ACCELERATING DRUG DEVELOPMENT USING SMALL SCALE, DATA INTENSIVE, ITERATIVE DESIGN APPROACHES

MERCK
INVENTING FOR LIFE

09APR2019

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ACCELERATING DRUG DEVELOPMENT USING SMALL SCALE, DATA INTENSIVE, ITERATIVE DESIGN APPROACHES

- Where in the development lifecycle to deploy these tools?
- The experimental element
- The modeling element
- Extending the value: Model Based Product Design

Product Development Lifecycle: Where to apply iterative design approaches

Development Phase

- PI Prototyping
  - Formulation Prototyping
  - API phase selection
  - Process selection

→ Free to explore formulation composition and process → Iterative design

- PIIB pre market formulation
  - API attributes/Excipient studies
  - Bio-comparison studies
  - Process robustness studies

→ Establish pK bridge to PI formulation, starting to lock composition and process. → Iterative Improvements Robustness Studies

- PIII/FSS final market formulation
  - Scale to commercial
  - Material Risk Assessment
  - Late Stage Risk Assessment

→ Effectively locked in to a composition and process, changes at the point are risky and often require BE → Final Image Optimization

Small Scale, Data Intensive Formulation Development Environment

- What are the attributes?
  - Use small amounts of drug substance
  - Need to be able to generate enough drug product material to run meaningful analysis
  - Flexibility to accommodate the range of process technologies and products
  - Data you generate must be actionable

- Ideally you also have
  - Data acquisition, and embedded context
  - Automate calculations and visualizations at the point of data generation
  - Data mining/empirical modeling
  - Fundamental modeling

What data do we really use to make formulation decisions?

(strength vs. pressure)
(density vs. pressure)
Friability (elegance vs. #revs)
Flow
Disintegration
Dissolution
Phys/Chem stability
…
All this as a function of composition and process

Formulation development is a multivariable, multi objective function optimization problem

Formulation Screening Center: Smart Throughput Analysis at the 5-50gm batch scale

Automated Powder Dispensing & Miniaturized Granulation Technology
Facilitate Small Batch Manufacturing

RC/DC

HME

SD

WG

Capabilities:

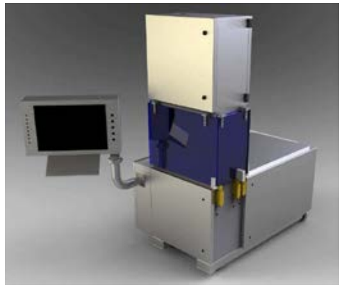
Flexible semi-automated tools

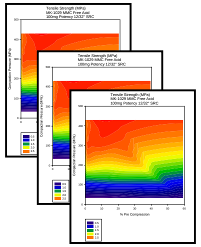
Formulation DOE/Optimization studies

Evaluation of Mechanical Properties, Compaction Performance, & Release Rates

Data Integration Lab, with automated calculations and report generation

Rapid Small Batch Compaction Analysis Maps
Formulation Mechanical Performance:
Tablet Strength & Disintegration Time





UV fiber optic probe dissolution system Automated Enables rapid prototyping and formulation optimization

Impact:

