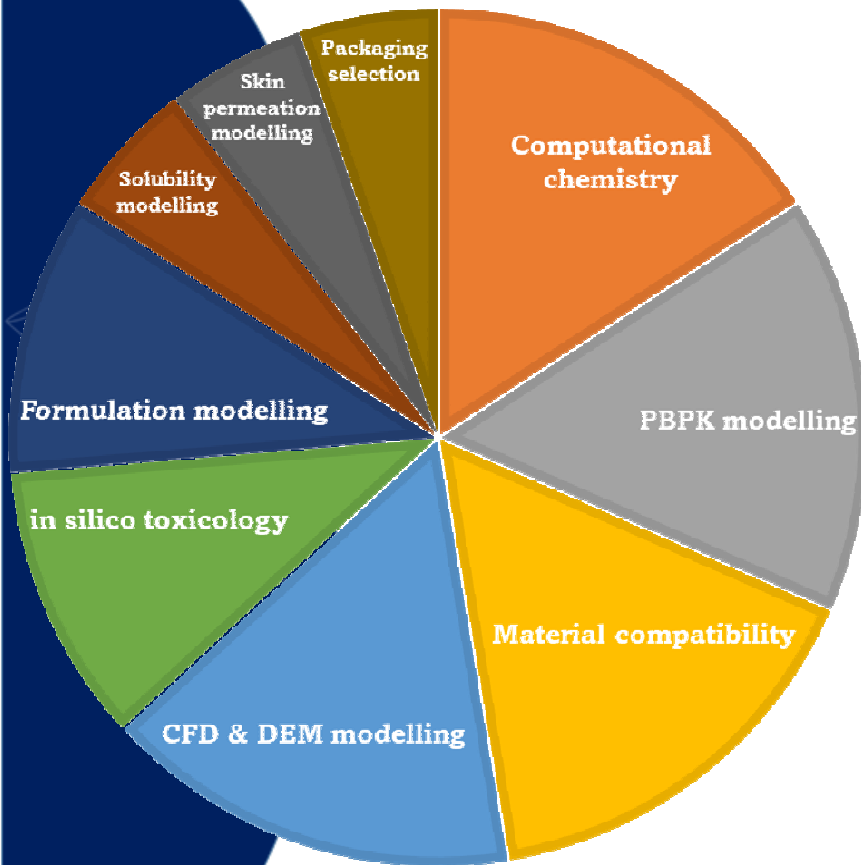
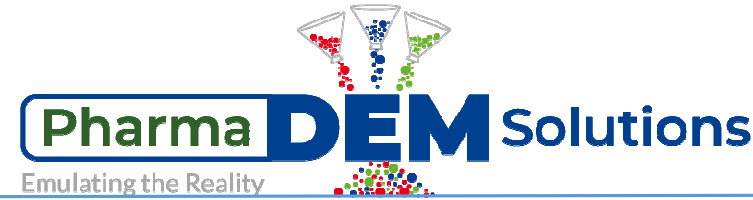




# ACCELERATING INNOVATION IN DRUG DEVELOPEMENT USING COMPUTATIONAL SIMULATIONS

Dr. Ravi P,  
PharmaDEM Solutions Pvt Ltd.

# About PharmaDEM



- PharmaDEM is a physics and chemistry modeling expert company for drug design and development
- Our vision is “Development and integration of structure & property-based simulation methods to enable drug product design & Process, with a focus on innovation-in utilizing state of the art modelling”.
- Solving critical process and formulation challenges at the interception of science, technology and health systems.

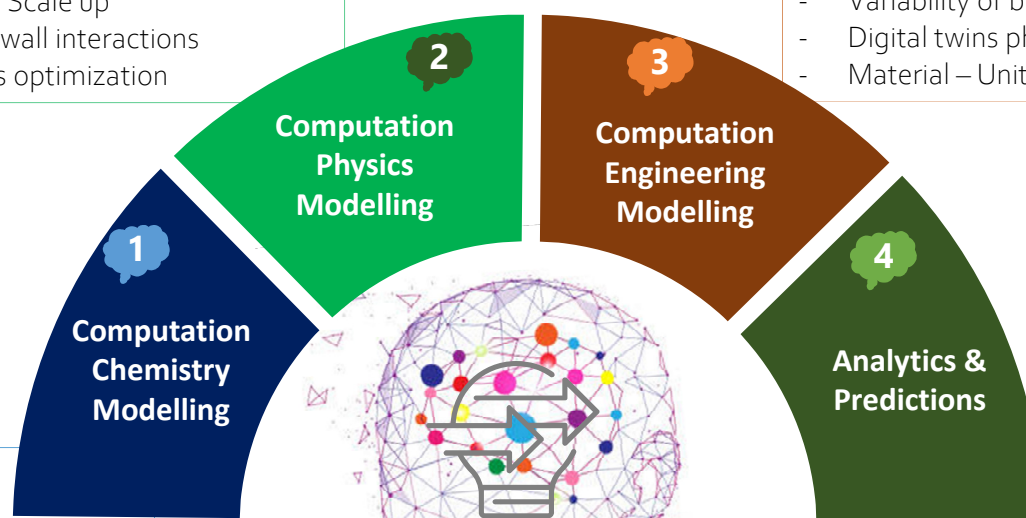
# One Stop Modelling & Simulation Solutions

## Physics computation modelling (DEM & CFD) -

- Particulate behavior. During Scale up
- Particle-particle & particle-wall interactions
- Scale-up issues and process optimization

## Engineering Simulation

- Variability of bulk flow of material
- Digital twins pharma equipment
- Material – Unit operation compatibility



