Applied Process Understanding in Drug Product Development

A combined pharmaceutical science, materials science and chemical process engineering approach

17 October , Heidelberg, Germany

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The Unpredictability of Dose Forms

- What we want:
  - Design Space: “The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” *- ICH Q8*
- What we usually have:
  - ‘Unpredictable’ Dose Forms

  Definition: “Incapable of being determined in advance whether by observation, experience or reason.” – *Projectauditors.com*
- What we would benefit from
  - A more prominent use of physics, chemistry and engineering within a ‘framework’ that can guide our drug development efforts”

The Materials Science Approach

Need to capture the right information about the raw material properties

RAW MATERIALS
PROCESS

The process will impact on the functionality of the raw materials

Microstructure

Manifestation of materials & process

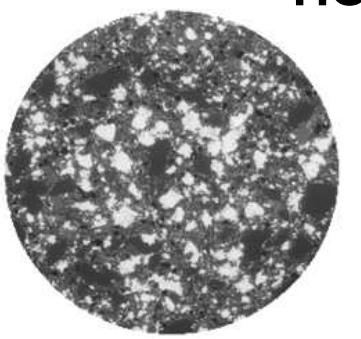
PROPERTIES

Physical
&
Mechanical

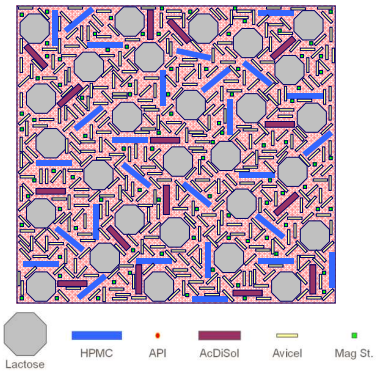
INGESTION
DISINTEGRATION
DISSOLUTION
ACTION

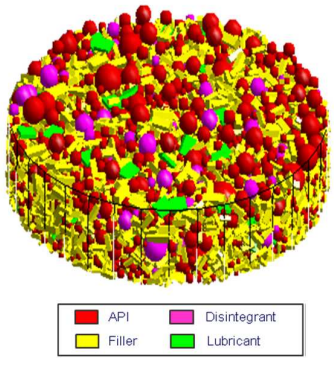
PERFORMANCE

HOW?... - Visualisation Tools



Microscopy can take time and requires an actual sample





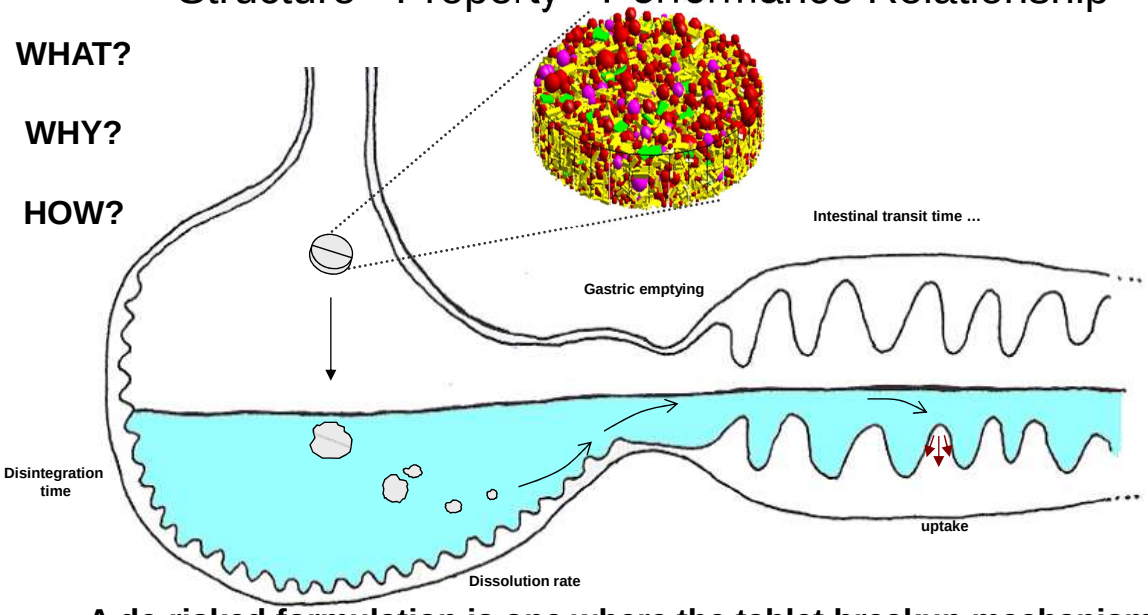
- A tool to generate structures in 3D could give clues as to how a microstructure should look.
- Be able to determine theoretical percolation points. (API-dominated or Excipient Dominated?)
- This virtual microstructure approach lends itself to QbD as one is able to do some virtual stretching of the raw materials as a precursor to any lab-based DOEs.