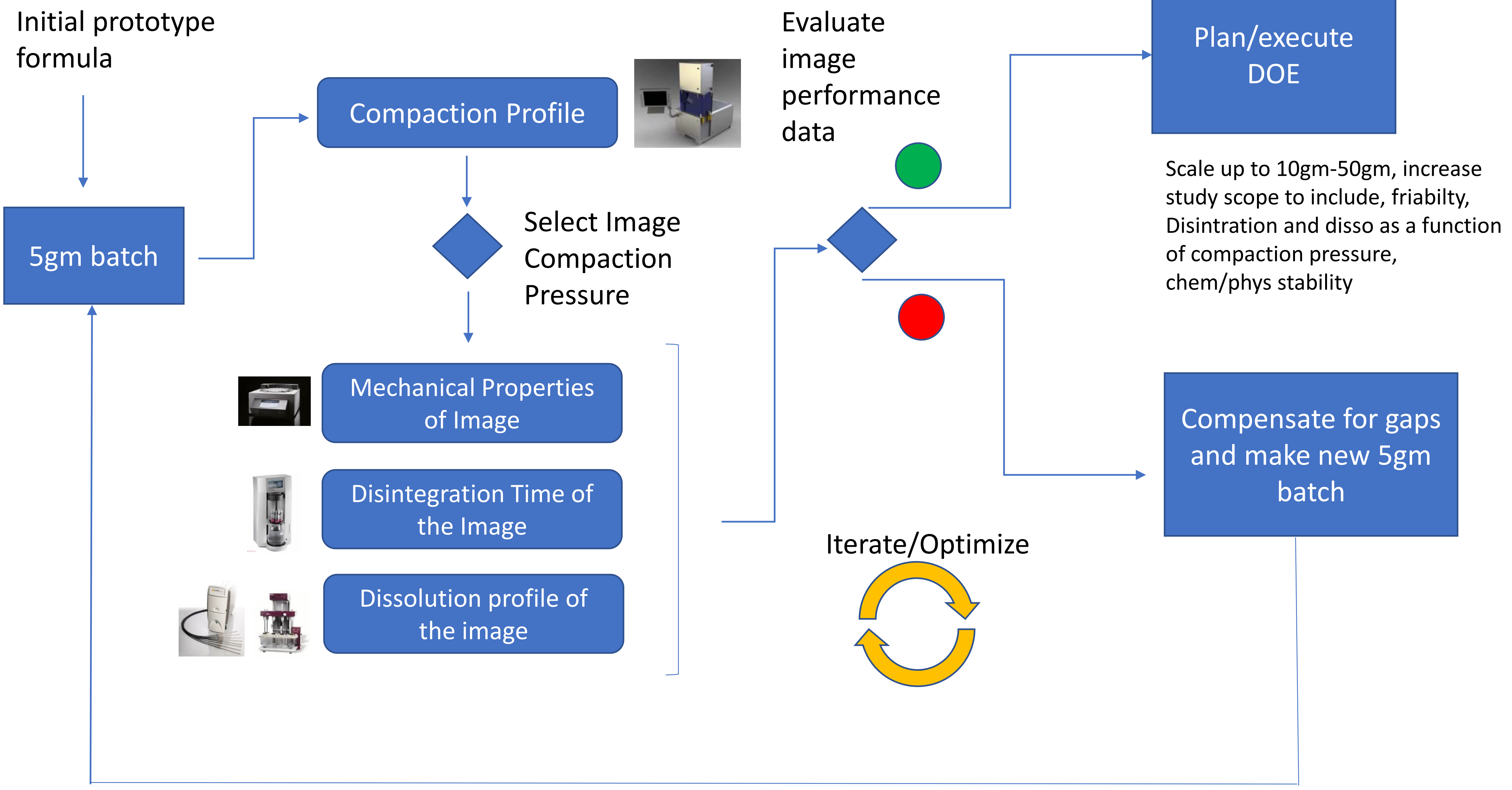
Speed & API utilization

Explore wider composition spaces

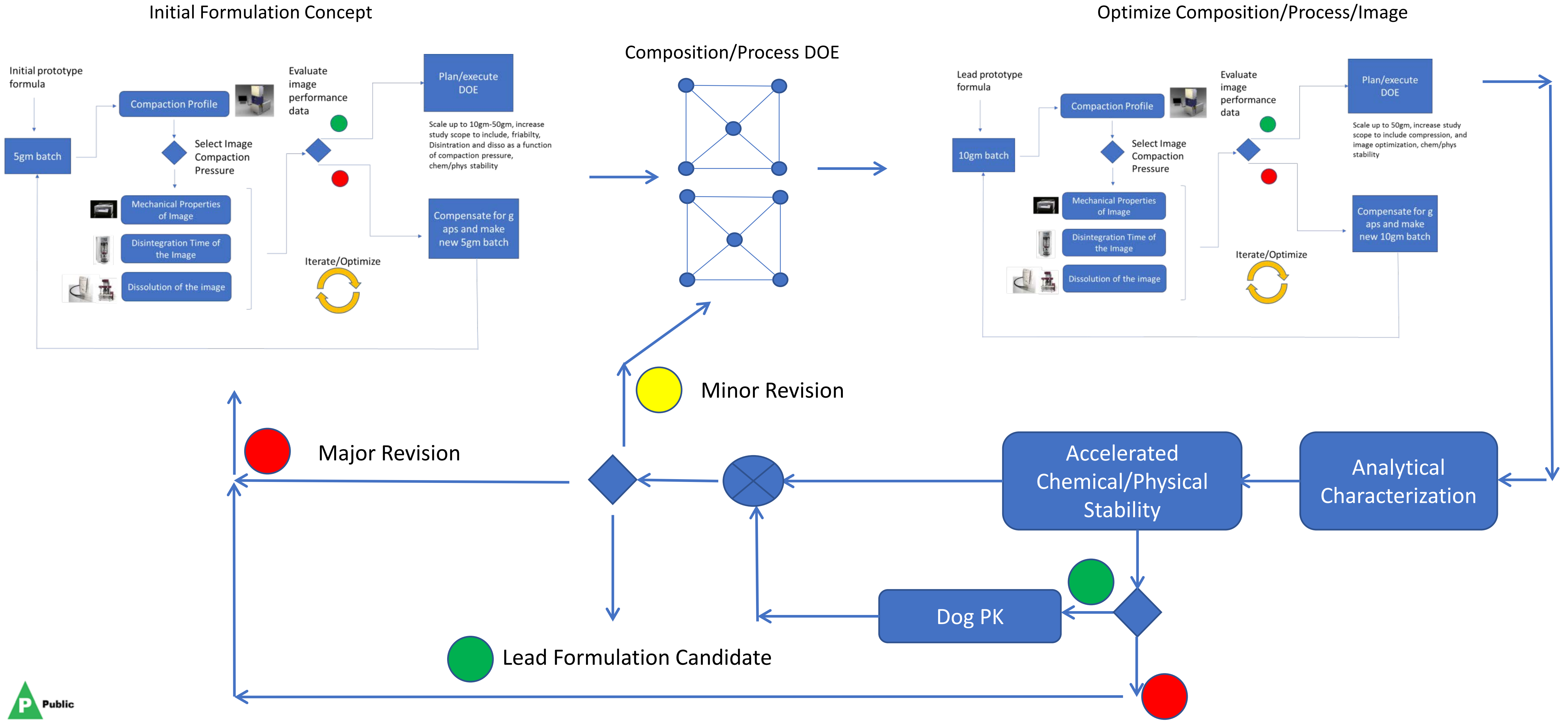
Increased product understanding

Systematic characterization enables cross program knowledge build

Small Scale Iterative Design

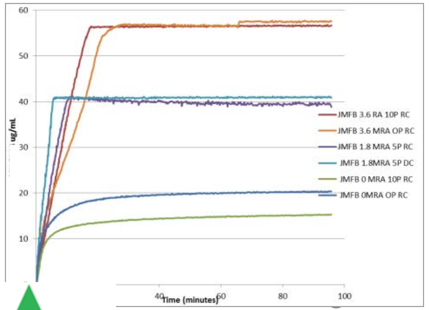


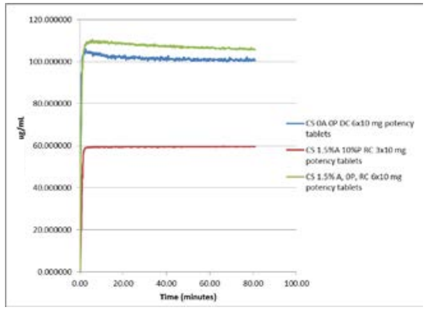
Iterative Design Cycle from Initial Concept to Lead Formulation Candidate

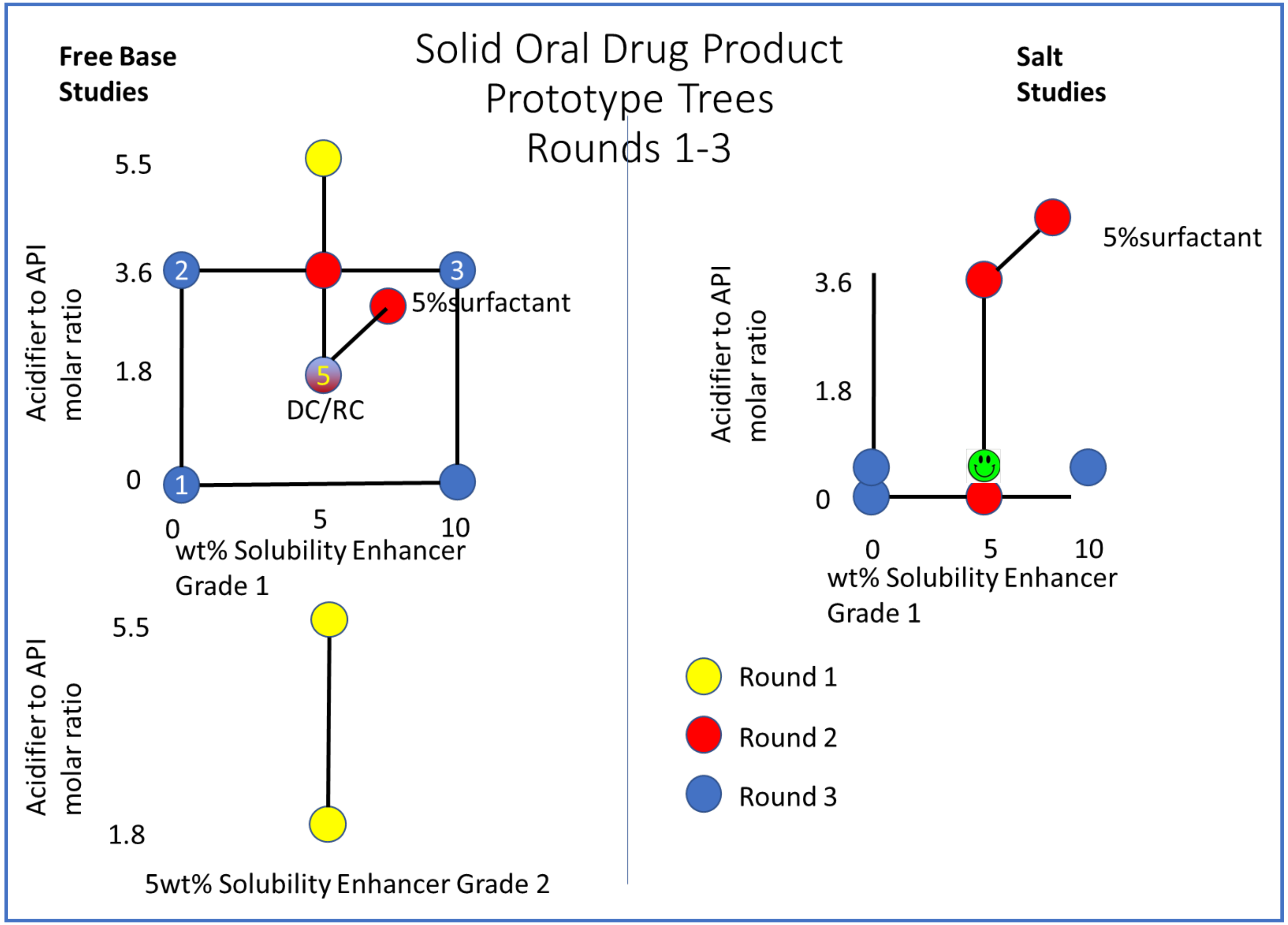


Solid Oral Drug Project Development Scenario:

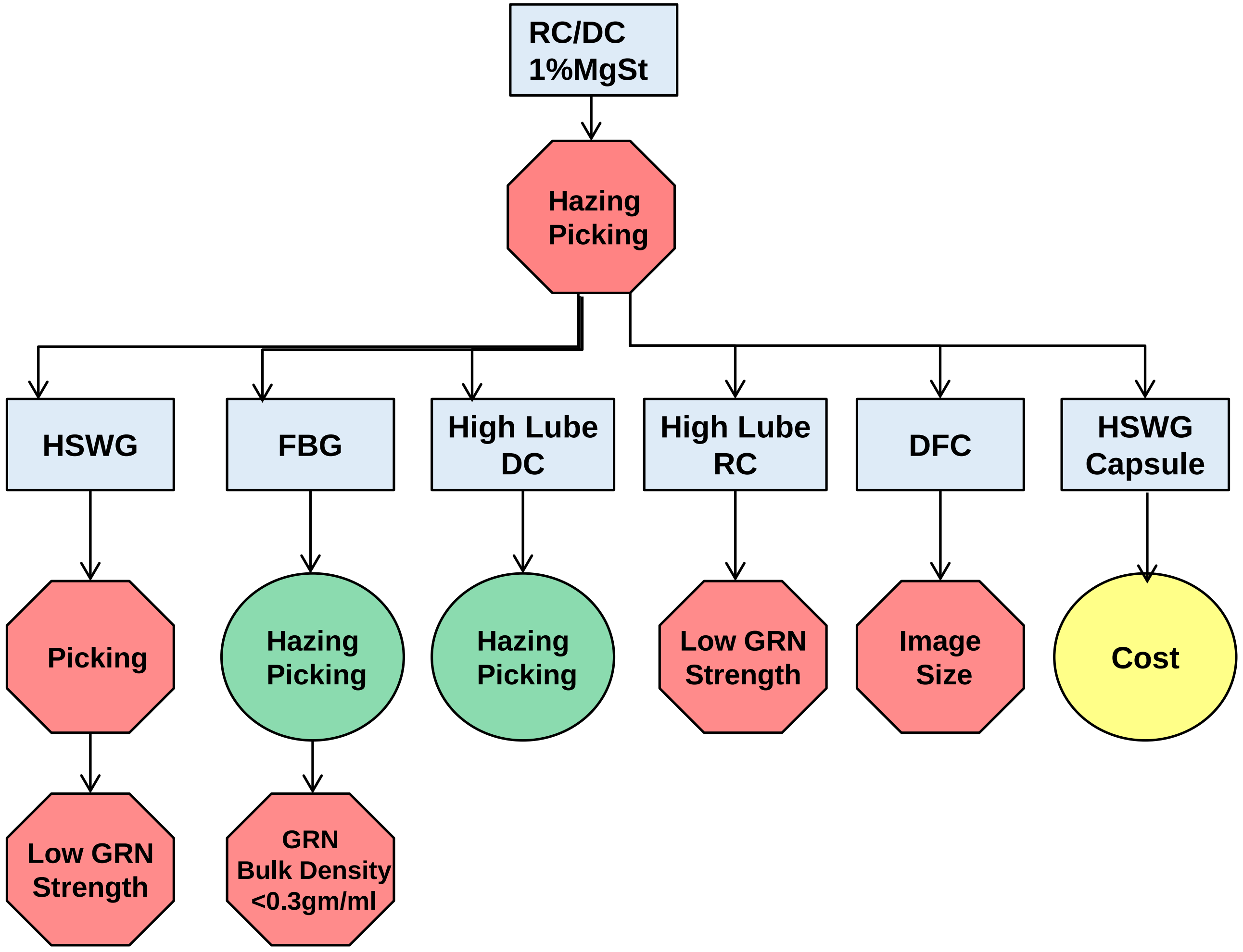
- Evaluate Two API phases
  - Free from & Salt form
    - Evaluation of API attributes
      - Un-milled, Wet milled, Pin Milled, Jet Milled
      - Particle size distribution
- Formulation Components
  - Acidifier
  - Solubility Enhancer
- Process Technology
  - Direct Compression
  - Roller Compaction