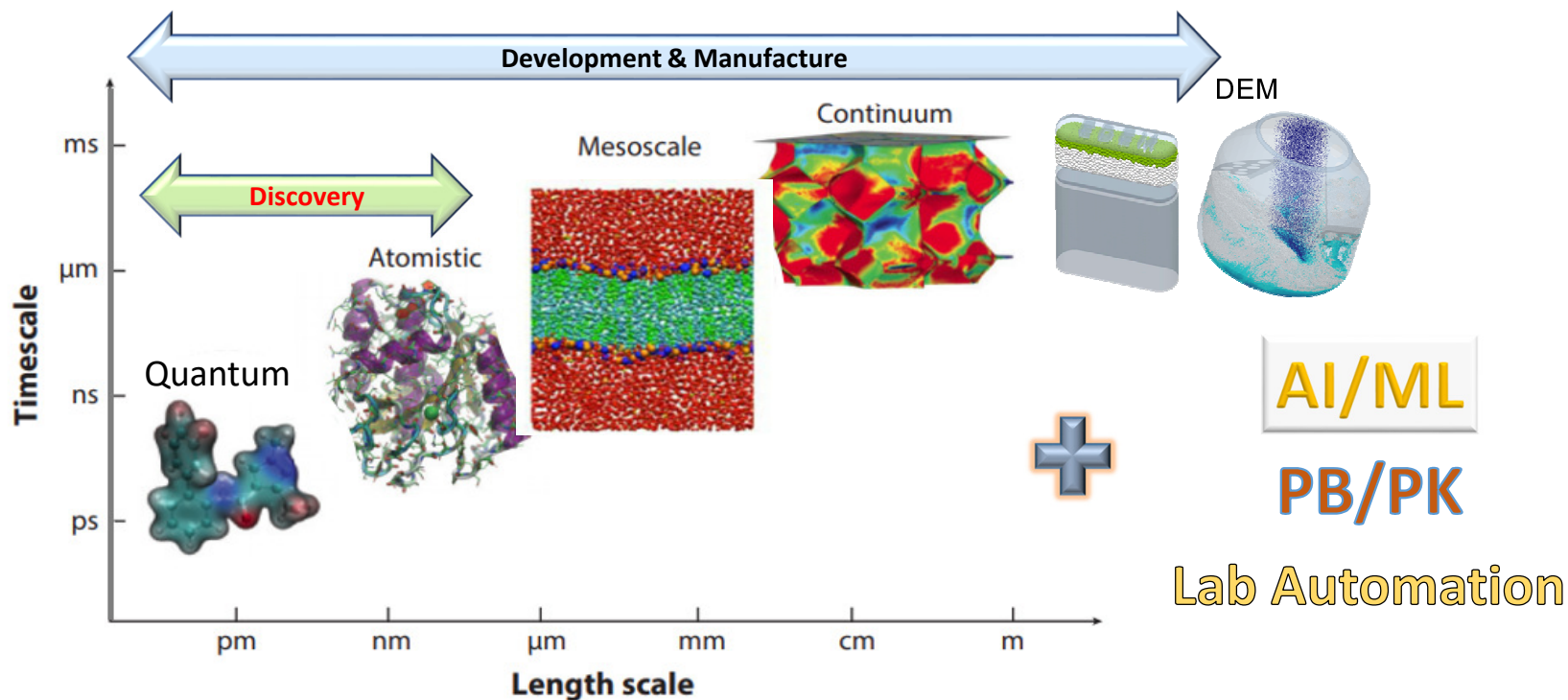
## Chemistry modelling

- Drug design
- Reaction design
- Solid state modelling
- Formulation design
- PB/PK modelling
- Toxicity, Extractables and leachable impact
- Packaging material selection

## AI based Analytics & Predictions

- Identifying and analyzing and past clinical trial events
- Custom AI/ML model for drug development
- AI/ML in VS and Drug design

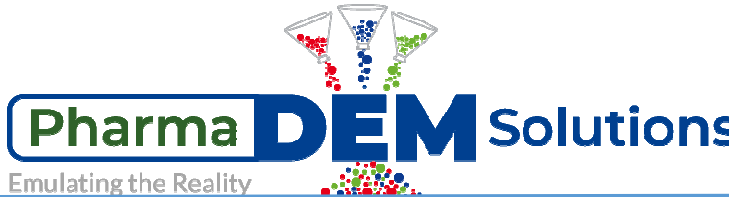
# All scales of modelling simulations\* Under one hub



- Pharma**DEM** has unique capabilities to provide all scales kinds of modelling solutions under one hub
- This enables the full integration of knowledge while product development

# Computational Modelling & Simulations

for Pharma product design and development



**Drug Design**

- ⑩ Disease to target
  - ⑩ SBDD & LBDD Screening
  - ⑩ Lead Optimisation
  - ⑩ GENOTOXIC impurity prediction
  - ⑩ Reaction safety modelling
- > Drug repurposing
    - >Hit identification
  - >API stability assessment
    - >Reaction design

**Drug Development**

- ⑩ Solid state selection
  - ⑩ API-Excipient compatibility
  - ⑩ Formulation Stability
  - ⑩ PB/PK modelling
  - ⑩ Packaging material selection
- > Polymorph screening
  - > Excipient-Unit operations
  - >Formulation optimisation
  - > Skin permeability prediction
  - > Mixing modelling

**Process development**

- Optimization of process
- Micro dynamics of powder particles
- Clear understanding of process
- Yield improvement
- CFD, Digital twins, DEM

