



# Digital Process Design for Nanoparticle Manufacturing

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# Modeling and Simulation Toolbox

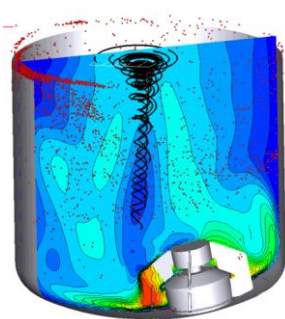
## Fluid Flows

CFD (Computational Fluid Dynamics)

Spray drying



Mixing



Fluidized Bed

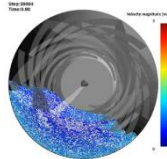


Software: AVL-FIRE®  AVL FIRE®  
OpenFOAM, ANSYS Fluent 

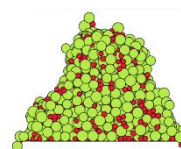
## Particle Flows

DEM (Discrete Element Method)

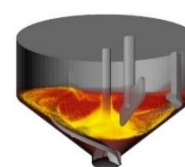
Coater



Cohesive Materials



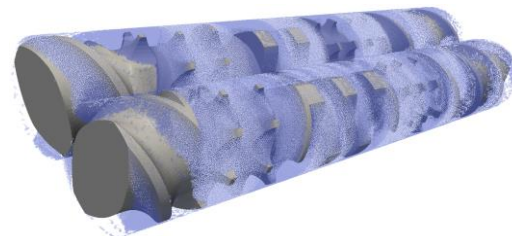
Blender/Mixer



Software: 

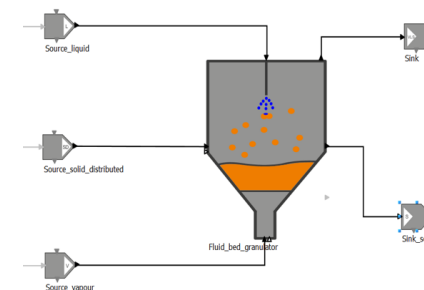
## Complex Fluids

SPH (Smoothed Particle Hydrodynamics)



Software: 