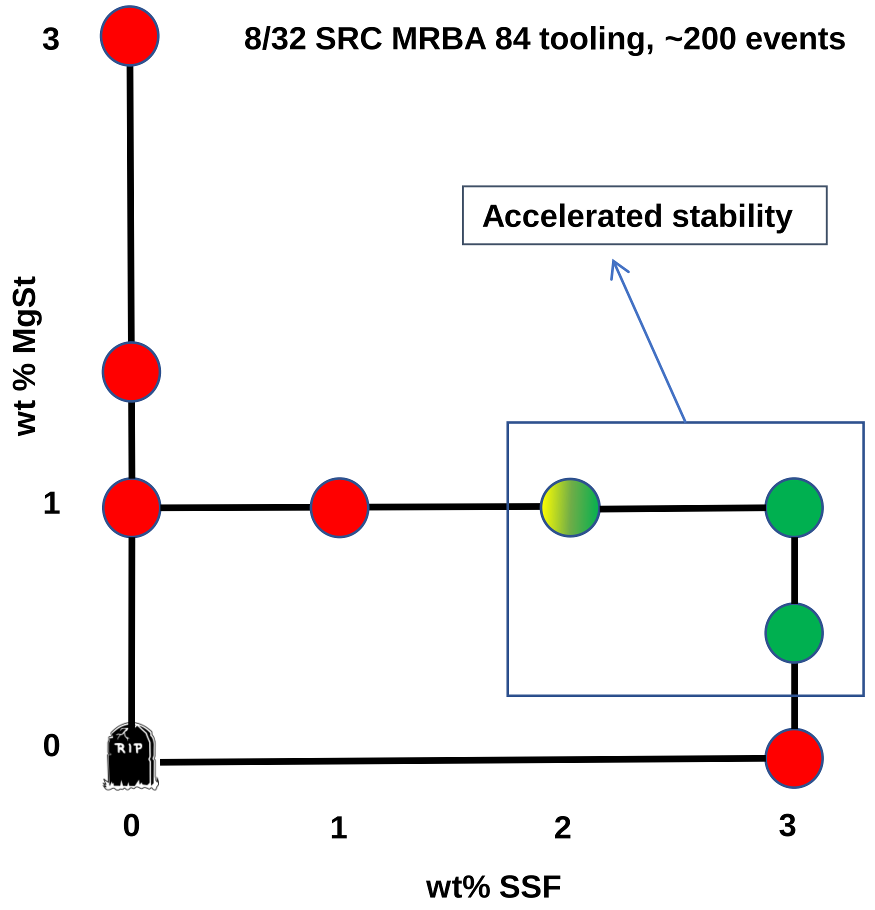






With these tools you rapidly make and test alternative formulations

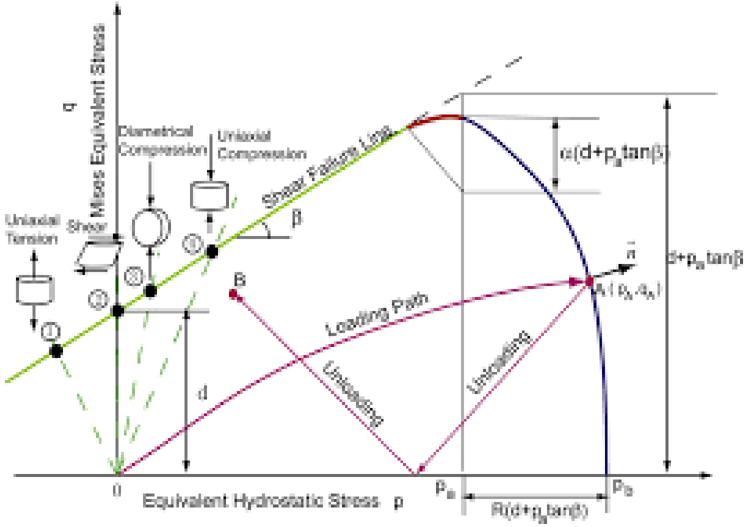




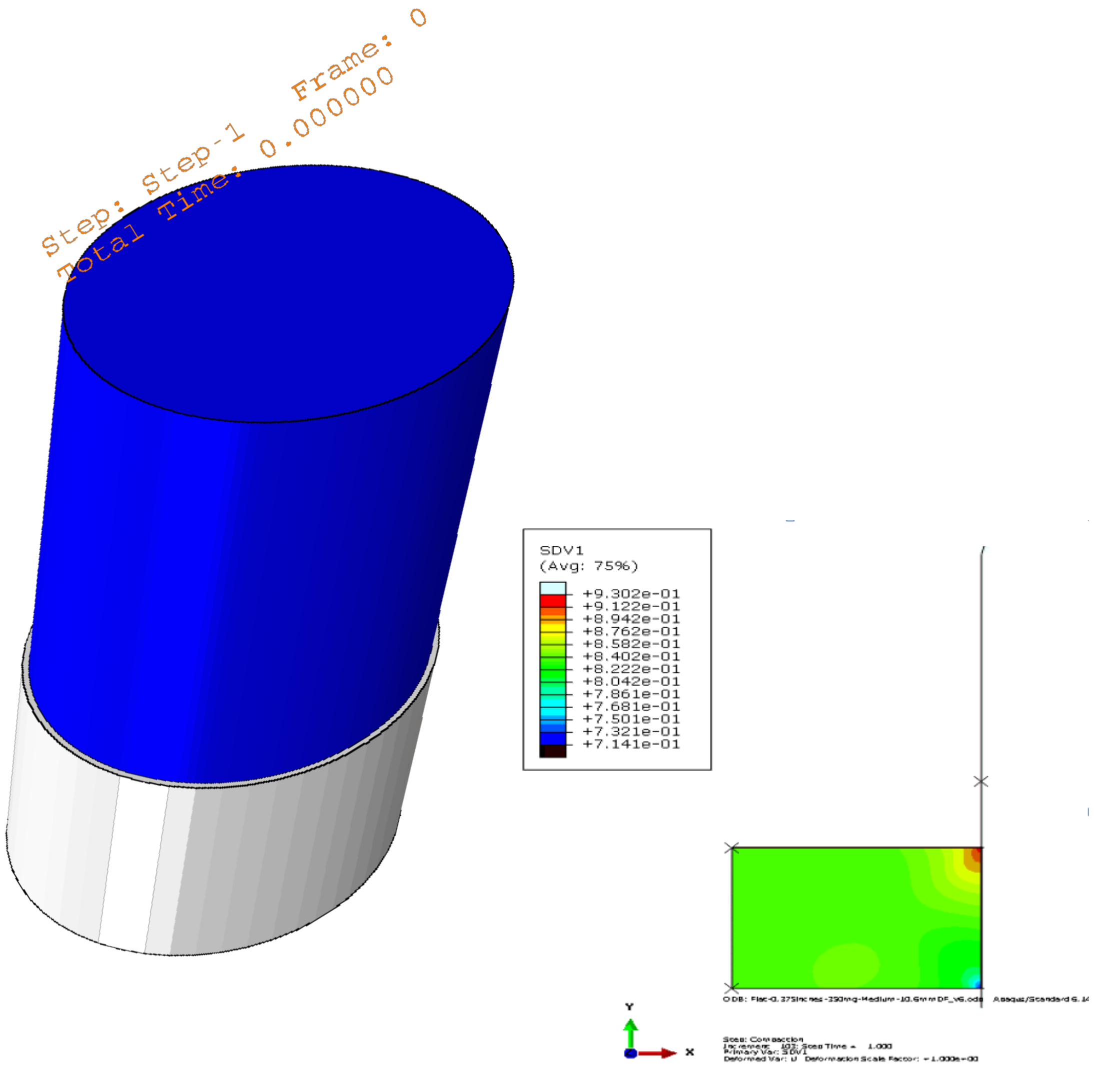
Finite Elements Modeling

Finite Element Modeling is a numerical method that can be used to solve boundary value problems for partial differential equations