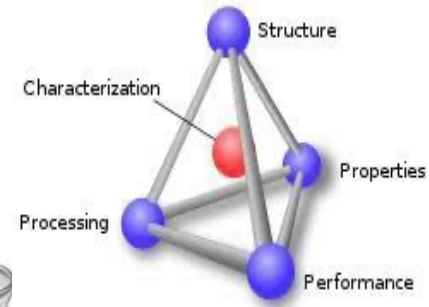
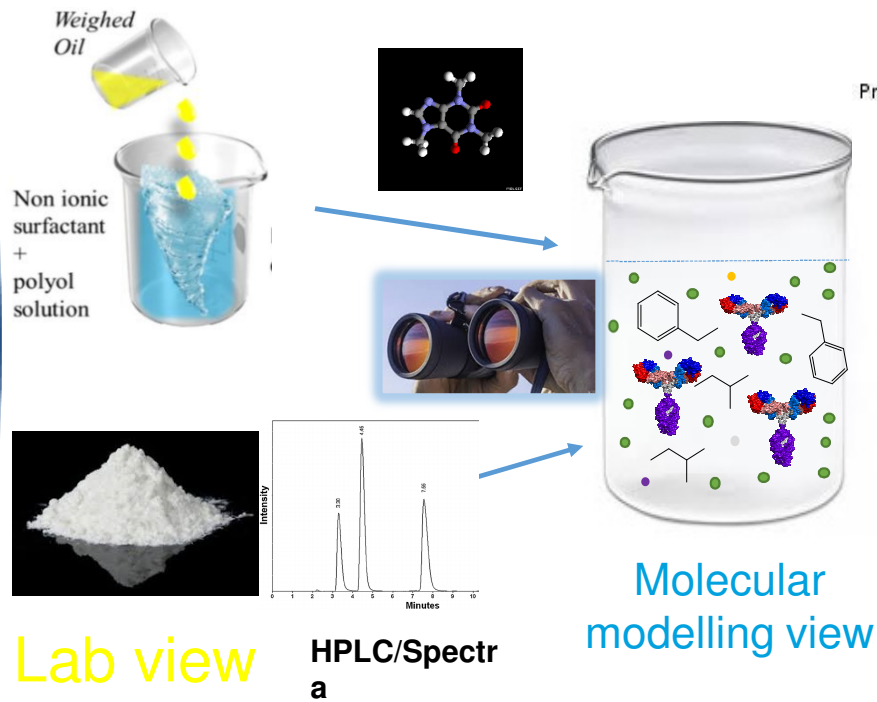


# CHEMISTRY MODELING



# CHEMISTRY MODELING

## Looking into molecules



**Material Interaction & Characteristics**

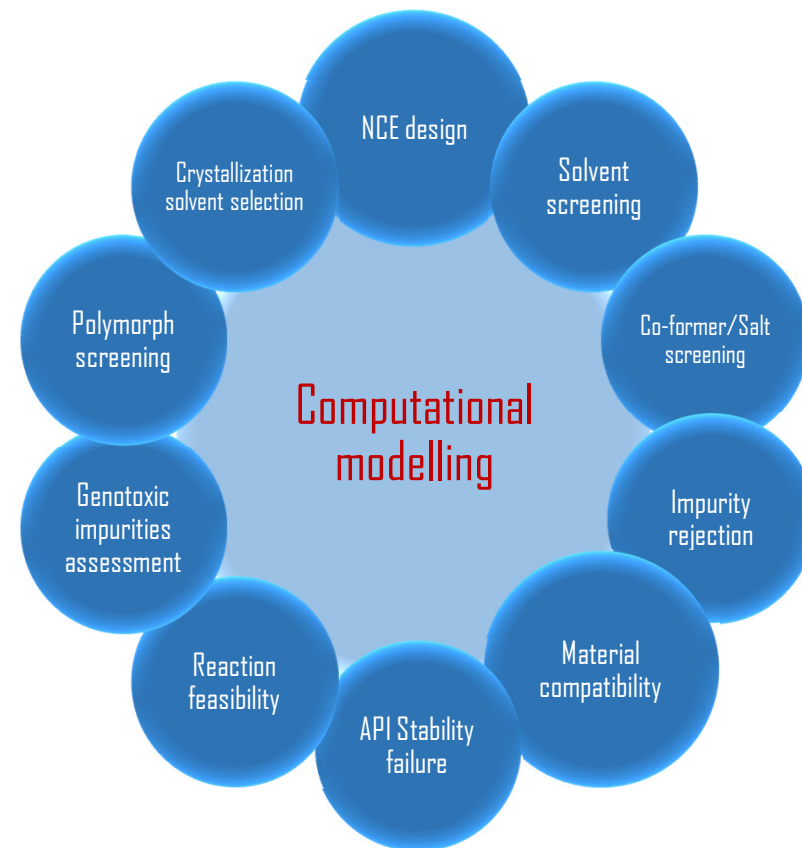
**Stability Shelf life**

- Atomistic level description and mimic the behaviour of molecules.
- Simulating the molecule behaviour with the equations of quantum and classical physics
- Optimise the solutions at molecular level to have full control on formulation chemistry

# in silico Reaction design & process development

## in silico modelling for API & process:

- Process safety & Predicting Heat of reaction
- in silico toxicology assessment for impurities
- API Yield improvement
- Form stability assessment
- Multi scale Reaction modelling & feasibility analysis
- Reactors and materials compatibility
- API-chemistry modelling:
  - Polymorph screening; API-Salt screening
  - Impurity rejection
  - Solvents, conditions for crystallisation
- Solvent swap – distillation modelling



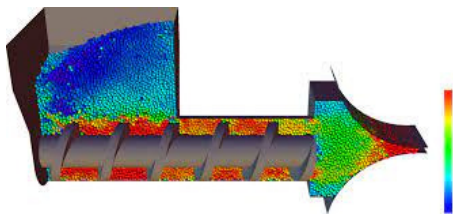
\*All models are proprietary to PharmaDEM



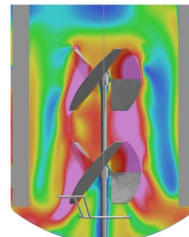
# Umbrella of Formulation & process models