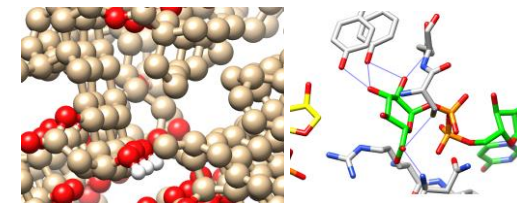
## Unit Operations



Software: gSOLIDS 

## Molecular Modeling

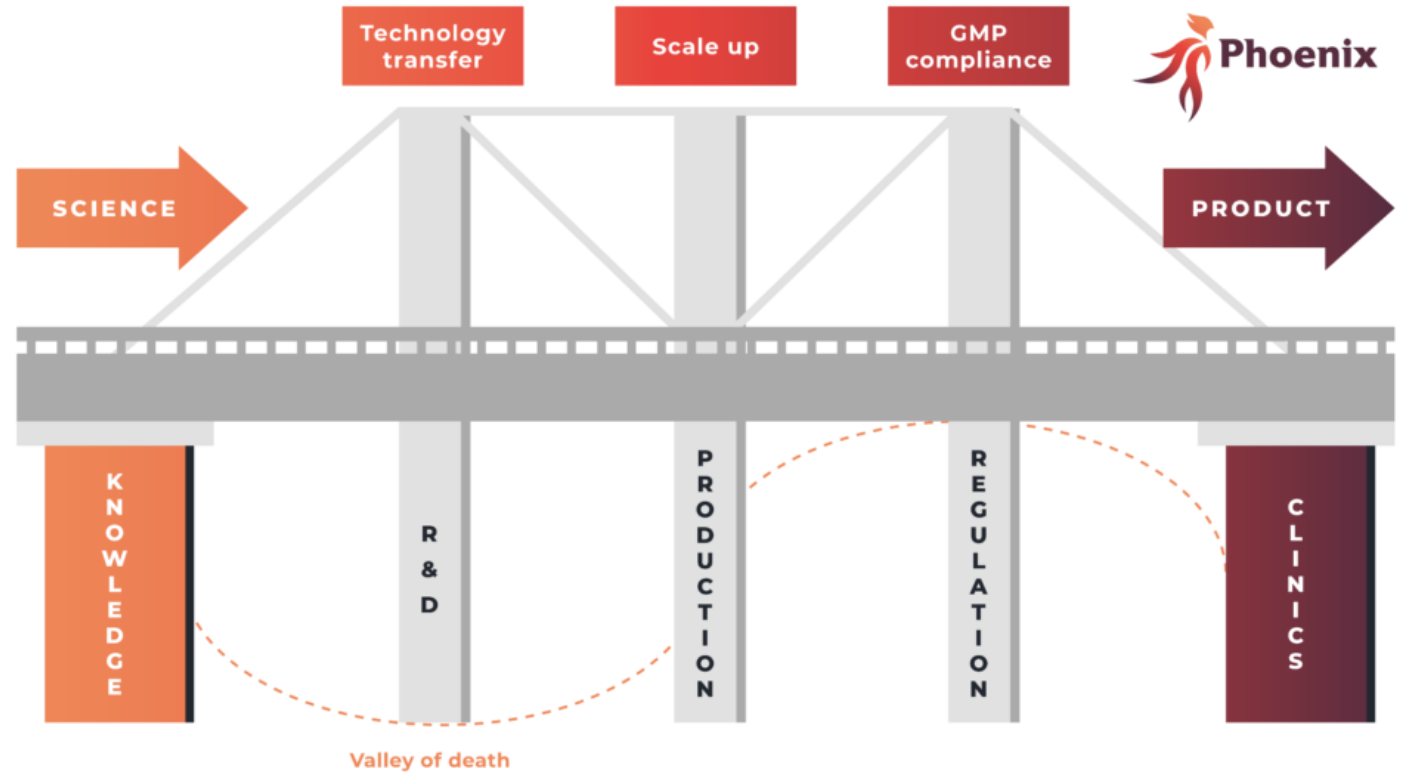
Predict stability & behavior of complex molecules (e.g., proteins)



Software: GROMACS, CP2K, ORCA

# PHOENIX OITB

Enabling Nano-pharmaceutical Innovative Products



# Our Aim within PHOENIX

## RCPE Goal

- Develop a Simulation Framework for Digital Process Design Studies

## Processes

- Nanocrystal formation (top-down)
- Nano-emulsion formation (top-down)

# Regulatory Framework

## Quality by Design (QbD)

- Accepted by regulatory agencies (ICH guidelines Q8 (R2), ...)
- Favors systematic process understanding
- “Quality by Design” instead of “Quality by Testing”

- CMAs (Critical Material Attributes)
- CPPs (Critical Process Parameters)



- CQAs (Critical Quality Attributes)