Model the effects of stress induced from the compaction process on the microstructure of the tablet (e.g. density)



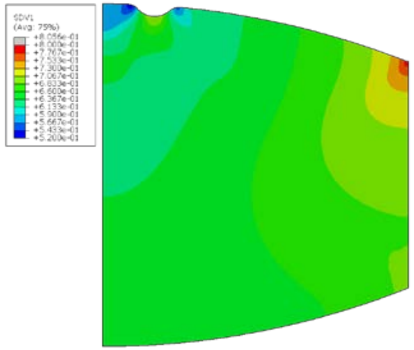
FEM to predict density gradients as a function of material properties & tooling geometry

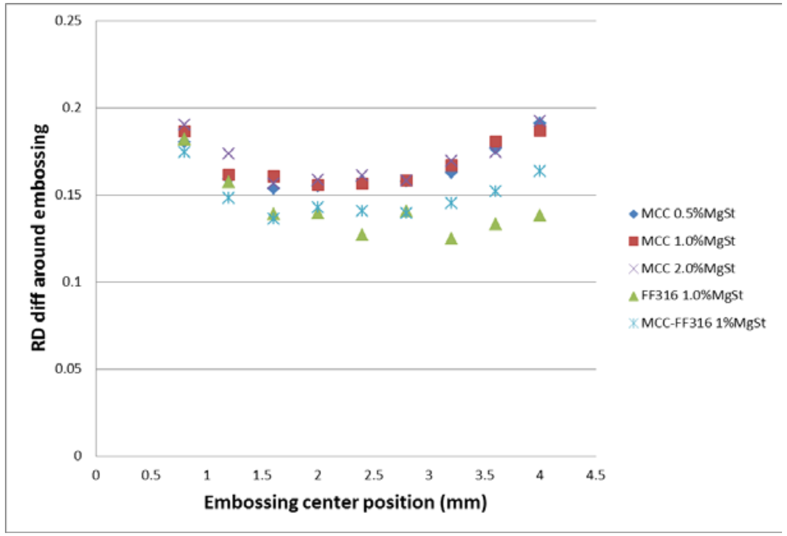


Large simulations that are run on supercomputers/cloud computers

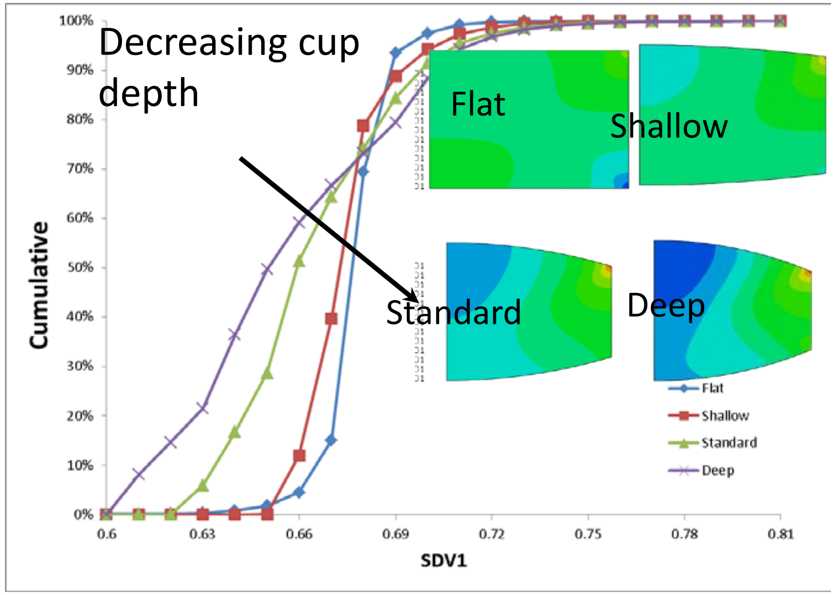
Optimizing the Design of Tablets from Mechanical Properties to Shape

Ideal embossing position dependent upon material





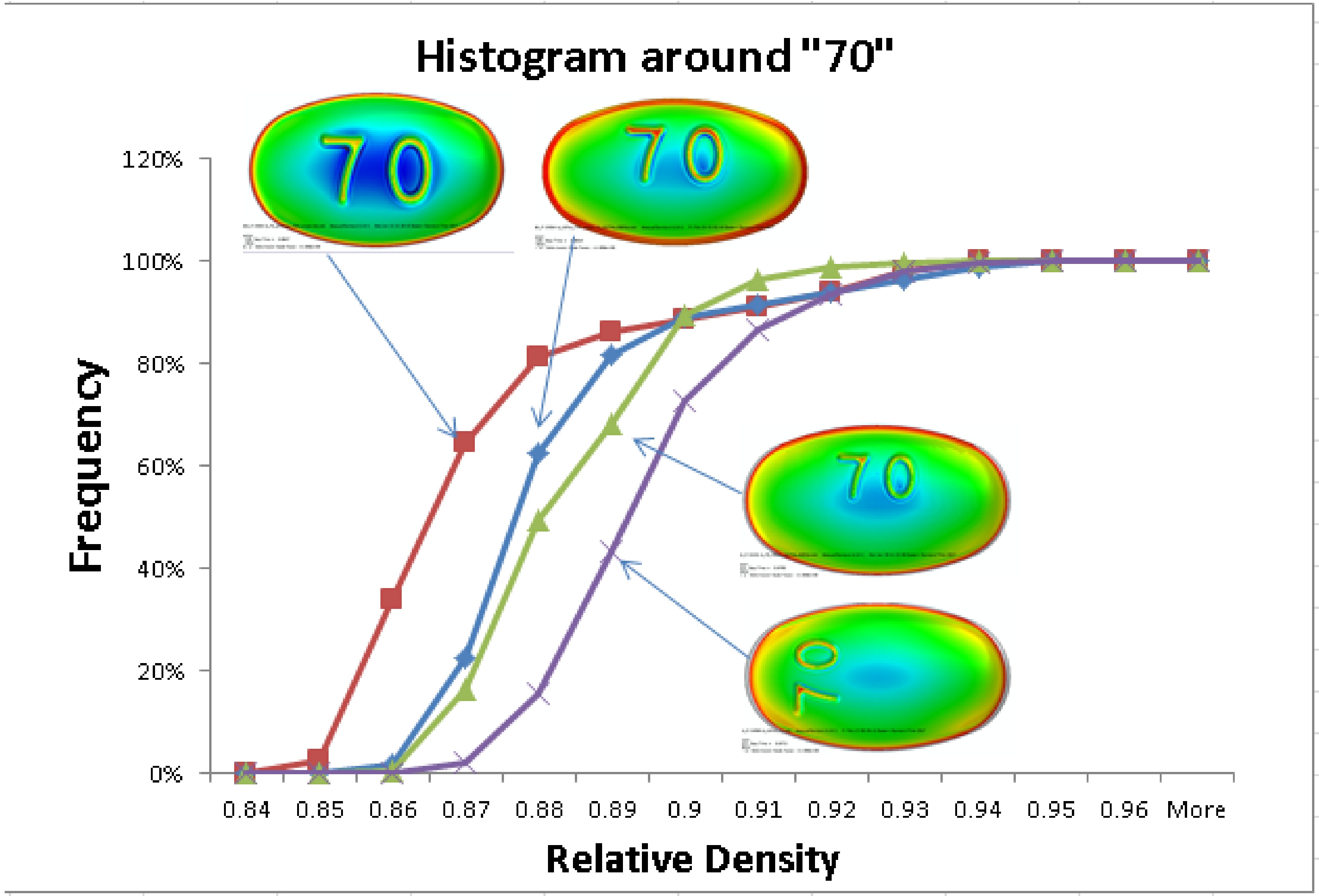
Cup depth drives density gradients in tablets



