet.</u>

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

Why Continuous Manufacturing



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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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Pharmaceuticals
Economics
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Innovation

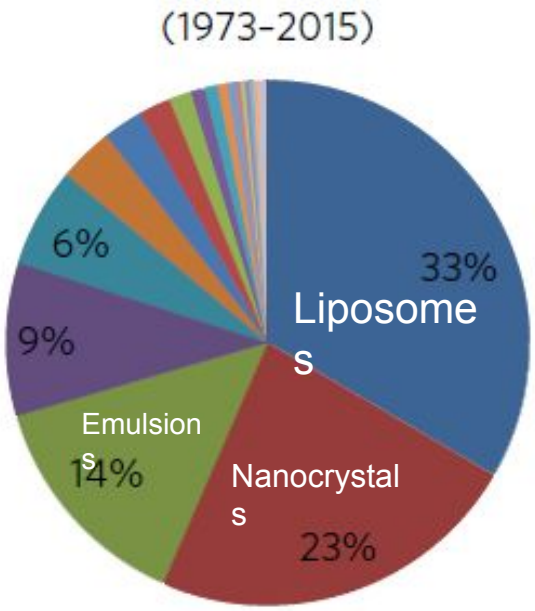
ABSTRACT

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 (8 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171–537 M in early revenue benefit.

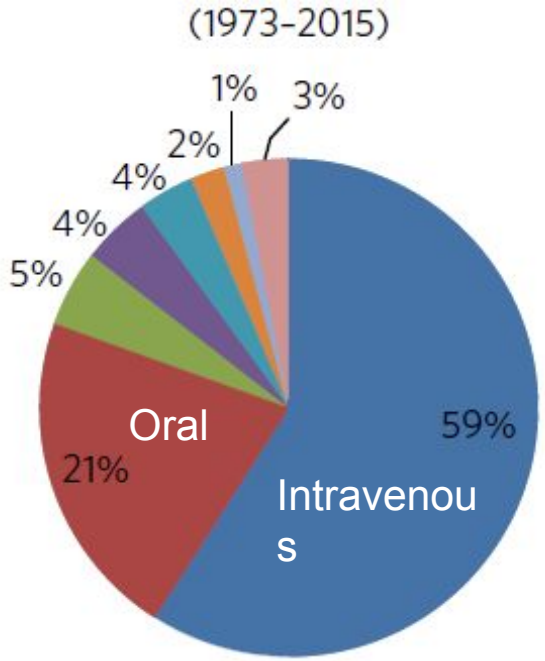
- **CM applicants had <u>shorter</u> times to approval and marketing compared to batch applicants**
  - 3 months faster to approval (median)
  - 4 months faster to marketing
  - ~$171-537M in early revenue benefit
- **No substantial regulatory barriers for CM related to:**
  - Manufacturing process changes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

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

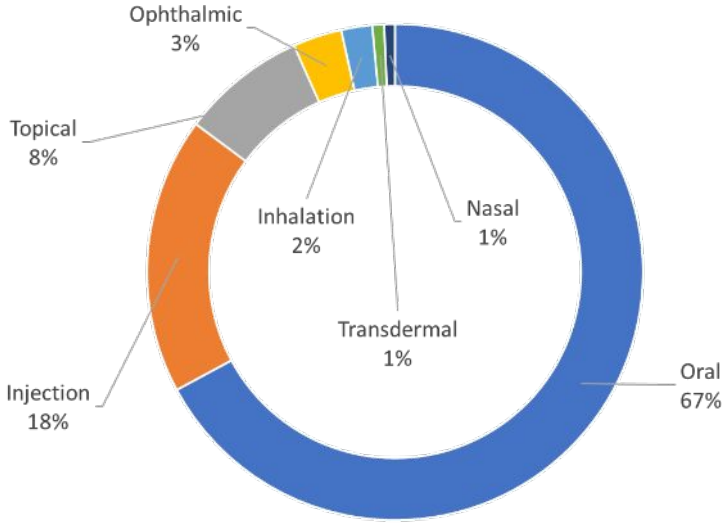
Opportunities in CM of Nanomaterials



Type of Formulation



Route of Administration for Nanomaterials

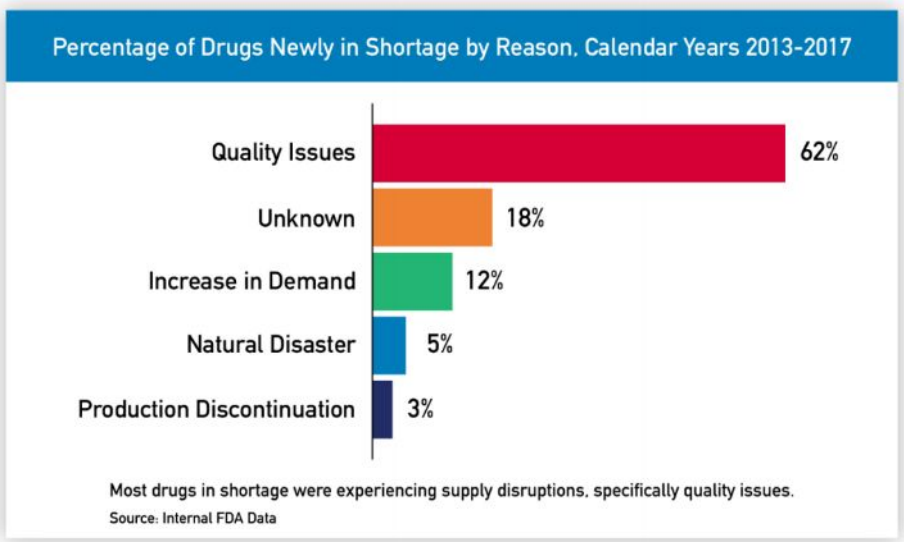


Route of Administration for All Approved Products
(data from Drugs@FDA)

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

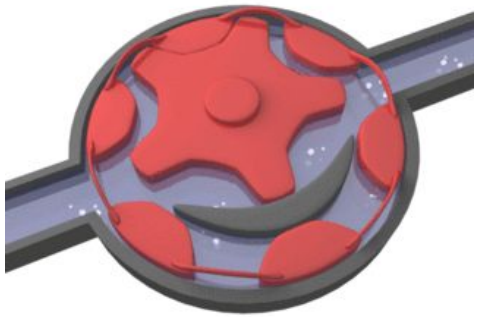
CM for Nanomaterials: Two Sides of the Coin

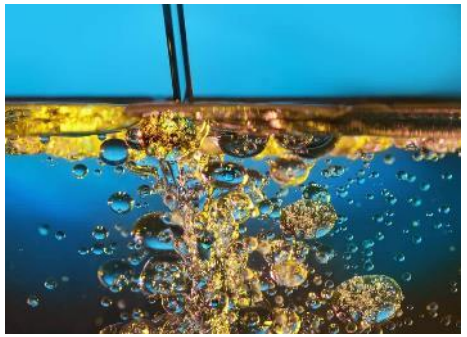
Quality issues were the most common reason for disruptions that became shortages