### Input

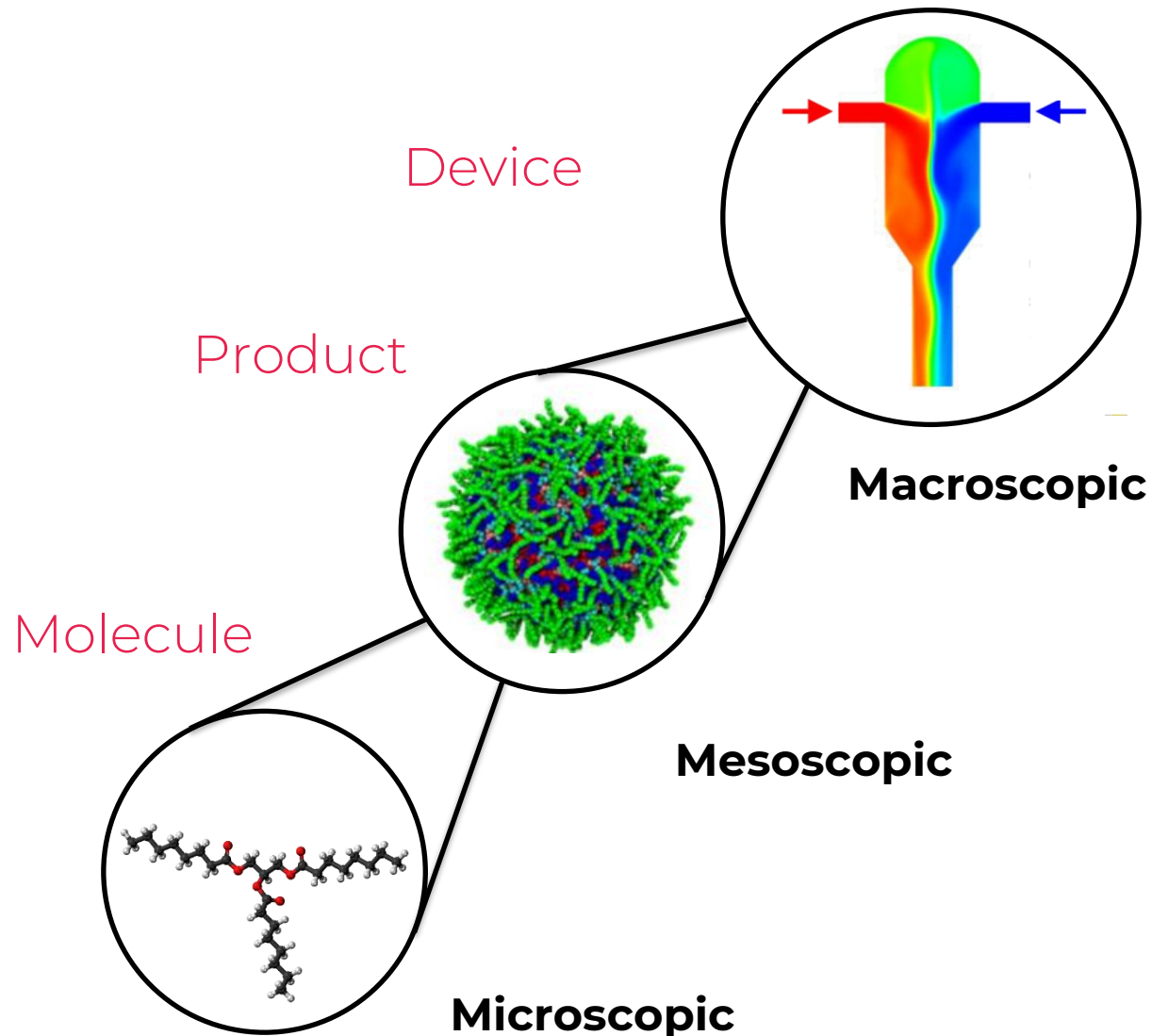
- Material Attributes
- Process Parameters



### Results

- Quality Attributes
  - Particle Size
  - Particle Size Distribution
  - Encapsulation Efficiency
  - etc.

# Multiscale Modeling of Nanoparticles

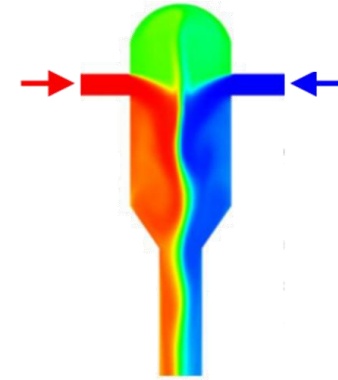


- Flow rates
- Pressure
- Temperature
- Composition

- Particle formation kinetics
- Aggregation kinetics
- Assembly kinetics
- Break-up kinetics, dispersion kinetics

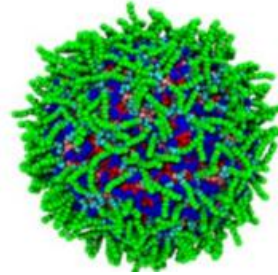
- Physico-chemical properties

# Simulation Methods



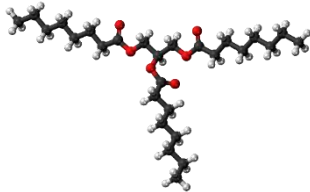
Device-scale  
Computation

- Computational Fluid Dynamics (CFD)
- Discrete Element Method (DEM)
- Smoothed Particle Hydrodynamics (SPH)
- Finite Element Method (FEM)