9

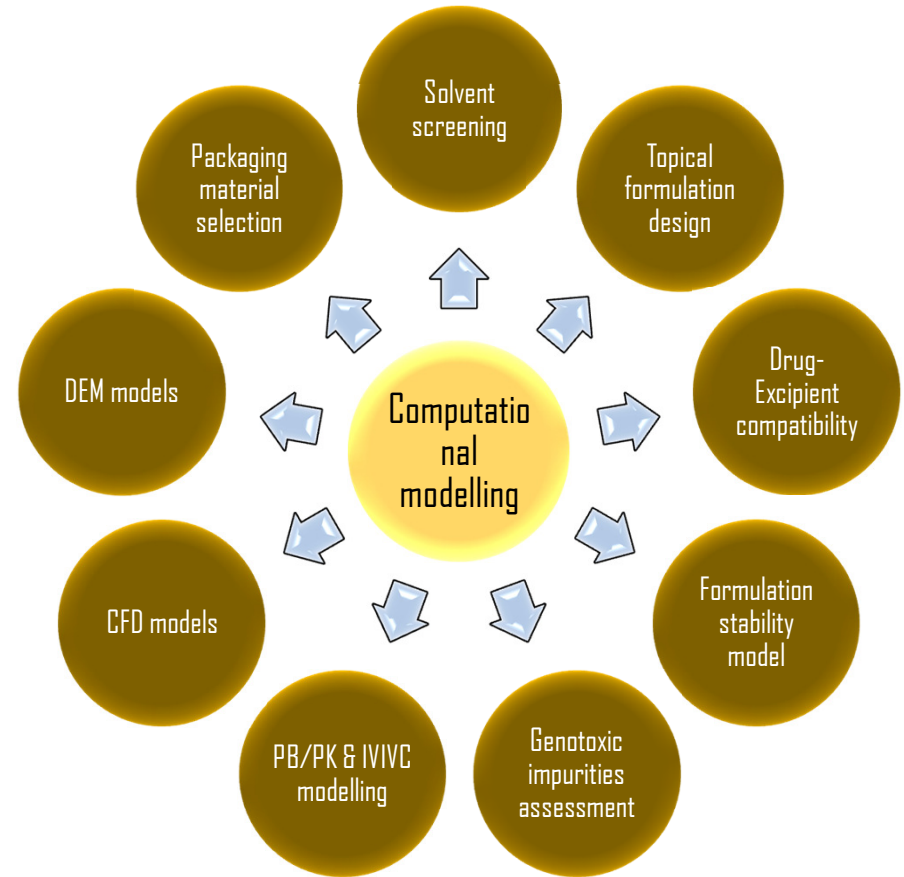
- Excipient's selection
- Formulation stability assessment
- Formulation optimisation
- Mixing calculations at CFD and DEM modelling
- Coarse grain modelling for polymers
- Packaging material selection for a formulation



Digital twin of particle compaction

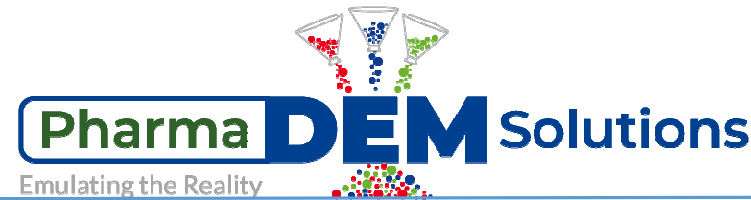


CFD of cream mixing



\*All models are proprietary to PharmaDEM

# The benefits of modeling in formulation development



Model-informed drug development, has already had a profound impact on drug development, yet its full impact is just now coming to light.

## Benefits:

- We can determine the compatibility of each component in the formulation
- Rational selection of excipients can give the better bioavailability and manufacturability without affecting the API stability
- Select the right concentration of excipients for API stability
- Simulate virtual dissolution/permeation studies to rank order the formulations
- Maximize the probability of RLD matching and commercial success

Example table

Polymer	Active ingredient					Rank**
	A	B	C	D	E	
1	Orange	Yellow	Red	Orange	Yellow	Benchmark
2	Yellow	Yellow	Yellow	Orange	Yellow	2
3	Yellow	Orange	Orange	Orange	Orange	3
4	Green	Green	Yellow	Yellow	Green	1

\*\*1-most suitable pack solution; 3-least suitable pack solution

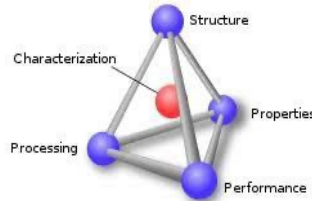
Least compatible    Compatible    Most compatible