Relative Density

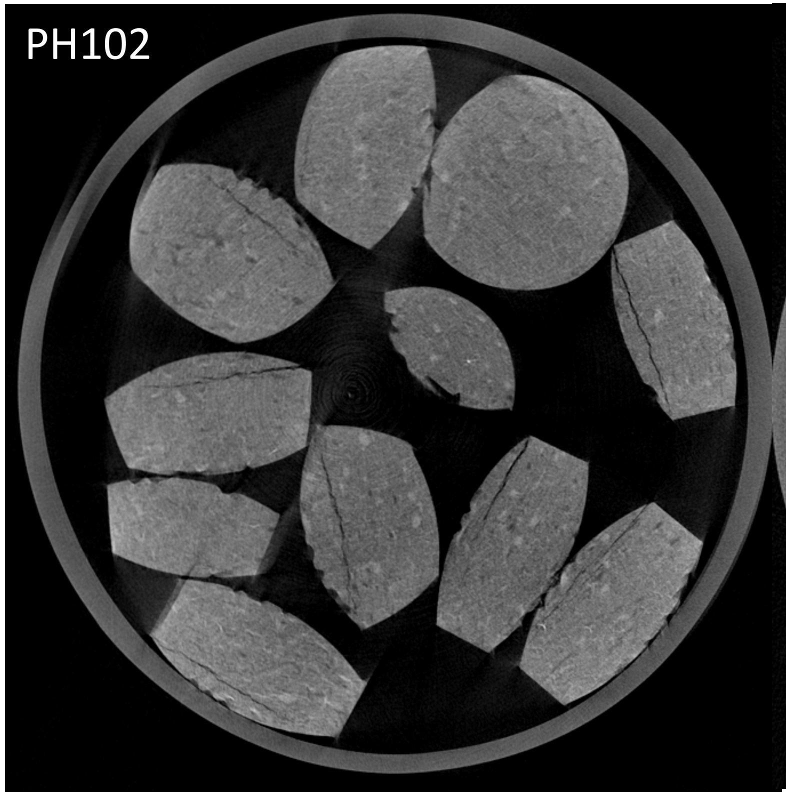
Taking what we have learned and apply to new development products

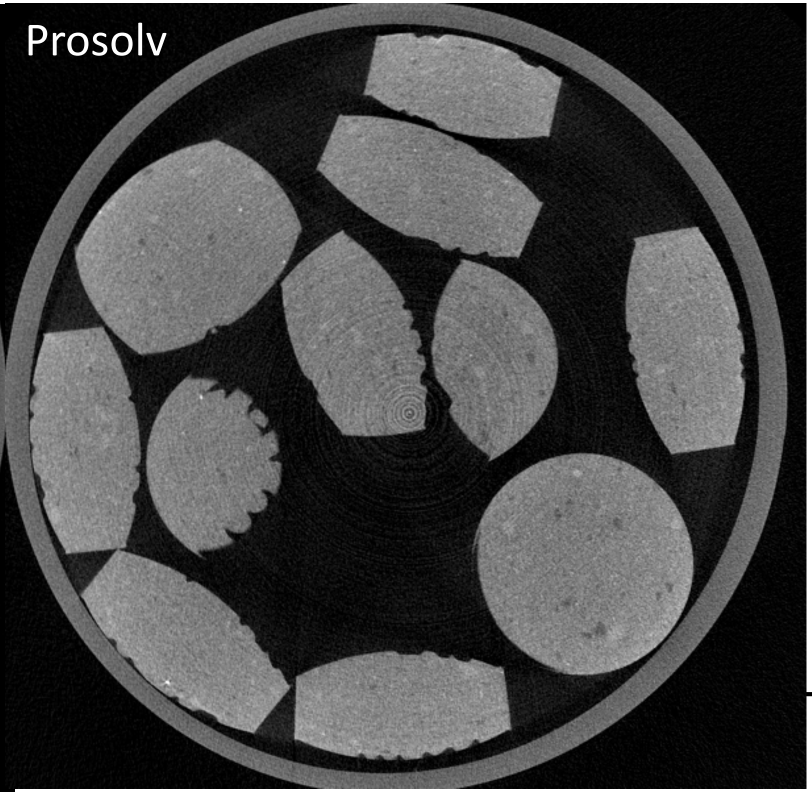
Optimizing the Design of Tablets from Mechanical Properties: Embossing Position



Smaller features and offset embossing placement reduce surface density gradients and improve product robustness

XRCT for exploring internal defects at high compaction speeds





High speed compaction (960mm/sec)

MicroCT images of tablets after production – cracking is evident!

Sample	Label	Bulk Density (10ml grad cyl)	Die fill for a 300mg tablet	Fill density (estimated)
1.	MK-XXXX PH102	**0.383g/cc**	10.5mm	**0.401g/cc**
3.	MK-XXXX Prosolv	**0.488g/cc**	8.1mm	**0.520g/cc**

Slower speed compaction shows no cracks in PH102!!!

Modeling Air Pressure Build up in tablets during compression

We can model air pressure gradients by using Abaqus for the density and displacements inputs to the air pressure model

$$\frac{1}{J}\frac{dJ\rho}{dt} = \nabla(\bar{v}\rho)$$

Jacobian — Velocity of air — Density of air

Assuming an ideal gas and Darcy's Law

$$(1-\varphi)\frac{d}{dt}\left(\frac{\varphi}{1-\varphi}\right) = \nabla\left(\frac{k}{\mu}P\nabla(P)\right)$$

Porosity — Permeability/ viscosity — Pressure

Boundary conditions:

1. **No resistance to flow out of die/punch gap**

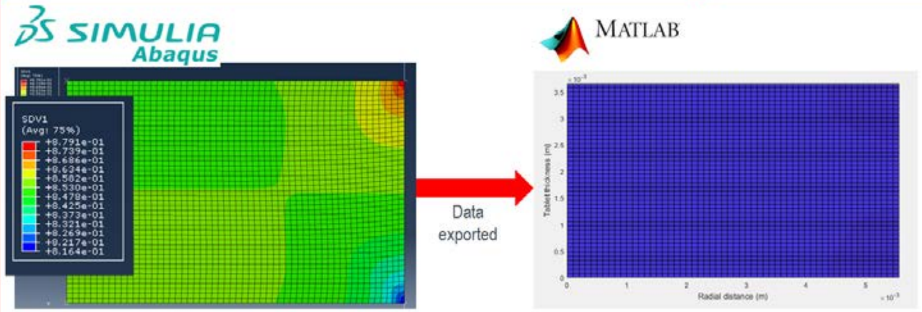
Several key assumptions:

- In die density = out of die density
- Permeability from literature
- Solid phase does not deform
- Density does not change with compaction speed

2D axisymmetric analysis – model setup

Model Material:

- Microcrystalline Cellulose + 2% Magnesium Stearate

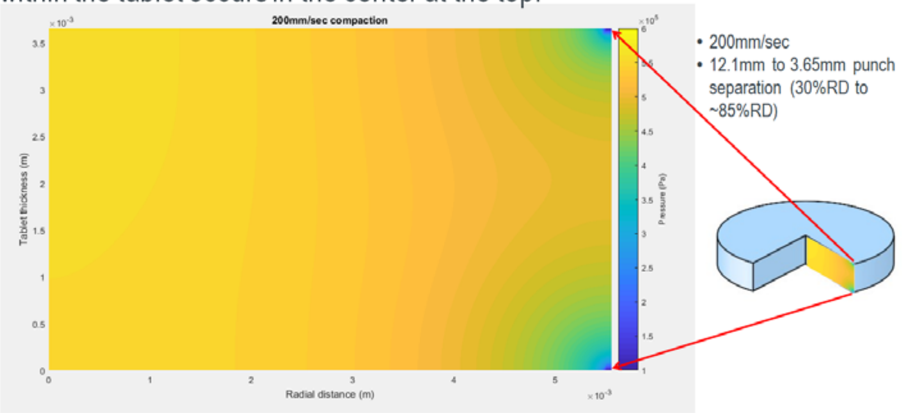


Drucker-Prager Cap model was calibrated for this material

- RD (SDV1) at node position

- Abaqus mesh made rectilinear
- Increased number of increments (temporal resolution)
- Finer mesh created (spatial resolution)

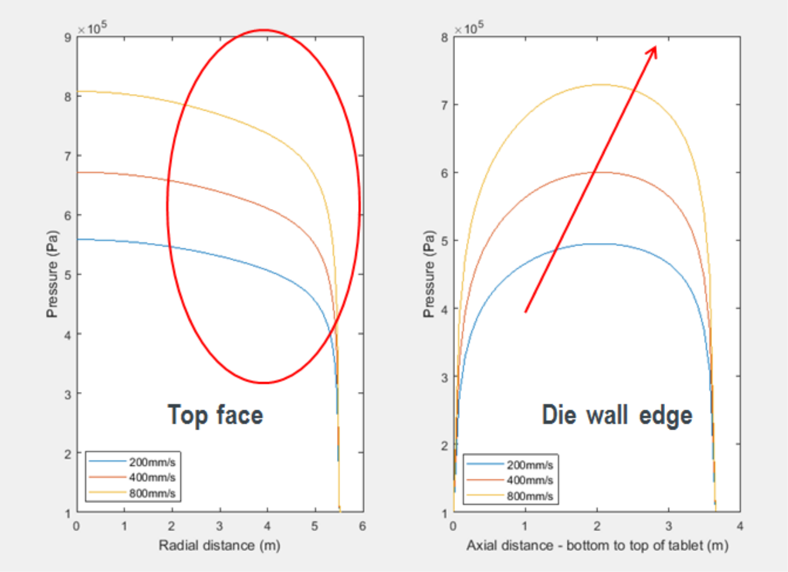
Full 2D solution with varying density shows that the maximum pressure within the tablet occurs in the center at the top.