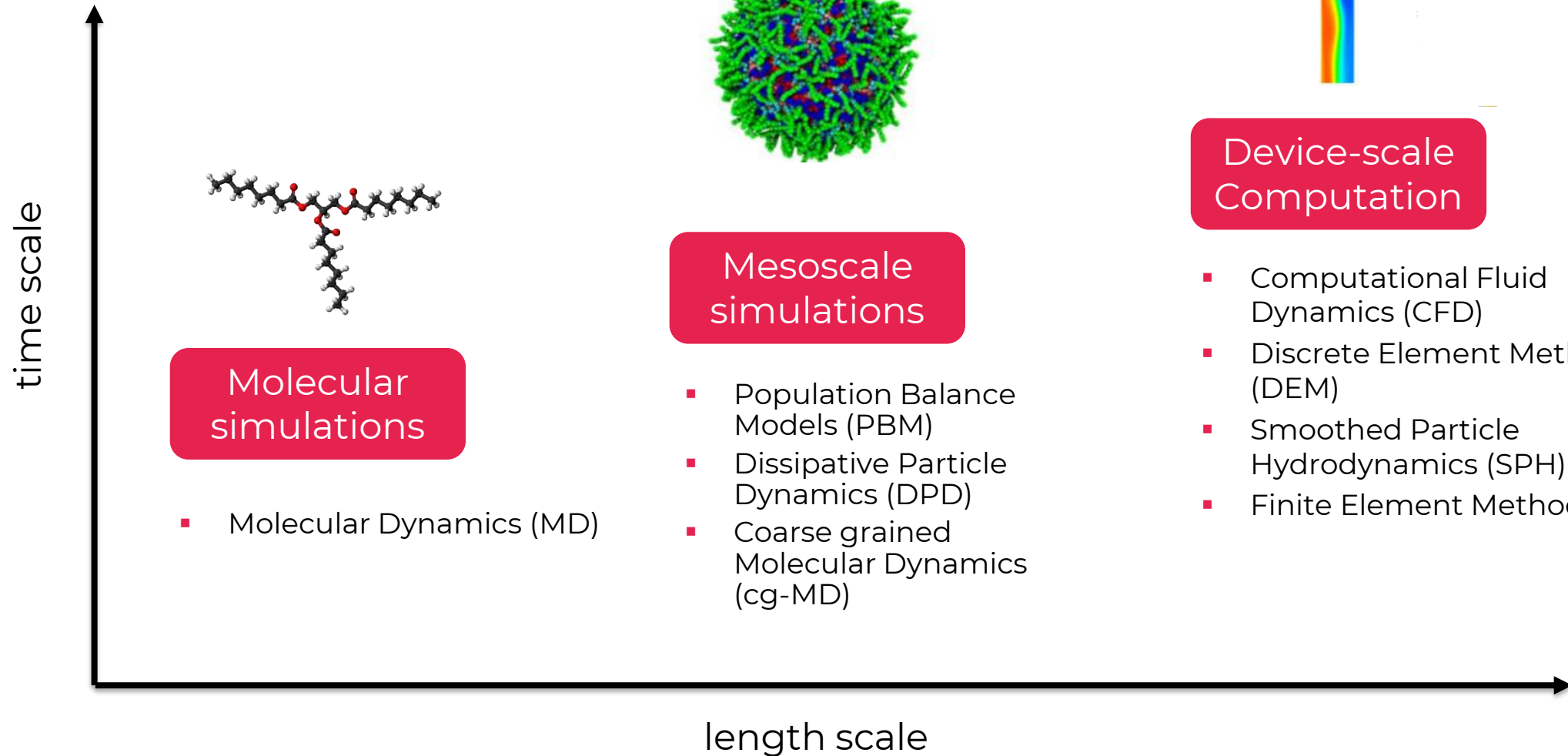
Mesoscale  
simulations

- Population Balance Models (PBM)
- Dissipative Particle Dynamics (DPD)
- Coarse grained Molecular Dynamics (cg-MD)



Molecular  
simulations

- Molecular Dynamics (MD)



# Benefits of a Simulation Model

- Demonstrates fundamental understanding of complex systems
- Digital magnifying glass
- Prediction of target quantities
- Narrow-down design space
- Results in reduced uncertainty/risk
- Results in improved quality
- Brings nanopharmaceuticals faster to the patient
- Valid over the entire product life-cycle