- Regulators Now Expect Sponsors to Use M&S

# FmDEM study



Formulation Properties



Material Characteristics



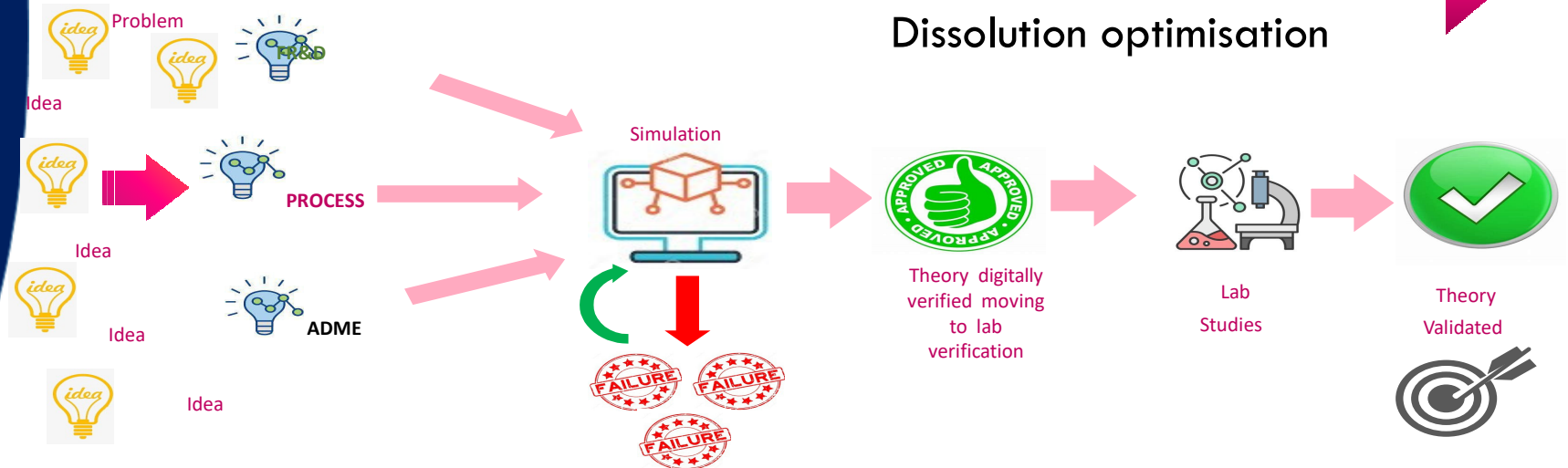
Chemical Stability & BA



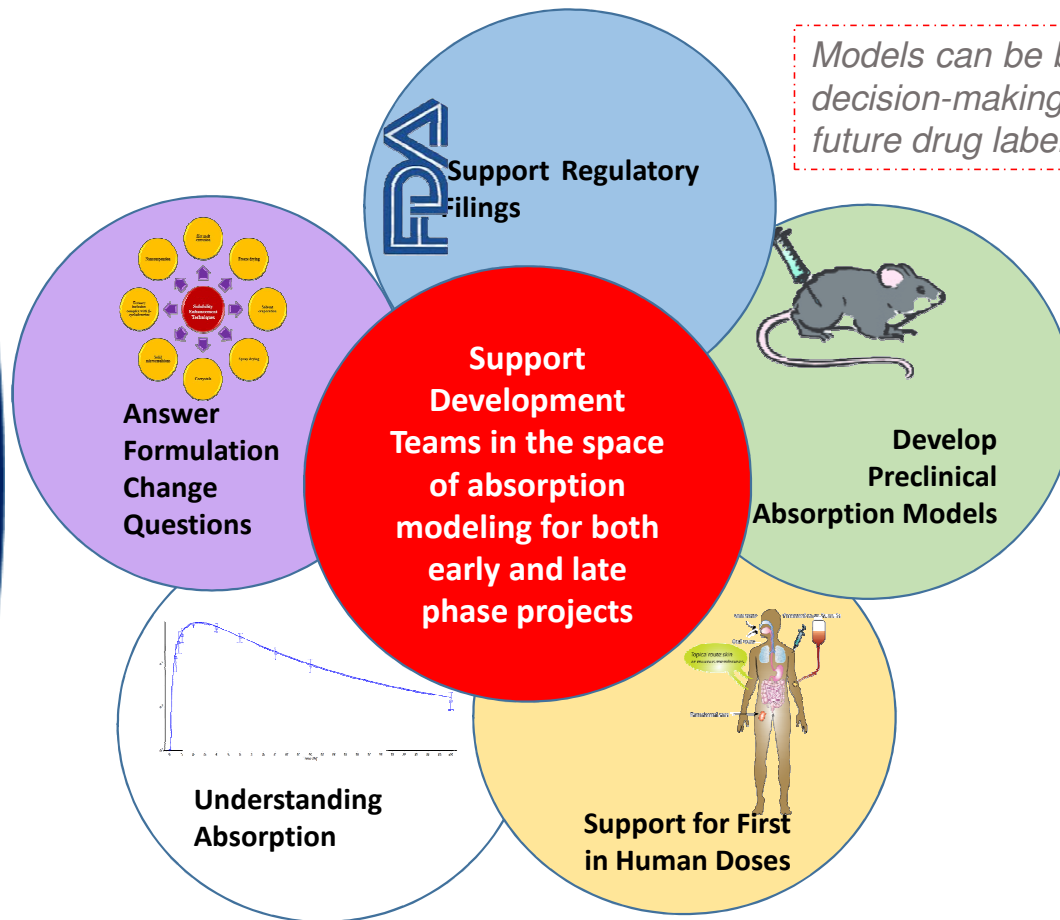
Digital design solution

**FmDEM: Drug-excipients compatibility, formulation design**

Dissolution optimisation



# Absorption & PBPK Modelling : Design, Engineering & Manufacturability (AbsDEM)



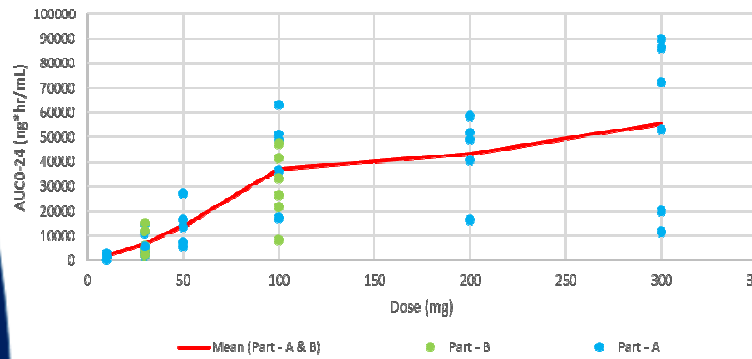
*Models can be built & refined with available clinical data; its decision-making powers expand with an eye toward the future drug label*

In this stage, PharmaDEM can provide guidance regarding

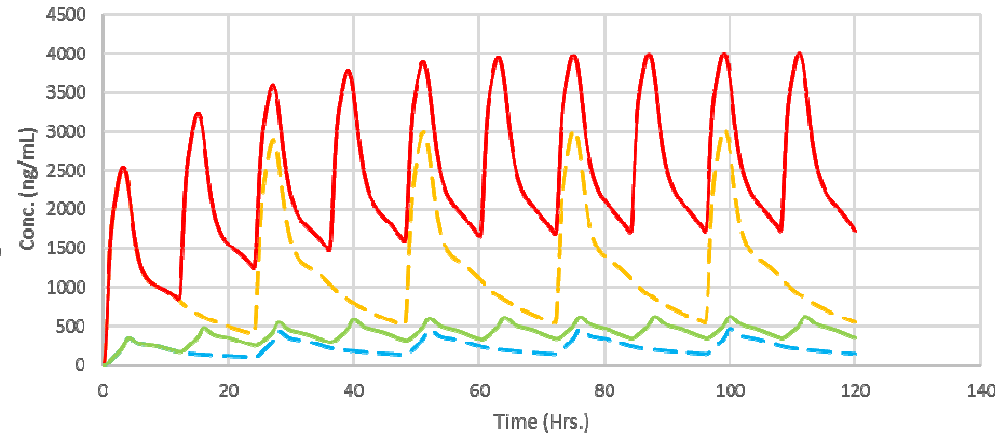
- ✓ Final dosing and alternate dosing approaches
- ✓ Optimal and alternate drug formulations
- ✓ Drug-Drug interactions and other safety concerns
- ✓ Drug Absorption