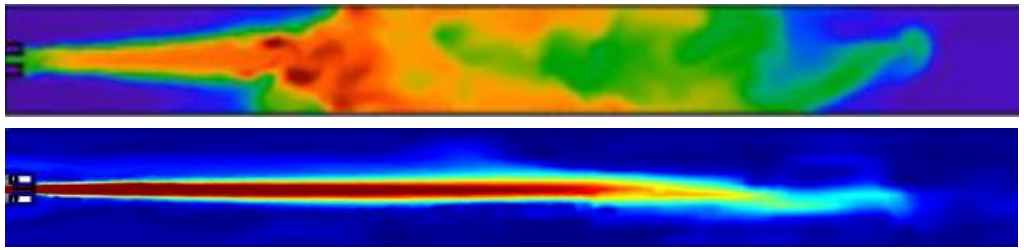


63% were Injectables

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







Drug Products Containing Nanomaterials - Research

- CDER maintains a robust research profile in the area of drug products containing nanomaterials
  - Internal projects
  - Extramural projects
  - Collaborations

- Research may focus on a product, class, or general questions surrounding nanomaterials in drug products
  - Quality considerations (e.g., characterization)
  - **Emerging technologies**
  - Pharmacology/Toxicology
  - Equivalence of complex drug products

Several research grants (e.g., via **Broad Agency Announcement, BAA**) were awarded to understand the technical challenges associated with continous manufacturing of nanomaterials, which also facilitates the responsible development and adoption of innovative technologies.

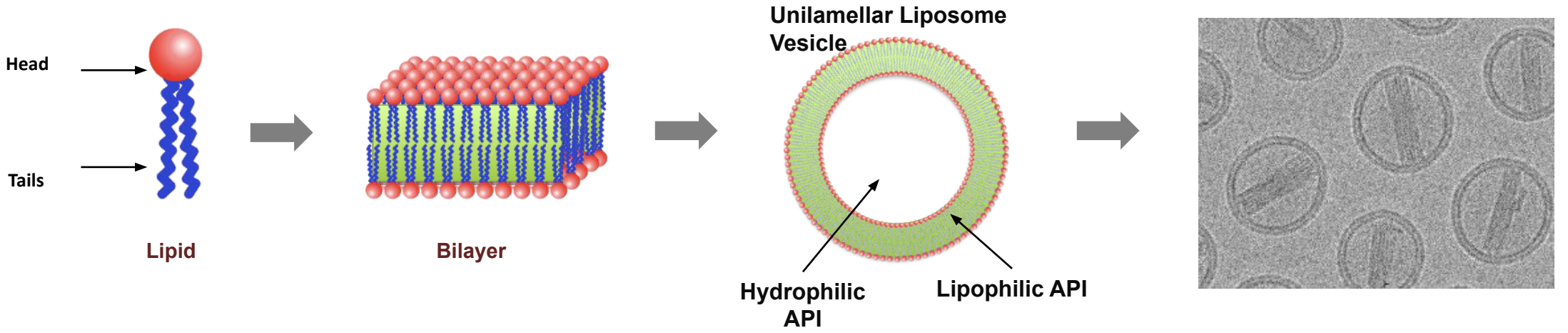
RESEARCH EXAMPLE

Extramural Research

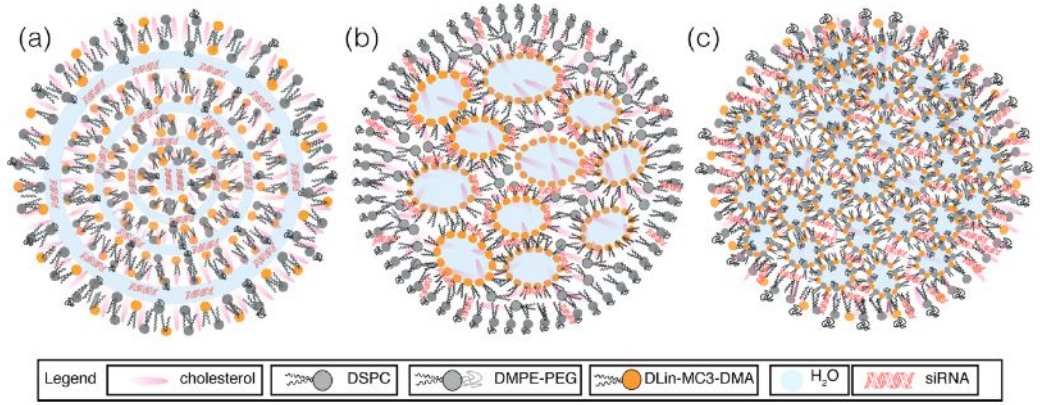
BAA and U01 grant#

1) HHSF223201310117C
2) HHSF223201610105C
3) 75F40120C00201
4) 1U01FD005773
5) 1U01FD006975

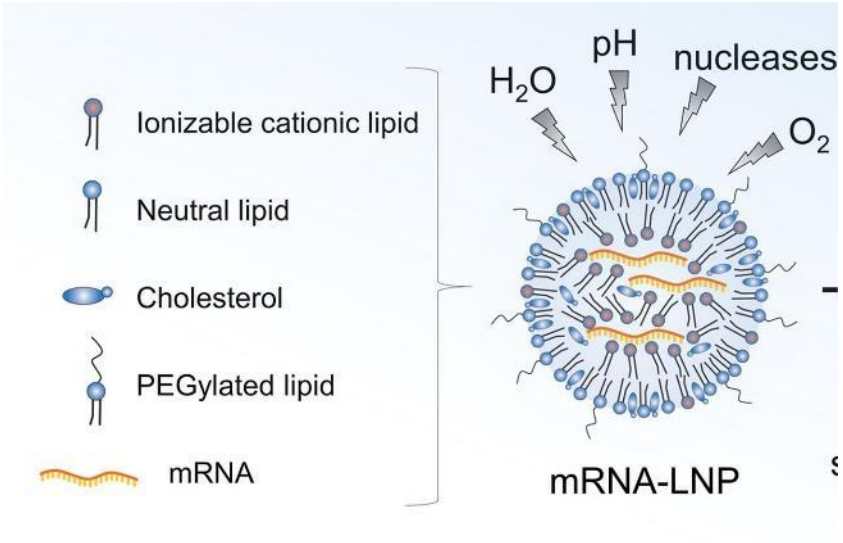
Liposomes and Lipid Nanoparticles



Scheme 1. Cartoon Diagrams of Three Models for LNP Structures[a]



[a](a) Multilamellar vesicles (onion), (b) nanostructure core, and (c) homogeneous core shell.