# Challenge: Disperse Multiphase Systems

## Process scale

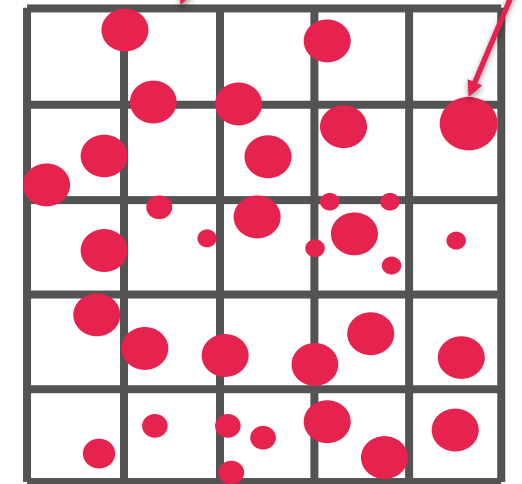
- Computational cells larger than particle size
- Keeping track of the fate of numerous nanoparticles
- Dense regime (interactions become important)



Reality

Computational cells

Disperse phase



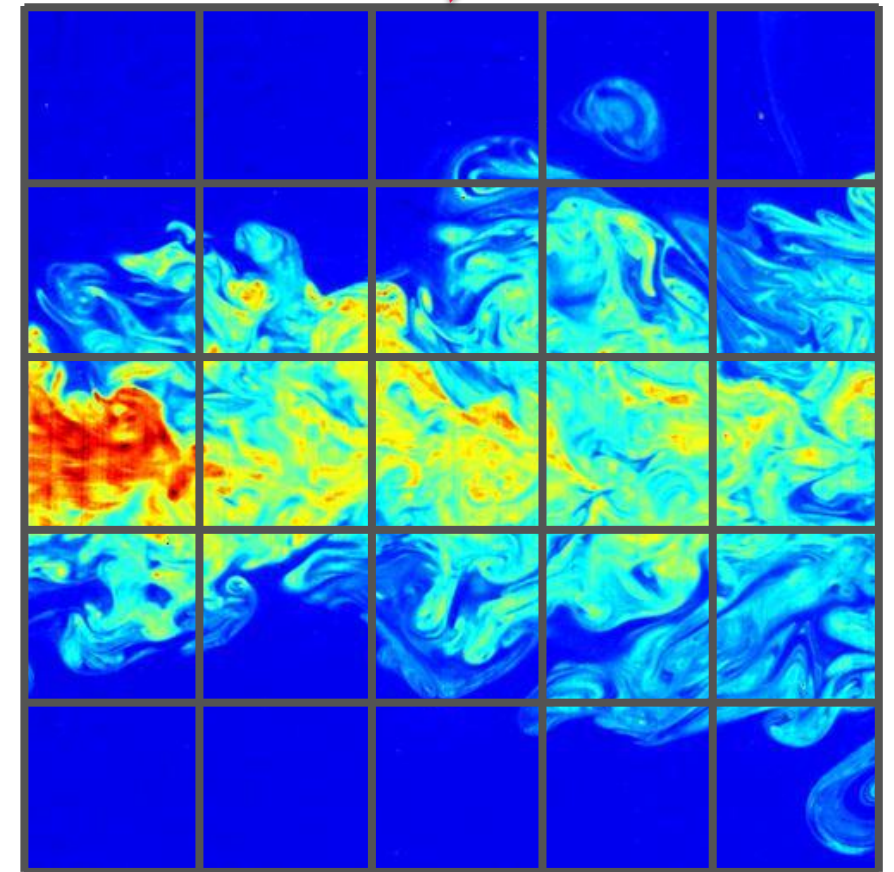
Simulation

# Challenge: Turbulence Modeling

## Process scale

- Fluid properties vary chaotically in space and time.
- Involves wide range of time and length scales
- Large number of computational cells and small timesteps
- High performance requirements for simulations (~days)

Computational cell  
(coarsened for visibility)



Flow visualization of a turbulent jet, made by laser-induced fluorescence. The jet exhibits a wide range of length scales, an important characteristic of turbulent flows.(source Wikipedia)