The importance of Micro - Structure
Structure - Property - Performance Relationship

WHAT?

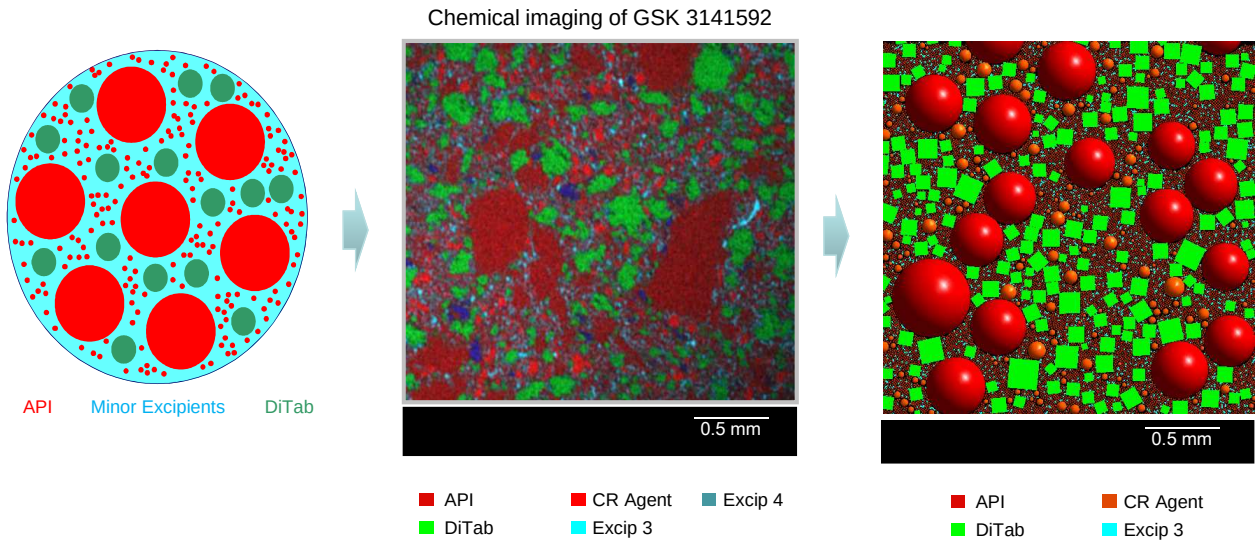
WHY?

HOW?

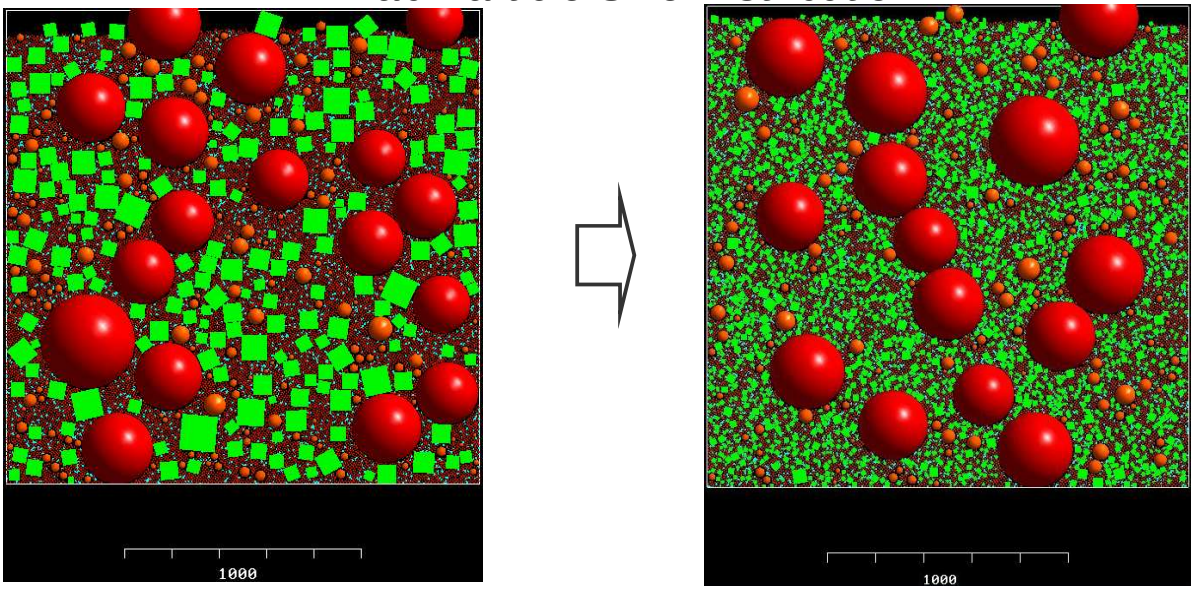


A de-risked formulation is one where the tablet breakup mechanism consistently ensures correct drug release rate and uptake