# Absorption Modelling – Applications

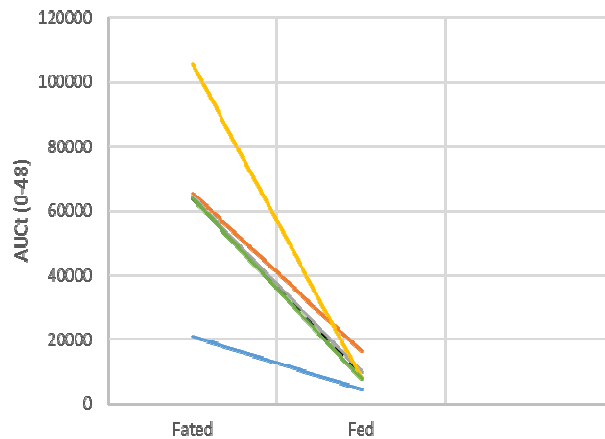
Dose Linearity – Fasted State



Stable & Unstable Simulated under Fasted & Fed With BD & QD



200 mg Fasted vs Fed

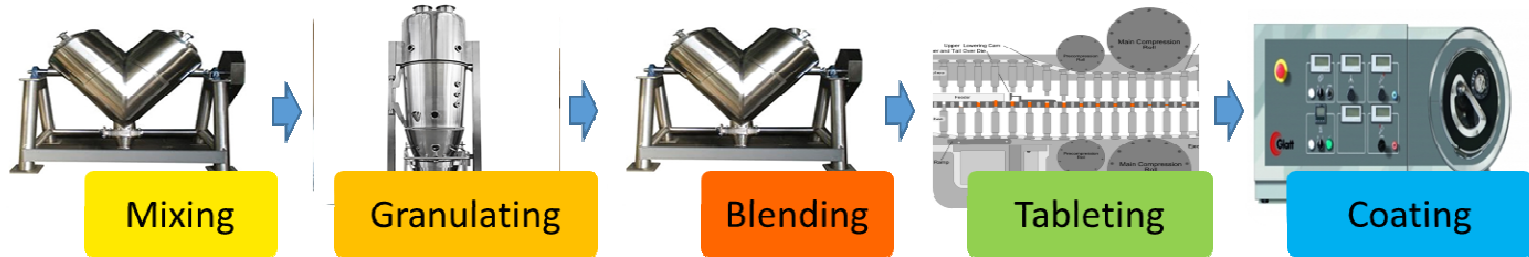


- This asset has a very high permeability with low solubility. The solubility decreases further as a function of time due to form conversion. It was hypothesized that form conversion is the reason for the negative food impact
- The model was able to explain the hypothesis and confirm that with existing formulation the target profile could not be achieved.

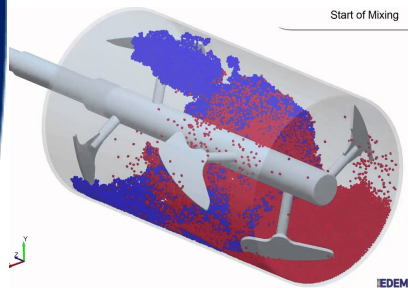


# PHYSICS MODELING DEM & CFD

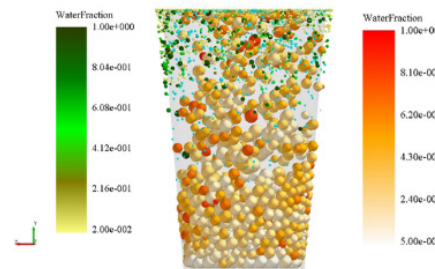
# Tablets Manufacturing Steps



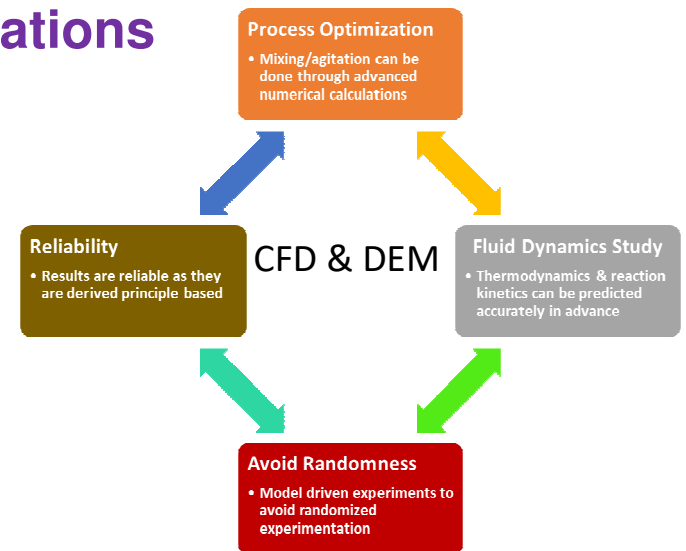
## Digital twins creation for each unit operations



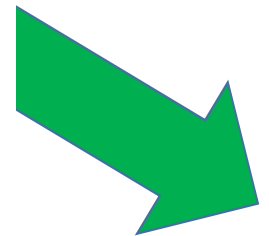
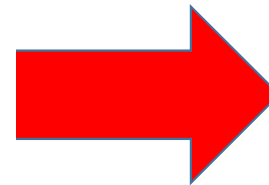
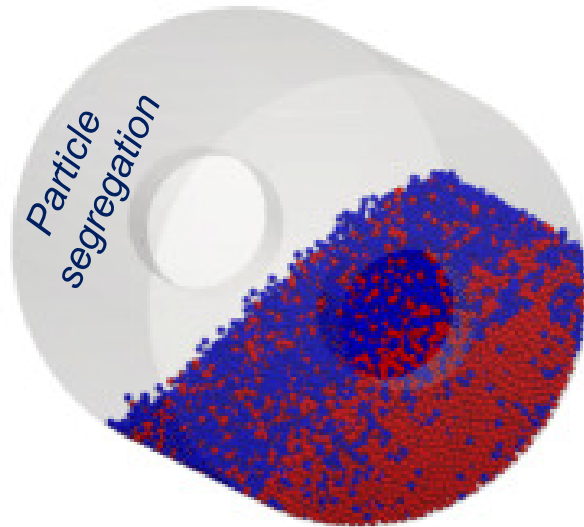
Mixing



Granulation



# Physics Based Simulations – Solid Dosage Forms -DEM



## Outcome Problems

- ❖ Particles segregation, Issues with Homogeneity and Uniformity
- ❖ Yield loss due to poor powder flow and compaction
- ❖ Out of specification and material non conformance
- ❖ Scale Up processing conditions mismatch
- ❖ As scale increase risk assessment becomes challenge