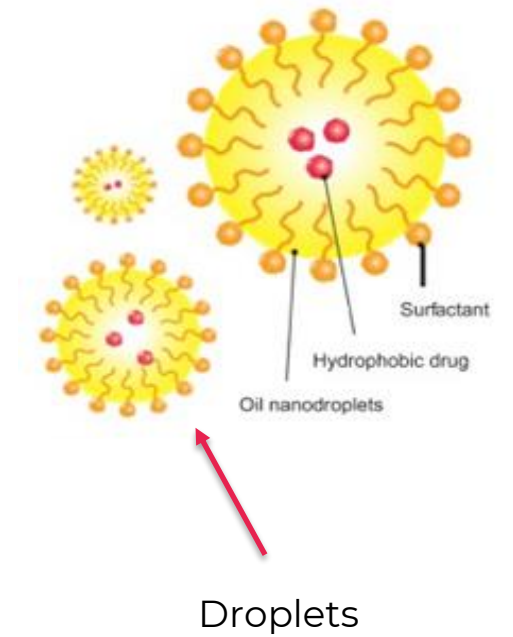
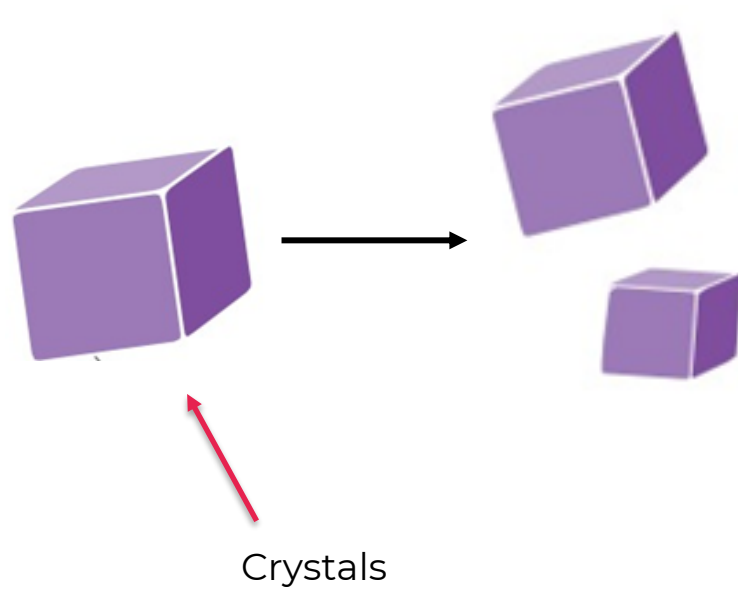
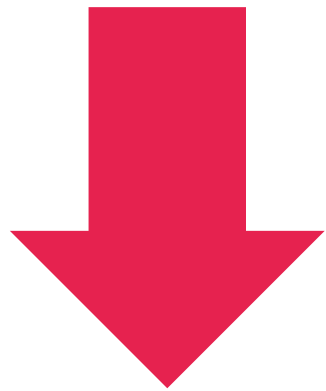
# Challenge: Formation Kinetics

Mesoscale

**Top-down**

**Breakage kinetics**

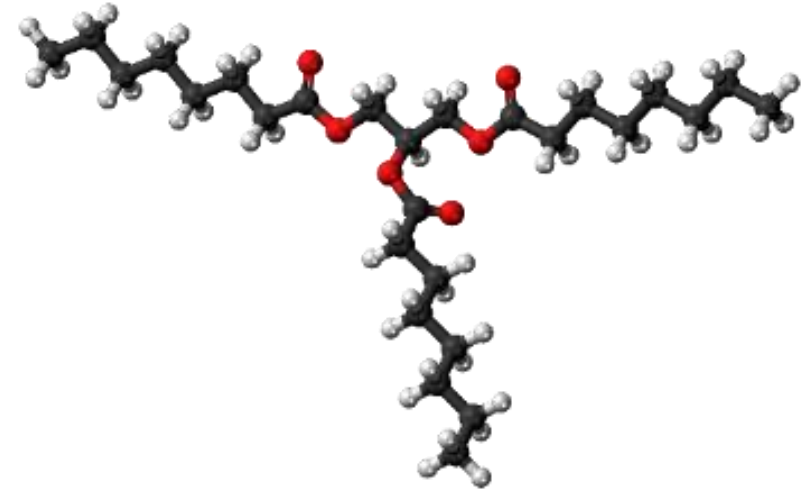
**Dispersion kinetics**



# Challenge: Physico-chemical Properties

## Microscale

- Governing equations depend on material properties.
- **Bulk properties** are often uncharacterized.
- **Interface properties** are often uncharacterized.
- Properties change with local thermodynamic state (p,T,c).



# Concluding Remarks

- Tools for integrated process and product design are available
- Multiscale phenomena
- Nanopharmaceutical-specific challenges remain
- Simulation model valid over the entire life-cycle

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