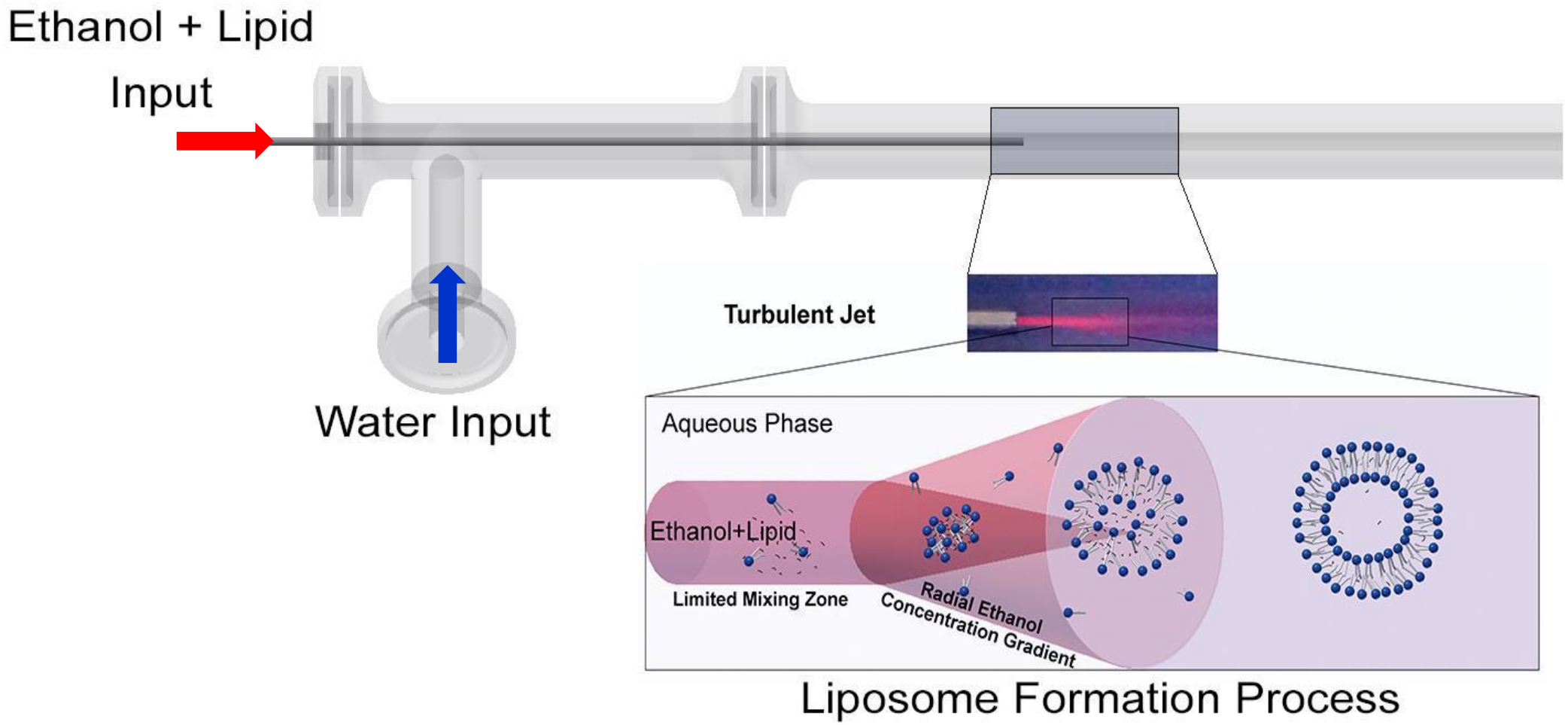
http://dx.doi.org/10.1021/acs.jpcb.7b10795

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

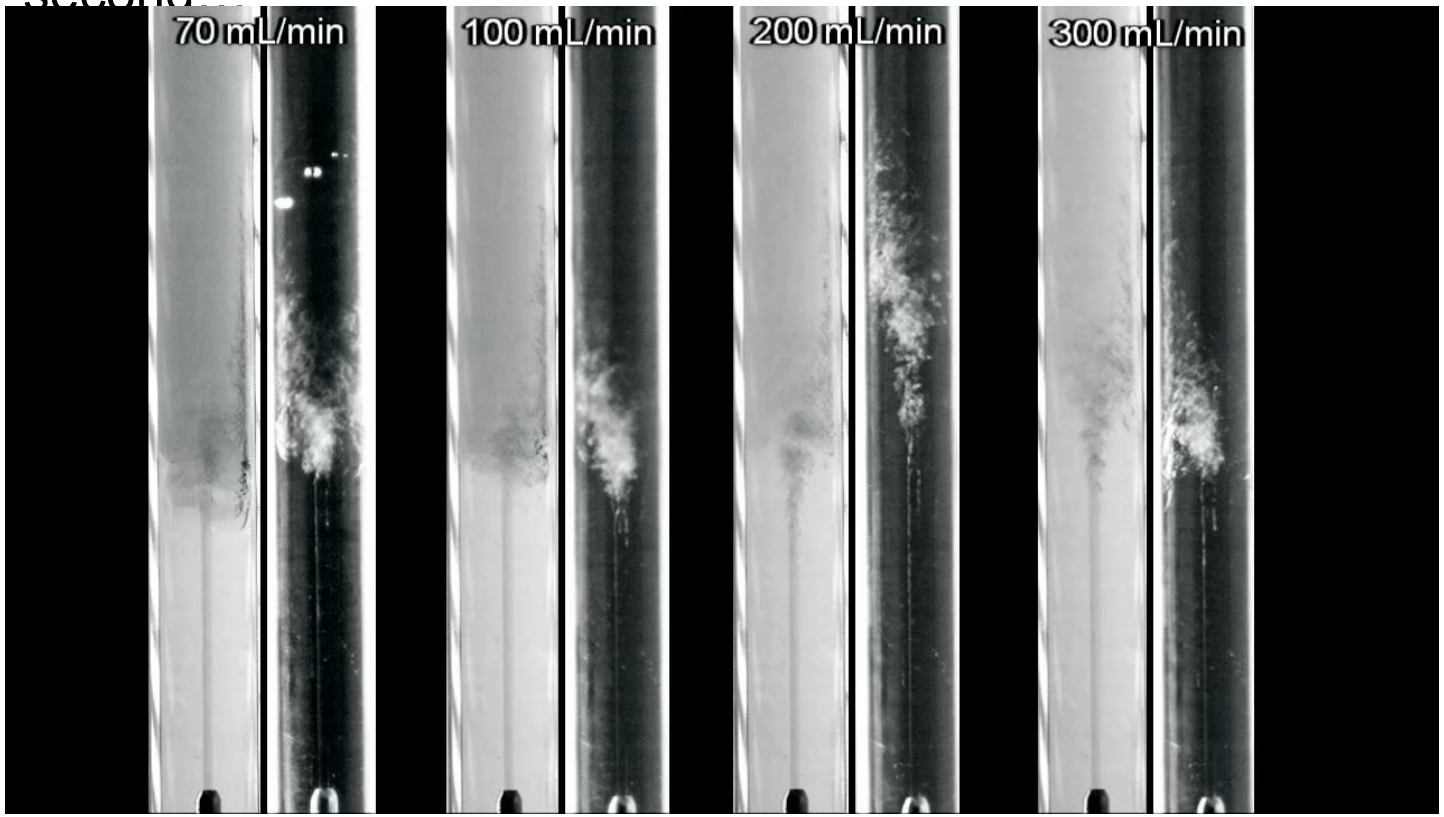
CM Enables One-step Unilamellar Liposome Formation