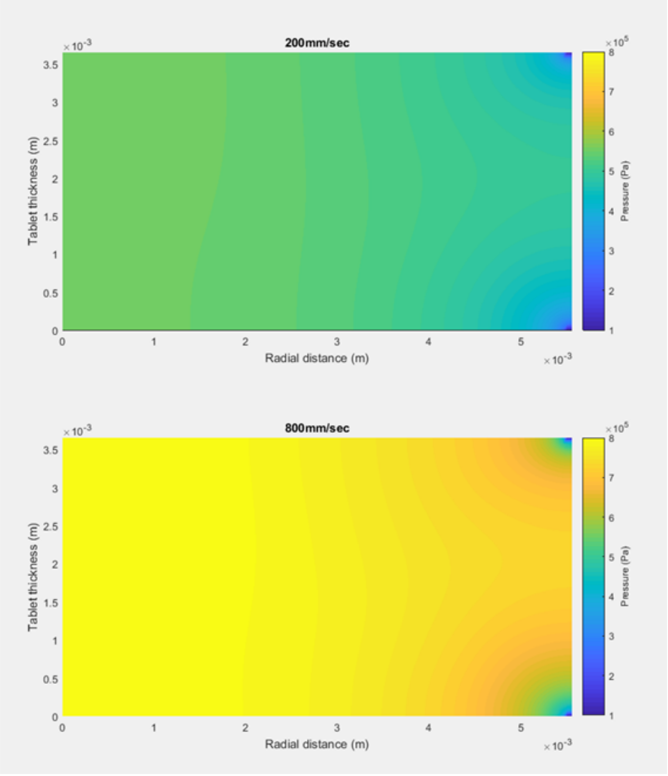


- 200mm/sec
- 12.1mm to 3.65mm punch separation (30%RD to ~85%RD)

Pressure distribution at end of compaction

Speed of compaction alters magnitude of pressure increase





- Increasing speed alters the pressure gradient along the top surface such that the change from edge to center is more severe
- Slightly different pressure profile along the tablet thickness at die wall edge with a trend of higher pressure towards the top of the tablet with increasing speed.

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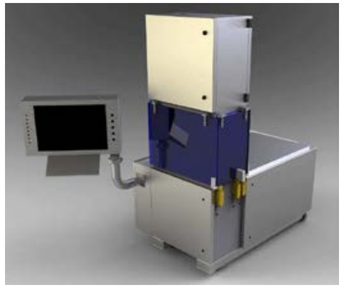

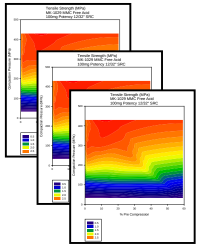

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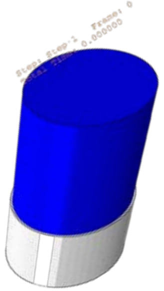
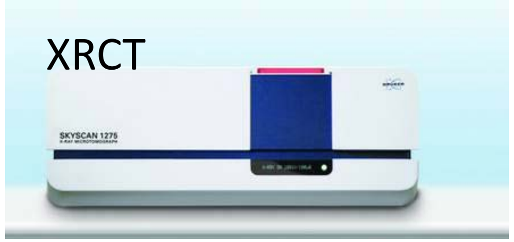




Public

Extending The Value: Adding the modeling component

Formulation Predictive Modeling Philosophy:

Advance our skills in Predictive Modeling

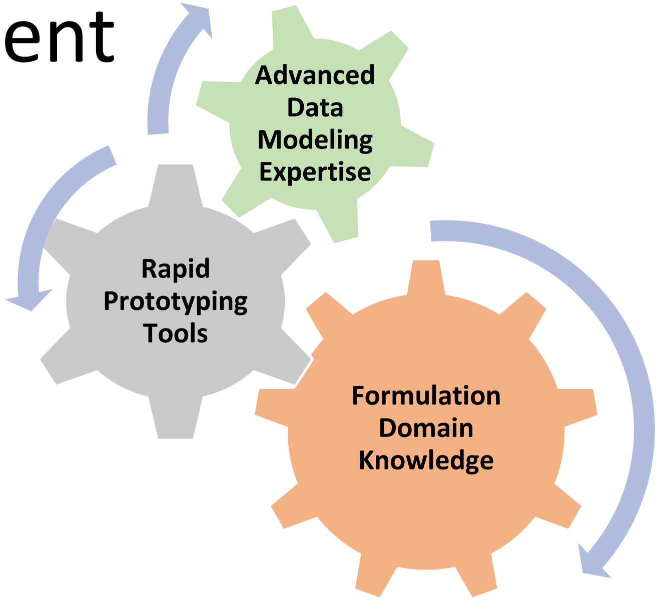
- Advanced Analytics &Classical statistics
- Data acquisition systems to support modeling

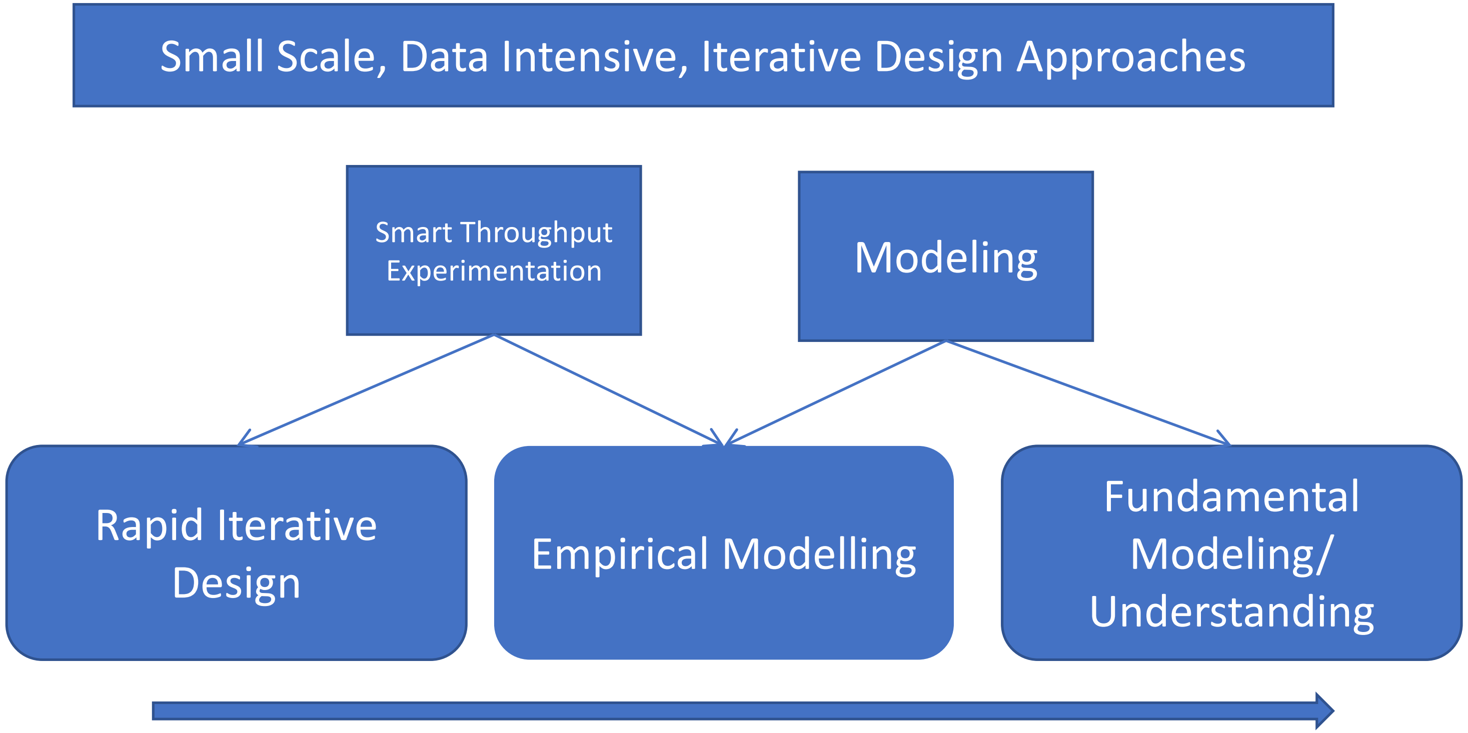
Create a suite of data driven analytic tools

- Formulation design, risk evaluation, due-diligence assessments,…

Work with modeling in mind

- Future state will have us making a battery of ***key measurements*** to directly support model development/maintenance



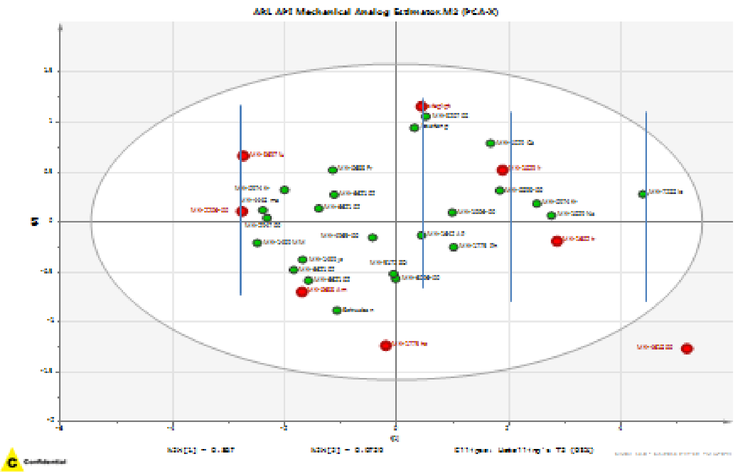


"The real power is in the combination of expertise in formulation, characterization, and data modeling"