## Unit Operation Problems

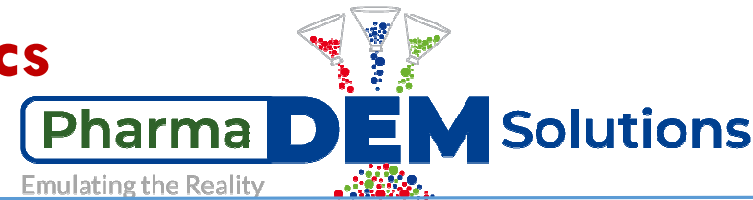
- ❖ Blending & Mixing: Unsure on blending equipment efficiency for increased batch size
- ❖ Coating: Dynamic bulk behavior of particles and their sizes resulting in bumpy surfaces
- ❖ Particle Motions: Geometry motions becomes complex to capture
- ❖ Scale Up Strategy: Scale up Strategy and physics first principles not employed
- ❖ Equipment Engineering: Hopper discharge patterns, Valves & feeders assessment & stagnant zones cannot be determined

## Simulation Benefits

- ❖ Reduction in no. of actual experimental trials
- ❖ Clear understanding of root cause(s) and identification of CMAs and CPPs
- ❖ Production rate and yield optimization
- ❖ Easier handling of high risk formulations
- ❖ Detailed micro dynamic study on powder particles and flow behavior
- ❖ Understanding on particle collision statistics



# Benefits of Modelling & Simulation – Physics Based - DEM



## Objectives of Simulation & Problem Statement Definition *(few but not limited)*

### Mixing & Blending

- ❖ Simulation to understand blend uniformity reach conditions in current scale and up-scale
- ❖ Blender design optimizations to regulate influencing factors such as time, size, productivity
- ❖ API & Excipients material behavior and determination of co-sifting and no-co-sifting process
- ❖ Assessments of CPPs, correlations & how they affect, segregation of materials & their mixing
- ❖ Simulations to get a clarity on Blender recommendations based on type of materials used in mixing and blending

### Scale-Up

- ❖ Implement correct scale up strategy, assessment of particles motions, geometrical aspects & particle's stress, absolute fill volumes through simulations to derive optimum process conditions
- ❖ Extraction of information is made easy, measurement of stress on each particle can be monitored on required time intervals to overcome any/all damages and implement necessary damage control processes

### Tableting & Coating

- ❖ Prediction on tablet appearance, surface texture, density through simulations and eliminate unexpected output which is affecting product outcome
- ❖ Assessment through simulation on coating homogeneity & dry performance in tableting process

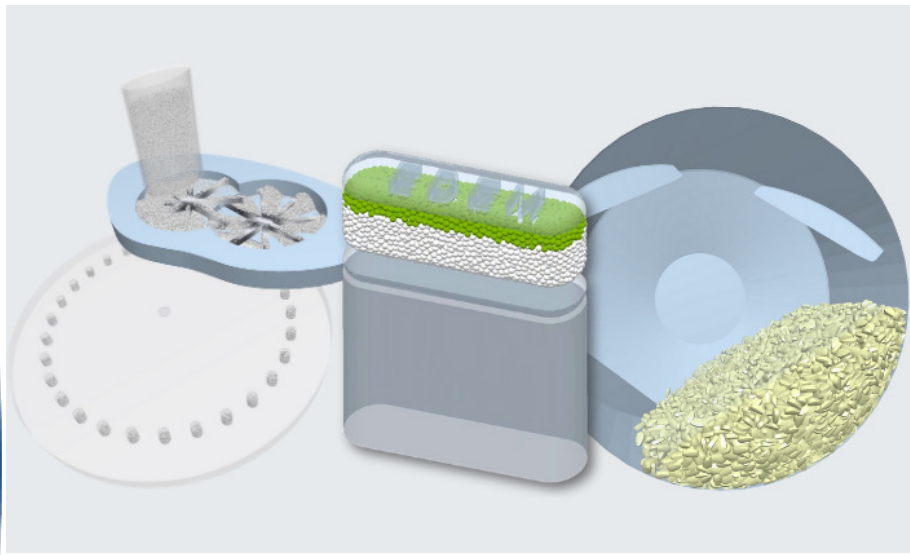
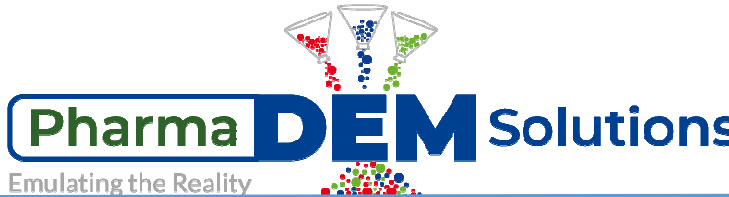
### Granulation

- ❖ Simulation to detect & predict agglomeration caused due to impeller speed and liquid addition and track liquid bridges between particles

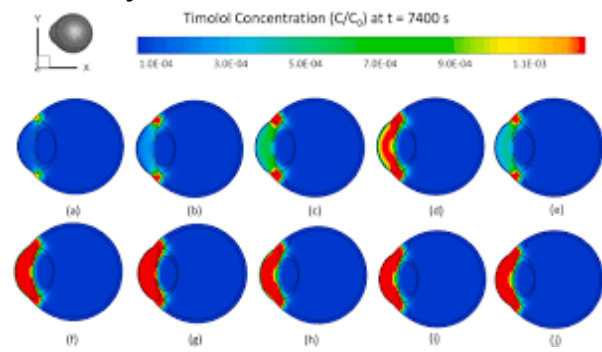
### Equipment Engineering

- ❖ Unforeseen risks in current equipment for any scale of manufacturing & plan risk mitigation
- ❖ Evaluations on material flow behavioral patterns, material unique distributions, material segregation assessments, material degrade realizations, dead spot identifications, material shear strengths, wall frictions on materials, Compression created within equipment, etc.,
- ❖ Hopper issues, evaluations & improvisation
- ❖ Mixing Device assessment based on "AS-IS" model and recommendations on new "TO-BE" model for better product outcome

# Physics Based Simulations – Liquids & Parenteral – DEM & CFD



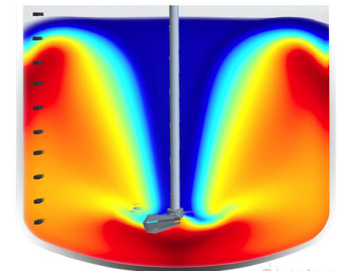
Analysis of topical dosing and administration effects on human ocular drug delivery



DEM and CFD modeling is a powerful tool, accurately analyzes the behavior of granular materials such as dust particles, tablets and capsules.