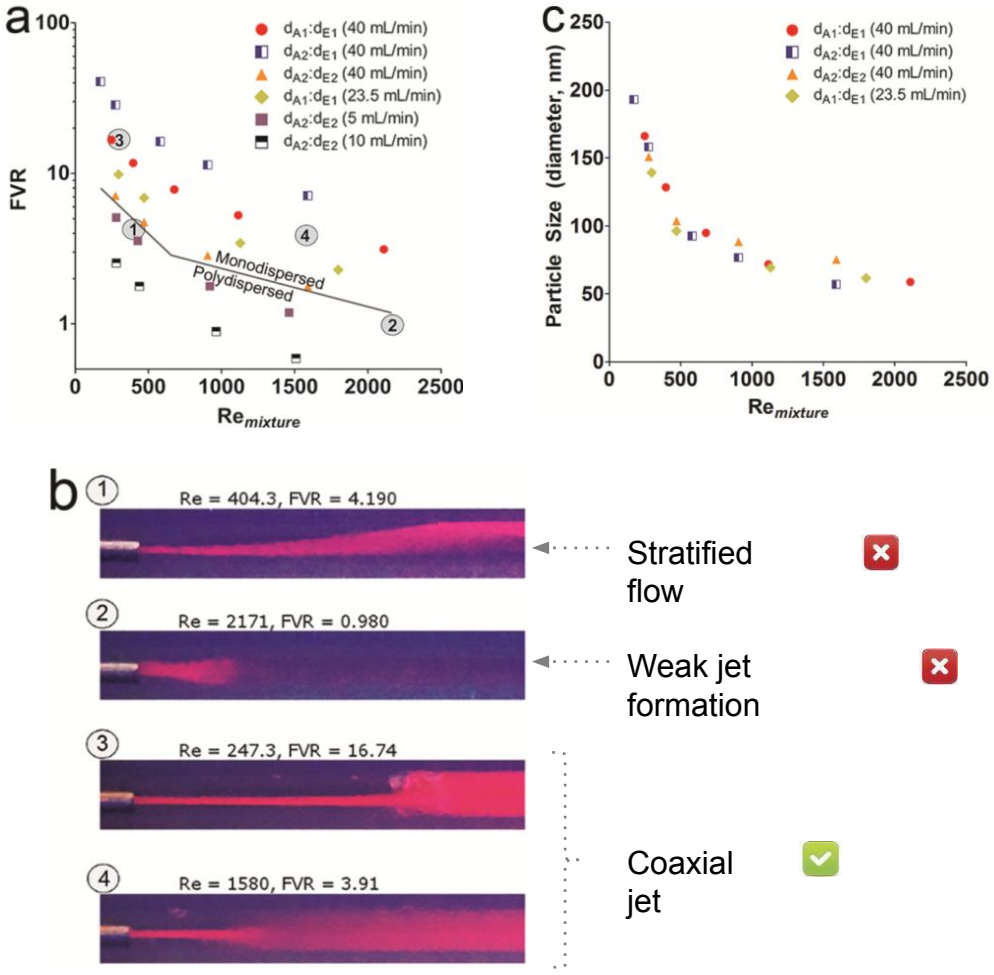


A.P. Costa, X. Xu, M. Khan, D.J. Burgess. Liposome Formation using a Coaxial Turbulent Jet in Co-Flow. Pharmaceutical Research. (**2015**), 33 (2), pp. 404-416.