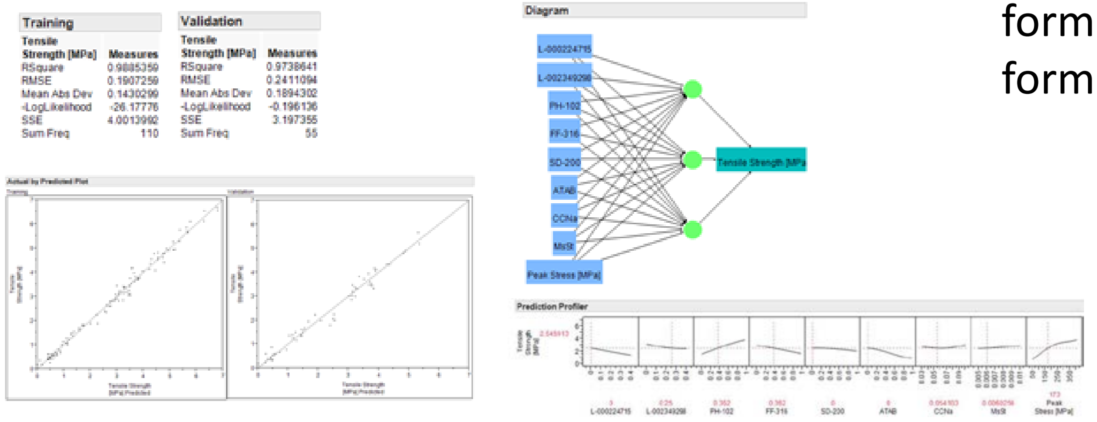
Formulation Predictive Modeling: Tensile Strength as a function of formulation composition

Compaction Profile is a key to understanding the strength potential of a formulation. It is experiment run by all formulators on all tablet formulations

Multivariate Characterization of Neat API Compaction Profiles
1st component is the most significant



Prototype Neural Network Model for Compaction Profile Prediction



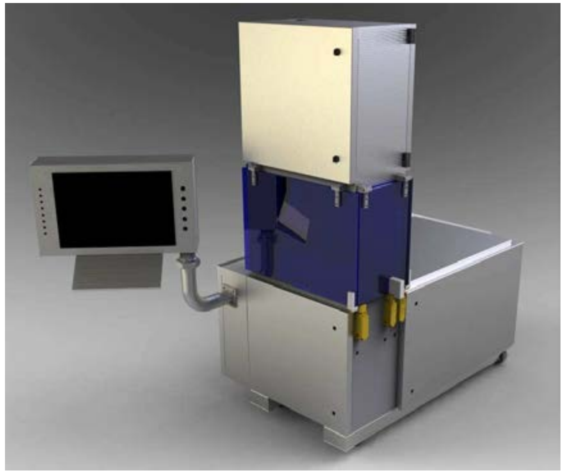
Current prototype model based on 2 Mk APIs and PBO mixtures as DC formulations. Output is Tensile strength as a function of compaction pressure.

Diluent Study Experimental DOE Design

FSC

JMP
Data Collection

Model Assessment



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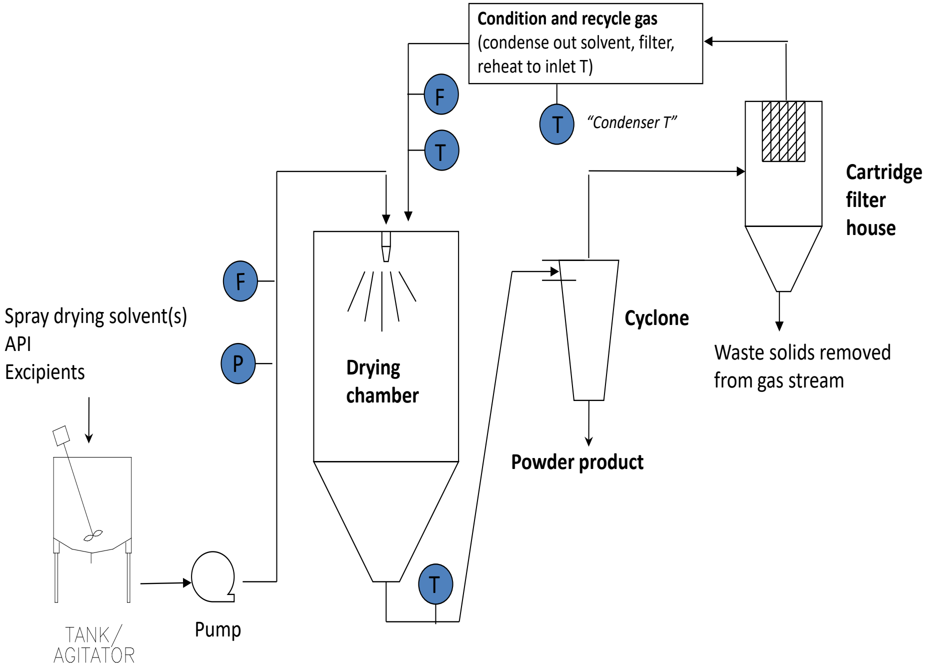
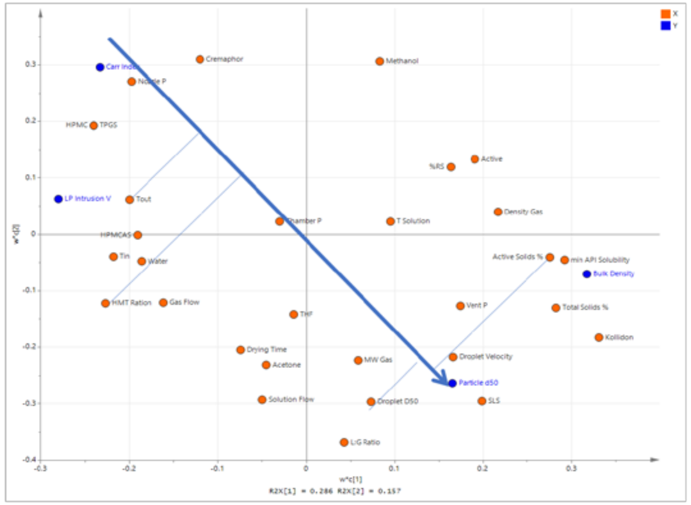
Data driven Model of Spray Drying Process and Formulation



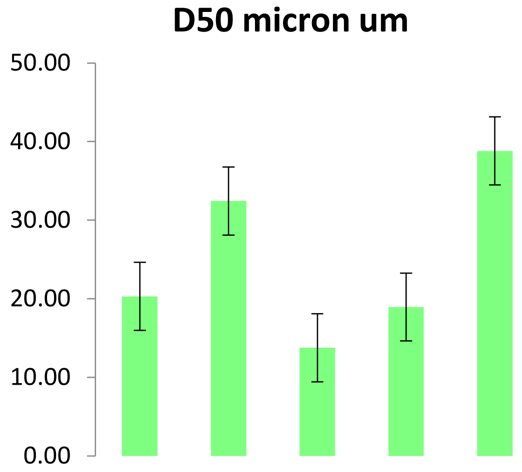
PLS weights plot of the multi-Y PLS exploratory model, PC1 vs. PC2

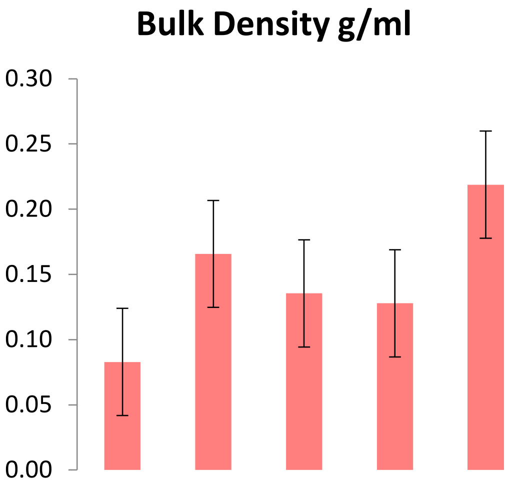


To Maximize Particle Size:
Increase → Droplet PSD, Solids Loading, Kollidon
Decrease → Tout, HMT Ratio, Water, Cellulosic Polymers

Input solvent, solids composition, and process conditions.