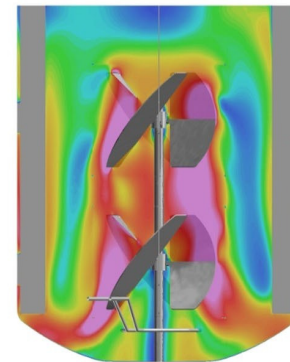
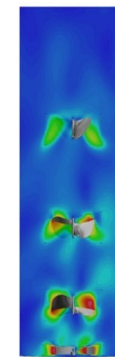
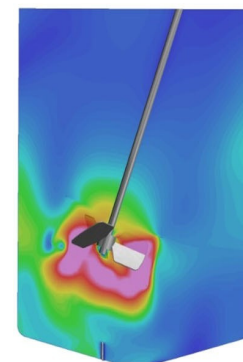
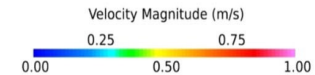
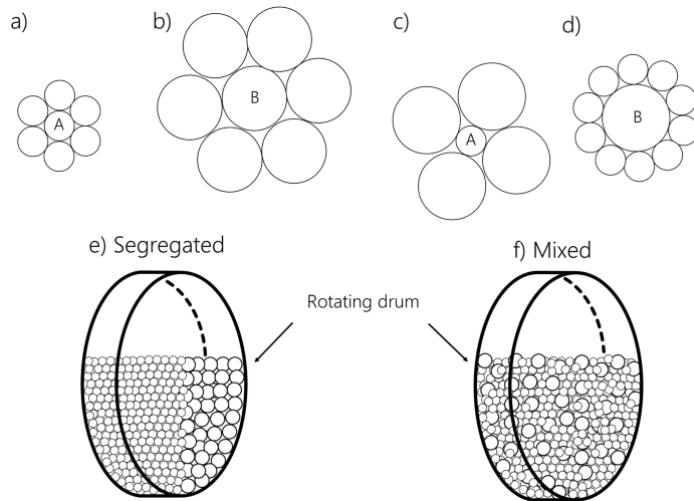
DEM is a powerful solution used to model pharmaceutical manufacturing processes such as coating, drying, granulation, solids mixing using digital twins

CFD ANALYSIS OF A SIMPLE HIGH SHEAR MIXER



<https://doi.org/10.1016/j.compbimed.2021.105016> Ref: B.S. Borys et al. / Biochemical Engineering Journal 133 (2018) 157–167

# Physics Based Simulations – Liquids & Parenteral



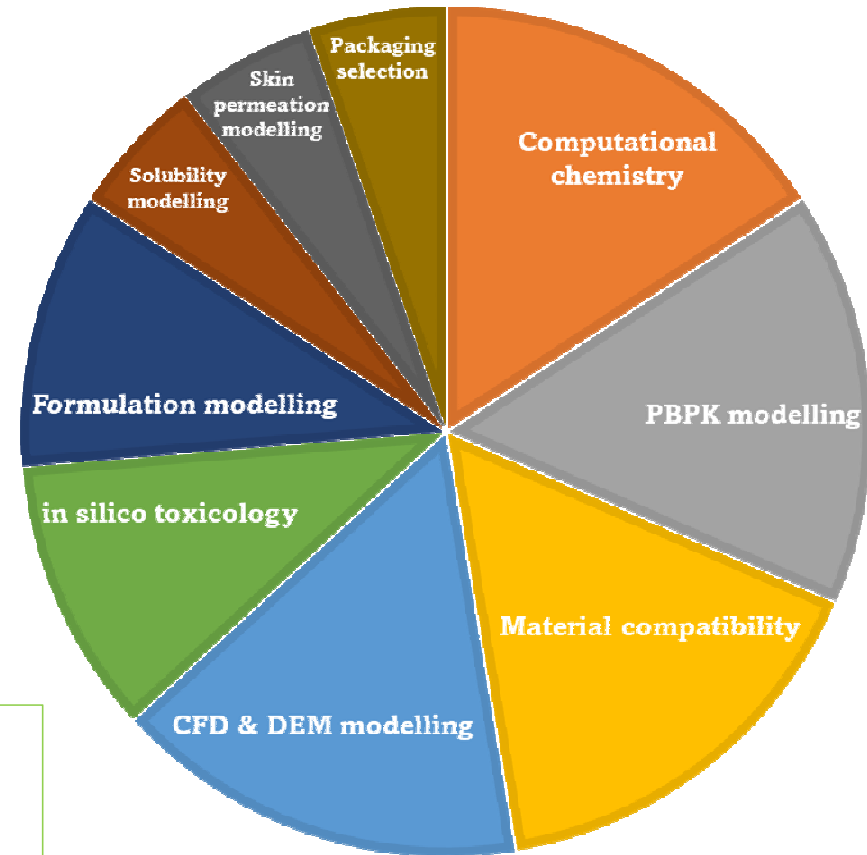
## 1. Key Aspects & Issues:

- ❖ *Reactors, Tanks & Mixers differ when compared with development scale thereby having scale up issues*
- ❖ *Apart from fluid dynamics, the thermodynamics change across scales is another issue which needs to be understood as it affects process*
- ❖ *Clueless on Optimum design space to monitor and control the range of PP*

## 2. Key Aspects & Issues:

- ❖ *How aggressive should pH control be applied and still avoid overshoot?*
- ❖ *How concentrated can the control base be, to avoid unacceptable local deviations during addition?*
- ❖ *How and where should solutions be added to the reactor?*

# Q & A, Contact



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