High-Speed Camera: Jet Formation

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

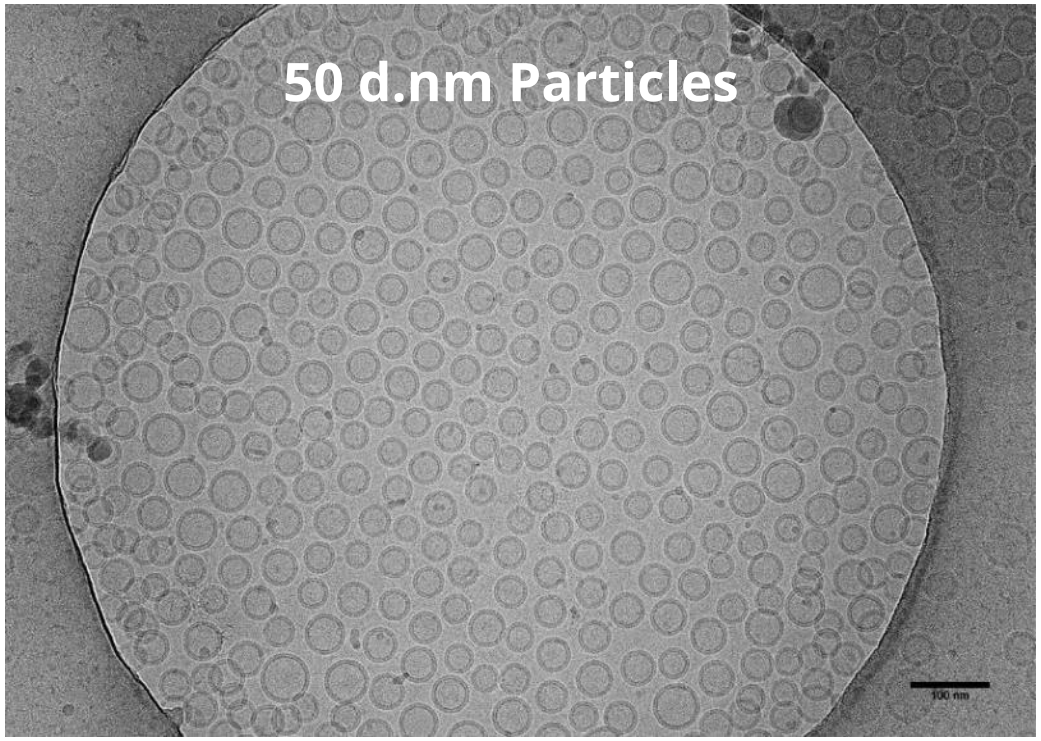


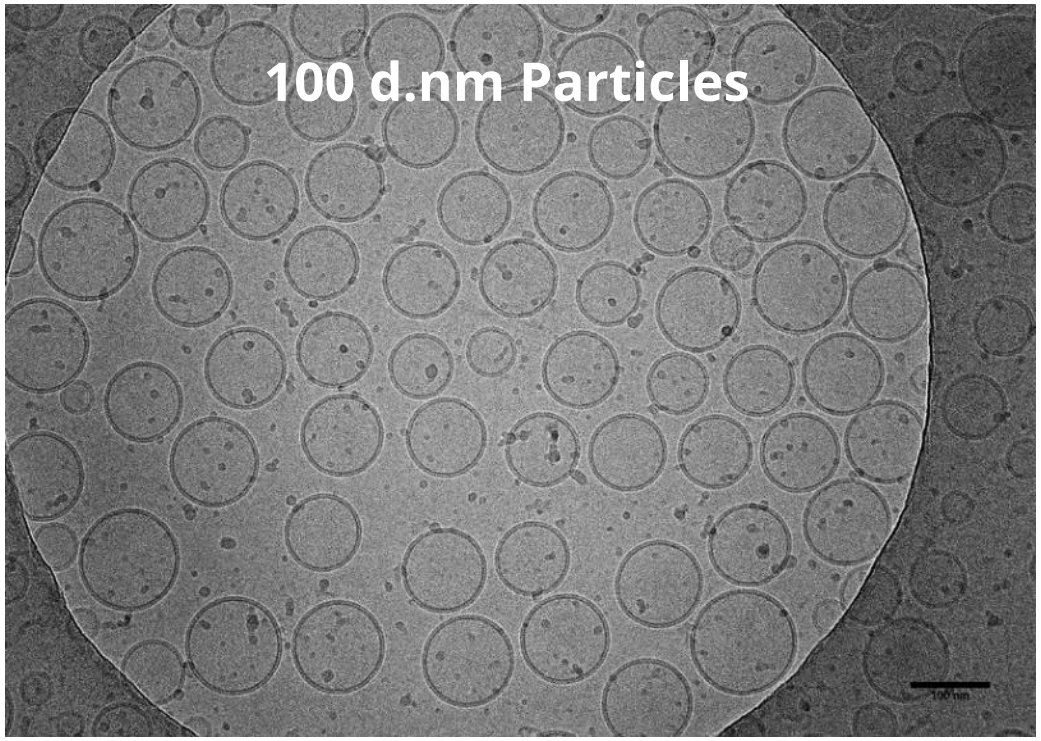


A.P. Costa, X. Xu, M. Khan, D.J. Burgess. Liposome Formation using a Coaxial Turbulent Jet in Co-Flow. Pharmaceutical Research. (**2015**), 33 (2), pp. 404-416.

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

Improved Precision and Robustness





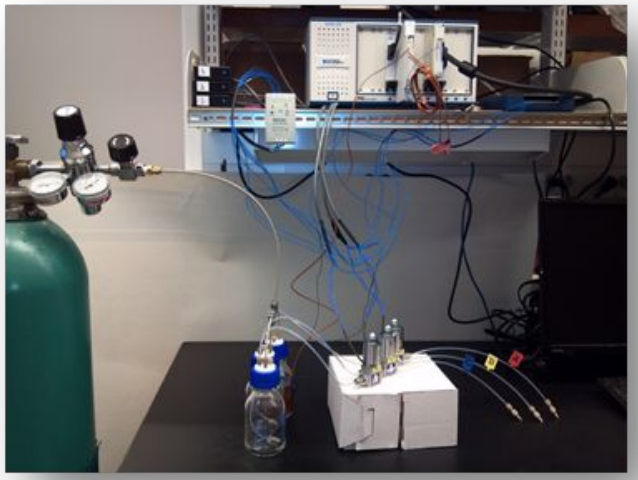
Sample ID	Z-Average (d.nm)	±	PDI	±
50 nm	50.1	0.3	0.029	0.015
100 nm	97.6	0.7	0.047	0.019

* Measured by Dynamic Light Scattering

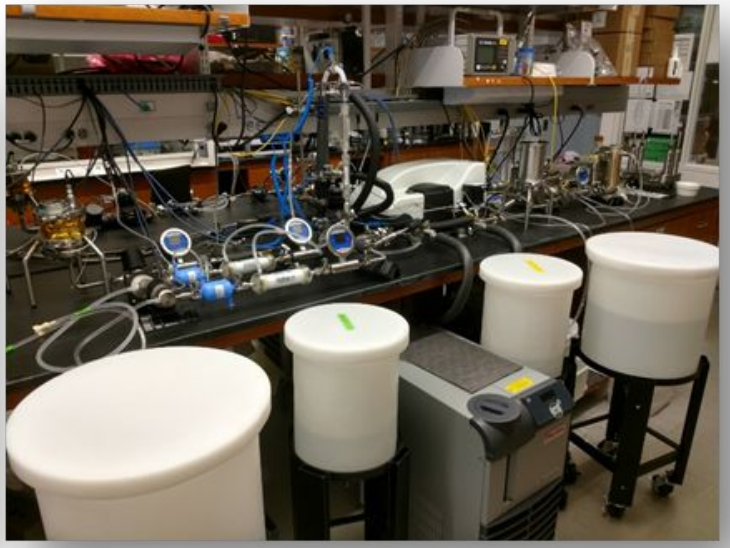
Yenduri, G., et al. "Impact of critical process parameters and critical material attributes on the critical quality attributes of liposomal formulations prepared using continuous processing." International Journal of Pharmaceutics, 619 (2022): 121700.