Predicts SDI particle attributes PSD and bulk Density



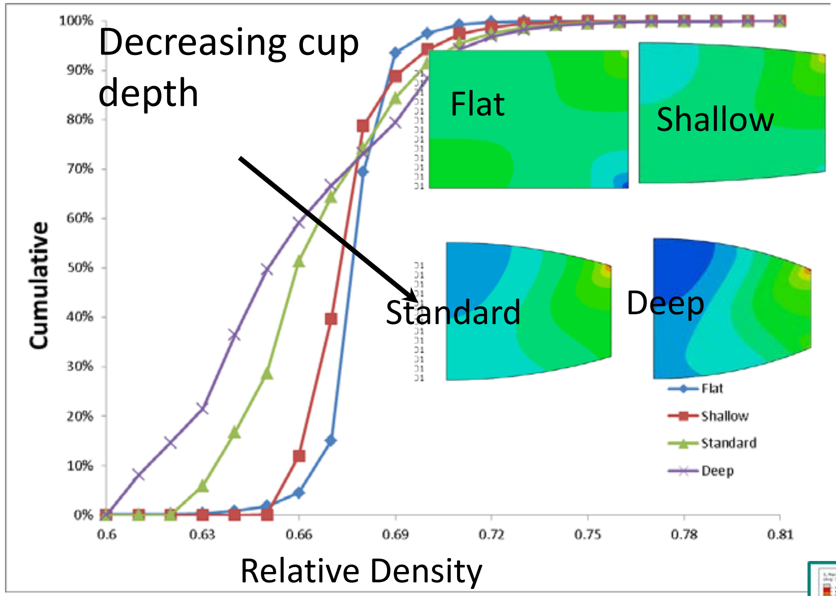


Fundamental modeling and simulations

Modeling Engine
FEM/FD/ML

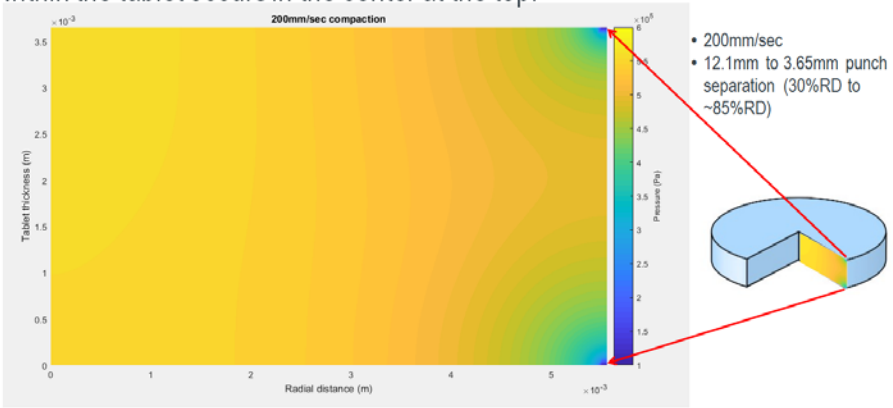
- Density/Stresses
- Air Pressure
- Drop Testing
- Embossing
- Stregth/Friability
- Phase Change

Shape Modeling



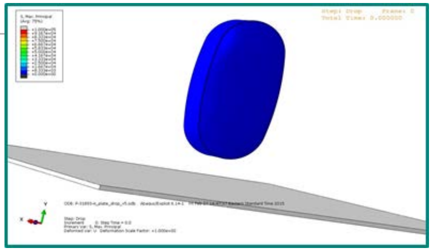
Air Pressure Modeling

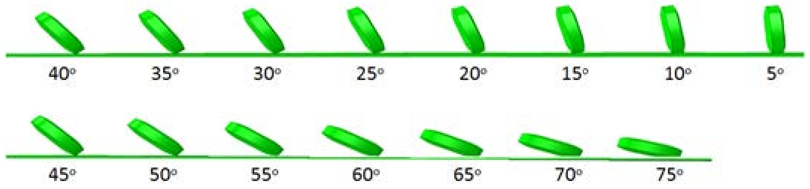
Full 2D solution with varying density shows that the maximum pressure within the tablet occurs in the center at the top.



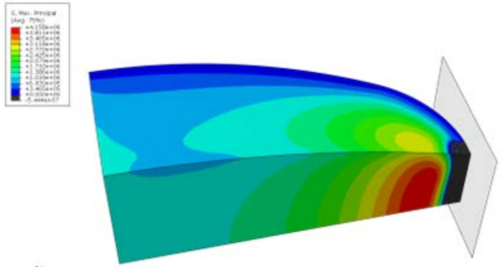
Pressure distribution at end of compaction

Drop Test Simulation

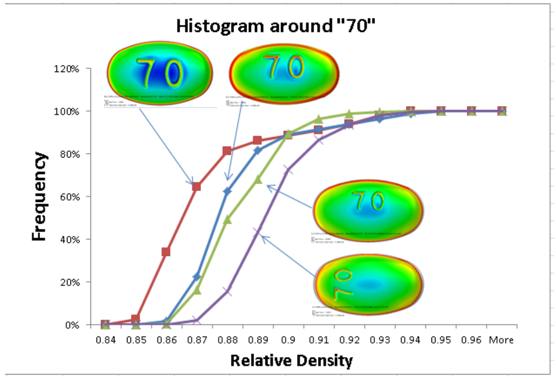




Hardness Test Simulation



Effect of Embossing on Density



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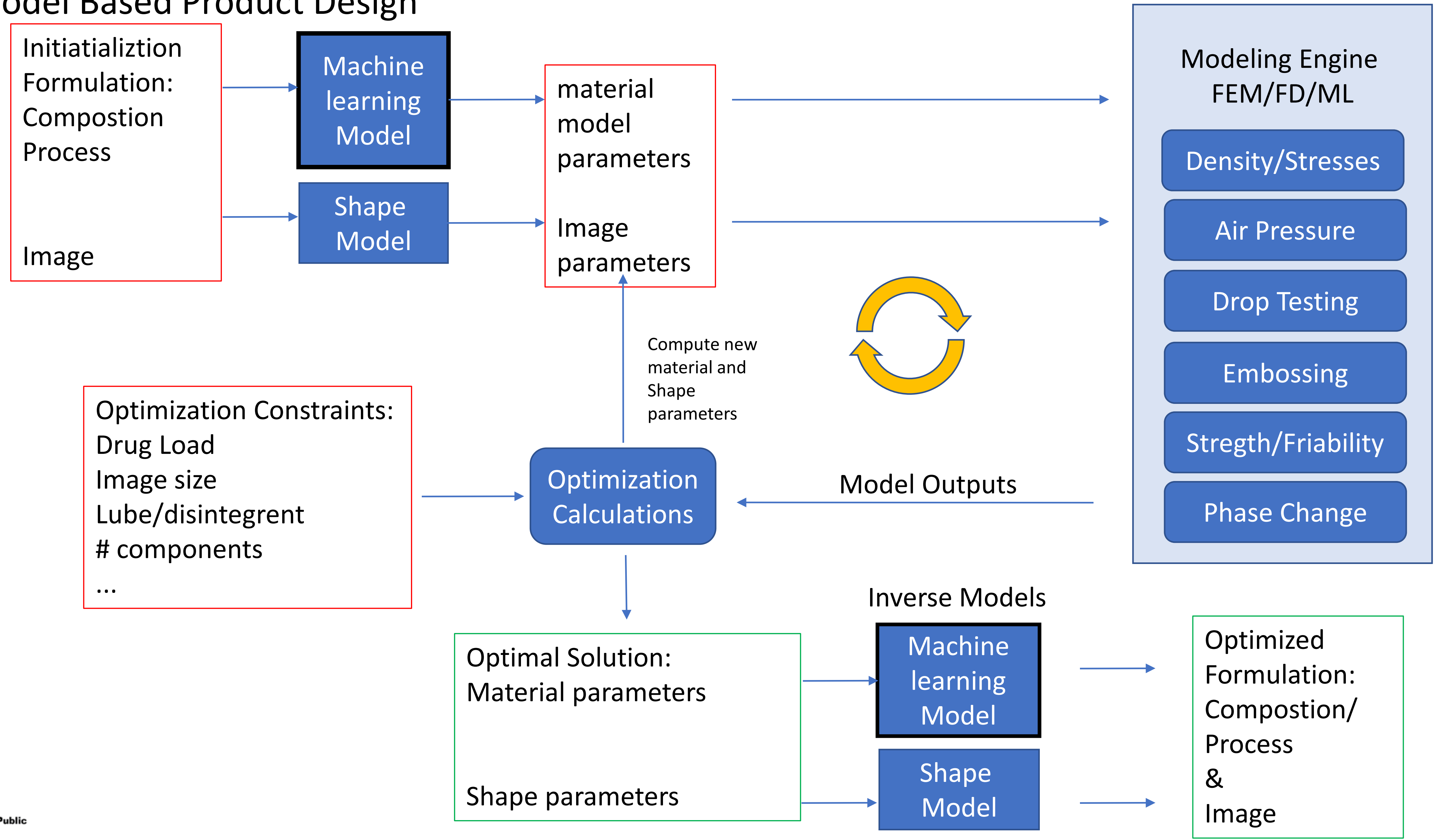
Model Based Product Design



Conclusions

- Value of Iterative product design during product prototyping
- Smart Throughput experimentation provides value throughout the development cycle
- These tools provide an opportunity to data mining and empirical model building
- Bridging the gap to fundamental modeling