Concept to Production: CM Development Journey

2014



2018

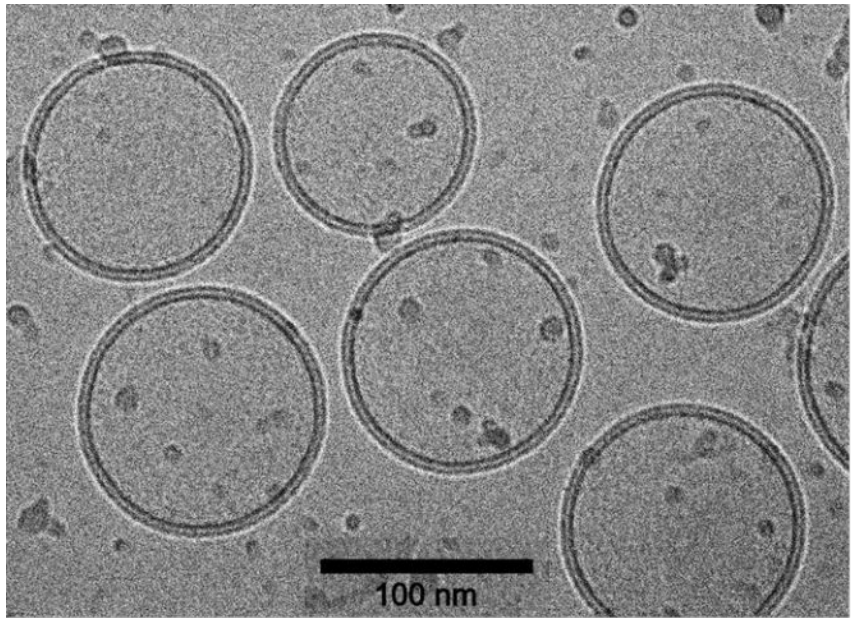


2022

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

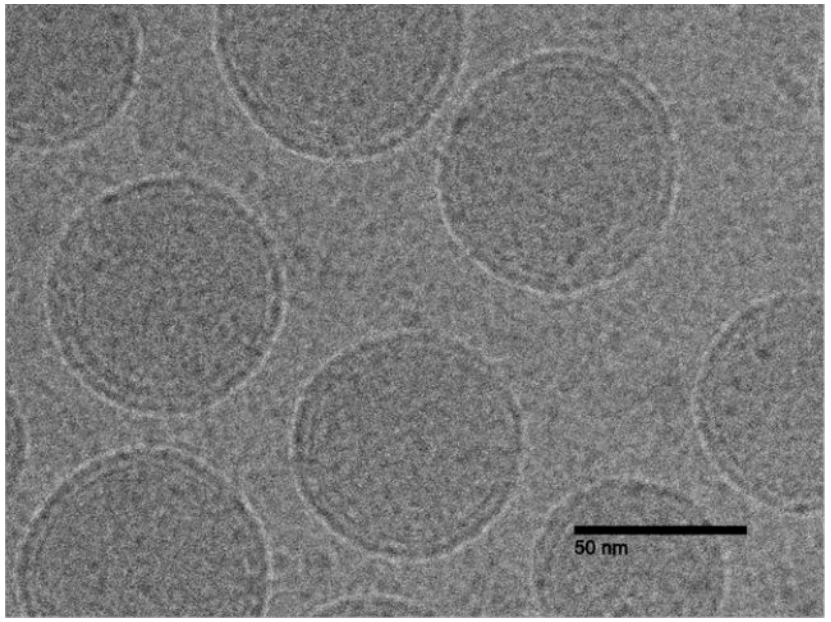
One CM System, Multiple Nanoparticles

Liposomes



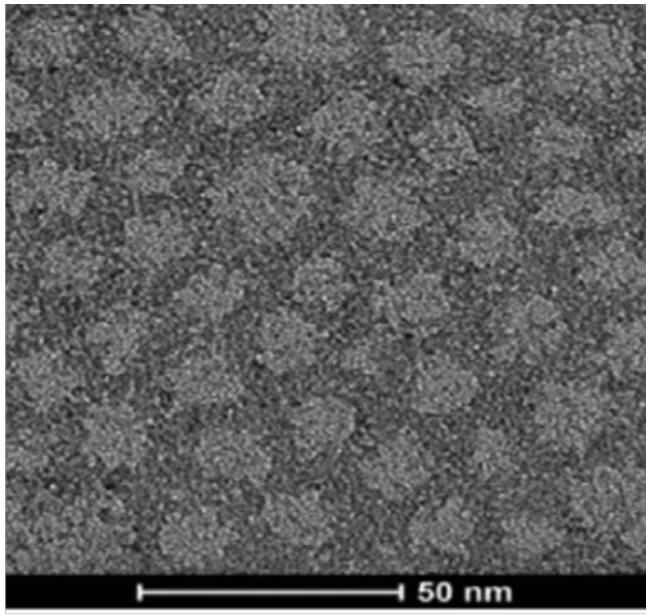
Bilayer Structure
Aqueous Core

Lipid Nanoparticles



Outer Lipid Layer
Aqueous/Lipid/Nucleic Acid Core

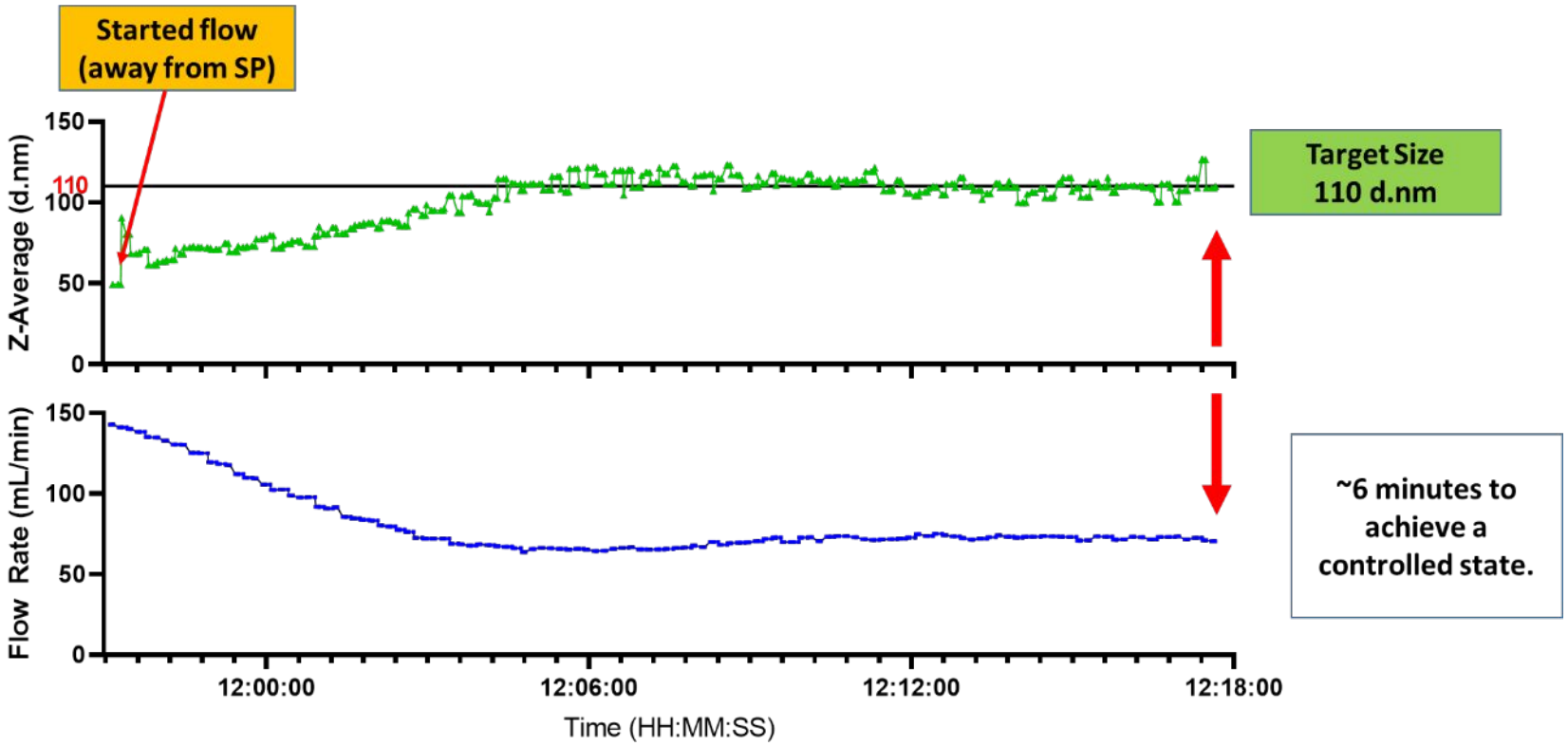
Polymeric Micelles



Block copolymer
Hydrophobic Core

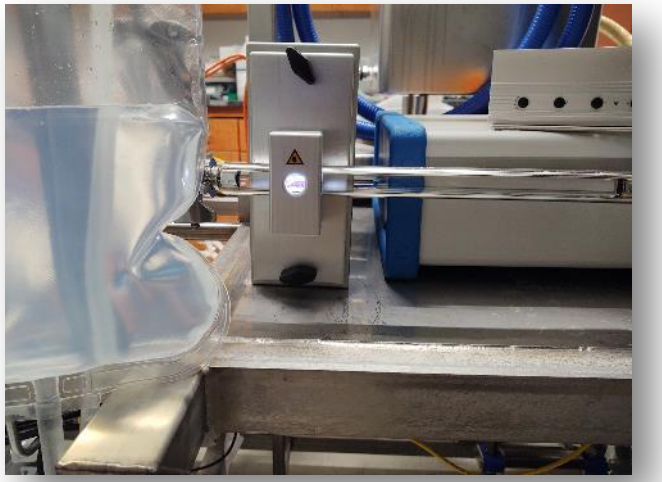
- Yenduri, G., et al. "Impact of critical process parameters and critical material attributes on the critical quality attributes of liposomal formulations prepared using continuous processing." International Journal of Pharmaceutics, 619 (2022): 121700.
- Gupta, A., et al. “Continuous processing of paclitaxel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

Enables Automated Process Control



NanoFlowSizer

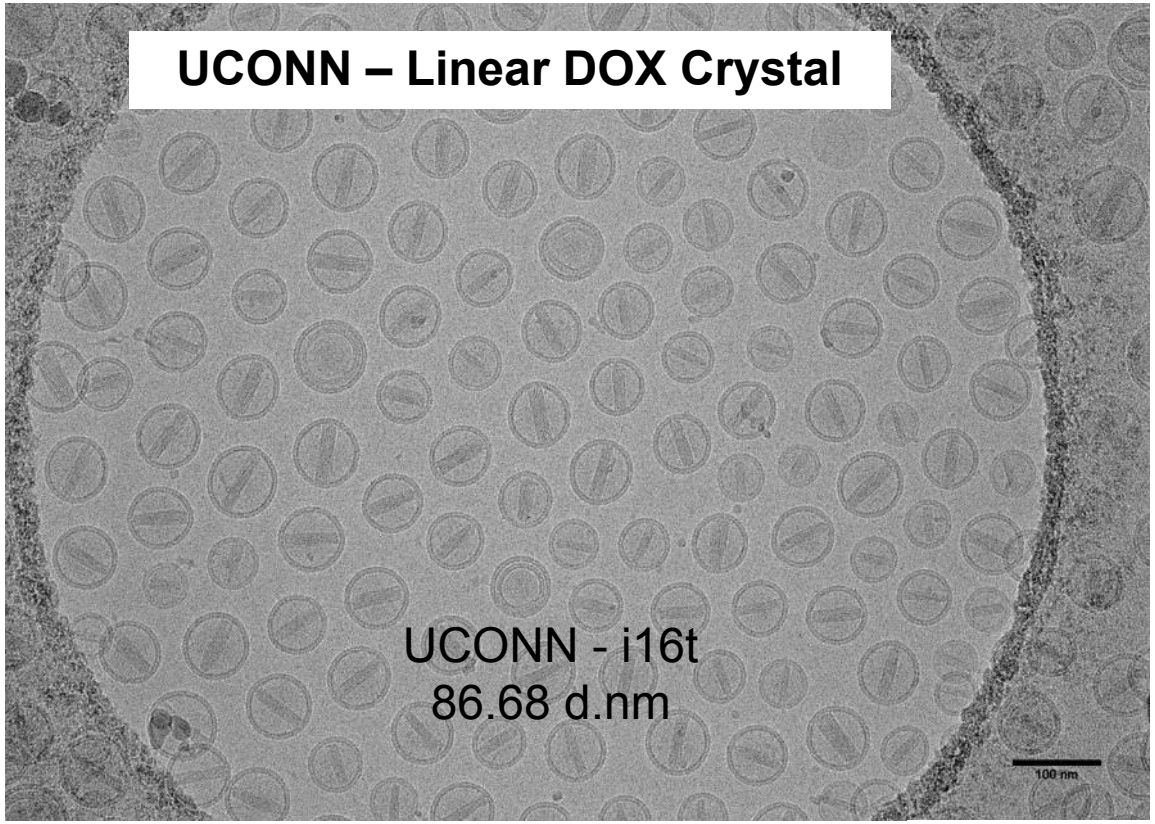
Spatially-Resolved DLS

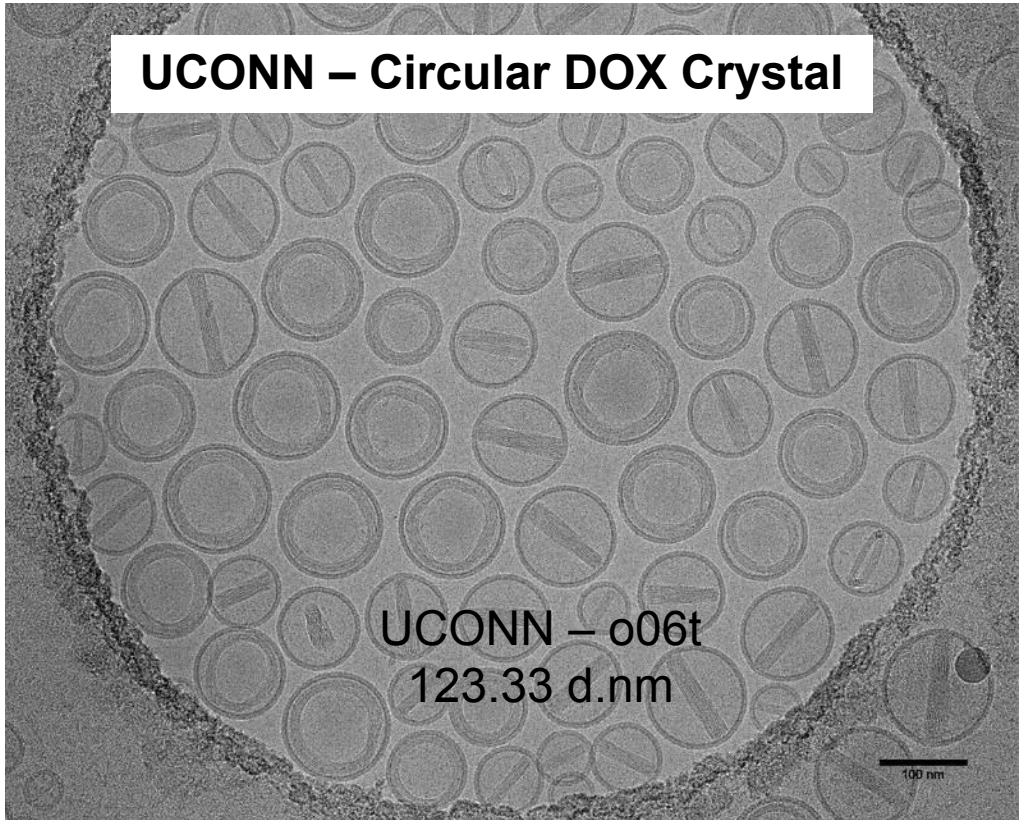


Example 20 Liters of Liposomes at 20 mM lipid conc. (about 3 hrs run)

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

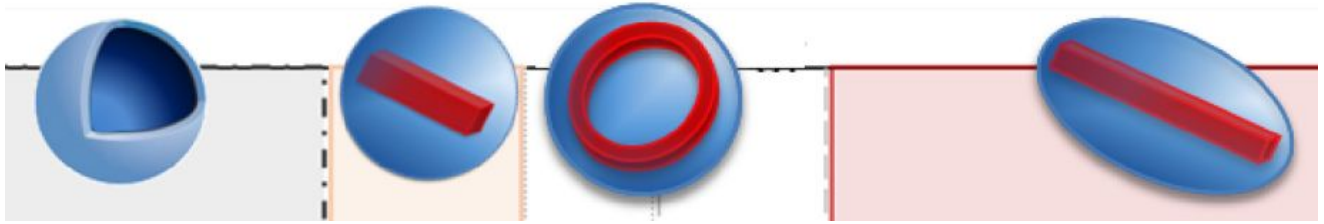
Does Shape Matter?





Two types:

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



Modeling and Simulation to Enhance Process Understanding

Coarse-Grained Molecular Dynamics Simulation

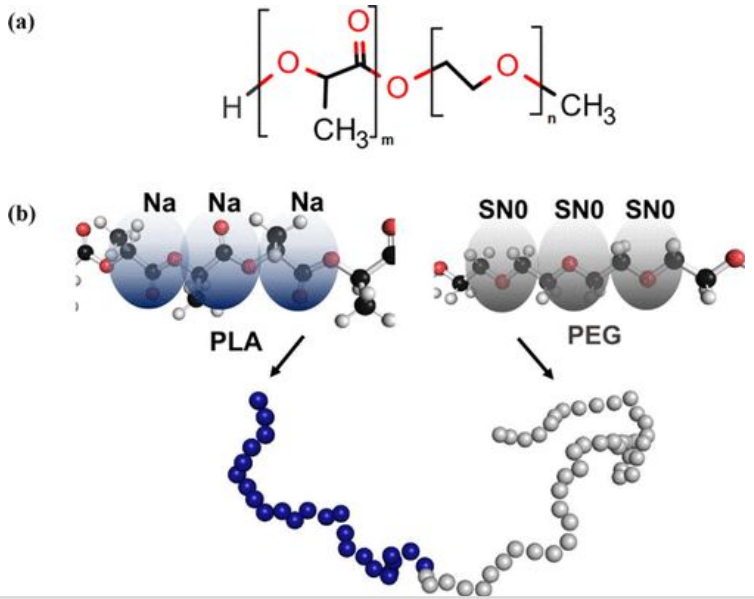


Figure 1. (a) Chemical structure of PEG–PLA and (b) correspondence between the AA and CG (MARTINI) models of PEG–PLA.

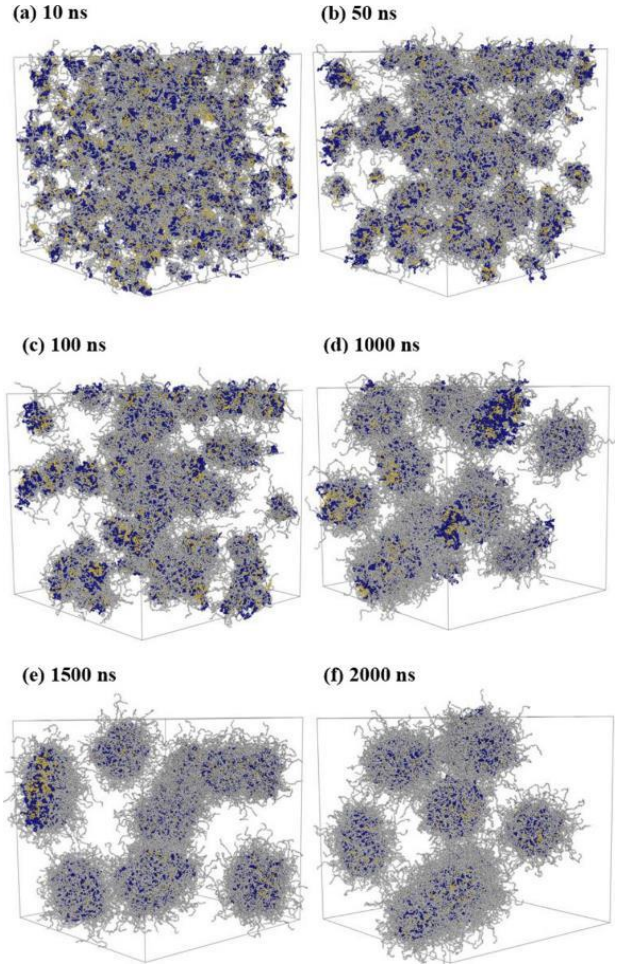


Figure 2. CG-MD simulation results of loading of the drug (paclitaxel) into PEG-PLA polymeric micelles over the course of 2000 nanoseconds

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

1. S. Sansare, et al. Artificial Neural Networks in Tandem with Molecular Descriptors as Predictive Tools for Continuous Liposome Manufacturing. International Journal of Pharmaceutics (2021), 603, 120713, https://doi.org/10.1016/j.ijpharm.2021.120713
2. T. Duran, et al. Coarse-grained Molecular Dynamics Simulations of Paclitaxel-loaded Polymeric Micelle in Continuous Manufacturing. Molecular Pharmaceutics (2022), https://doi.org/10.1021/acs.molpharmaceut.1c00800

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.

Acknowledgement

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- Gowtham Yenduri
- Tibo Duran


FDA
U.S. FOOD & DRUG
ADMINISTRATION