Using MacroPac to recreate Virtual Microstructures



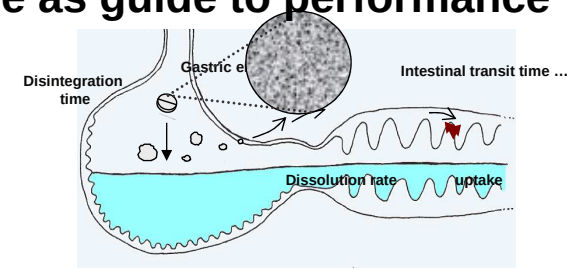
GSK 3141592 Raw Material CQAs II
DiTab Particle Size Distribution



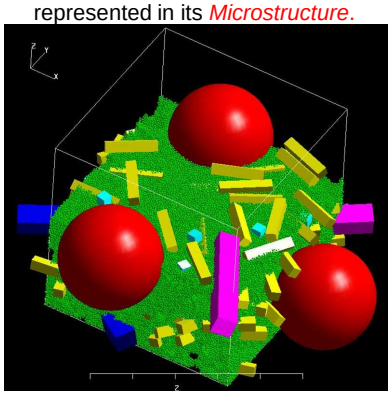
Smaller size of milled DiTab effectively **destroys the continuous phase** formed by the API

Formulation microstructure as guide to performance

- Visualise the microstructure of the formulation in 3D (simulation)
- Deduce performance relationship with observed microstructure
- Use virtual microstructure approach in QbD – virtually assess materials as precursor to lab-based DoEs
- Note proposed new USP General Information Chapter, Excipient Performance <1059>

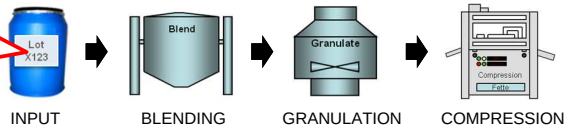


tablet break – up mechanism is a combination of raw materials & processing represented in its *Microstructure.*

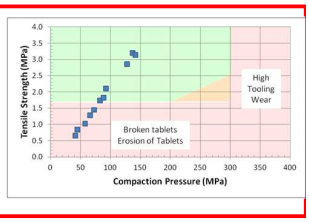


Formulation Risks & The Control Strategy

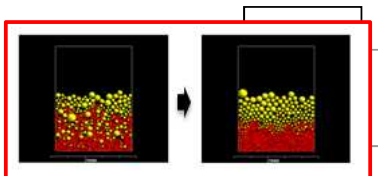
API Properties



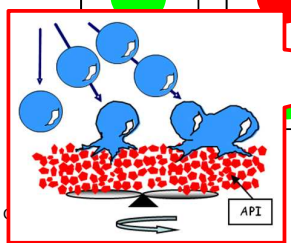
DP CQAs



Tabletability



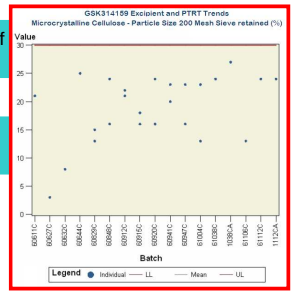
Particle Size
Size Distribution



Water Amount
Wet Massing Time

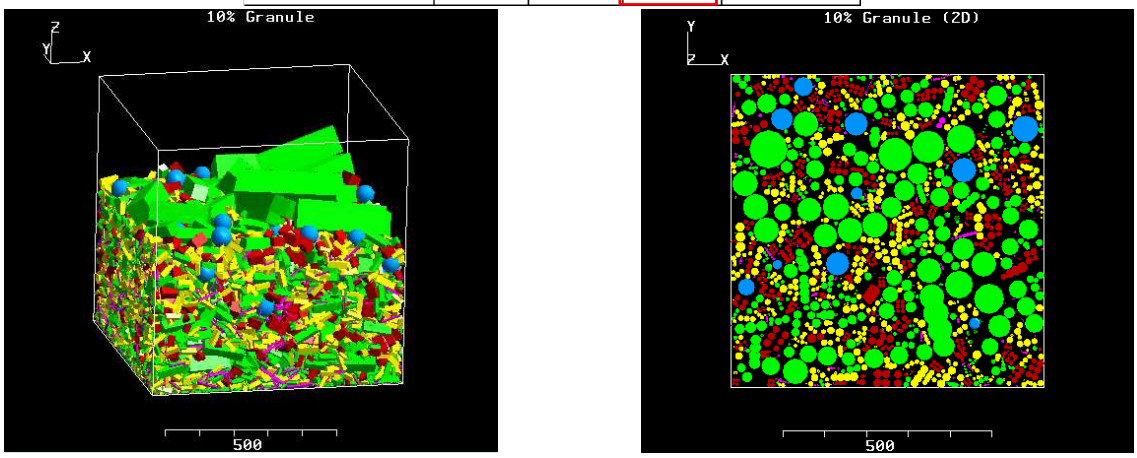
- Description
- Identification
- Drug related impurities
- Uniformity of Content
- Tablet Dissolution

What to Trend?



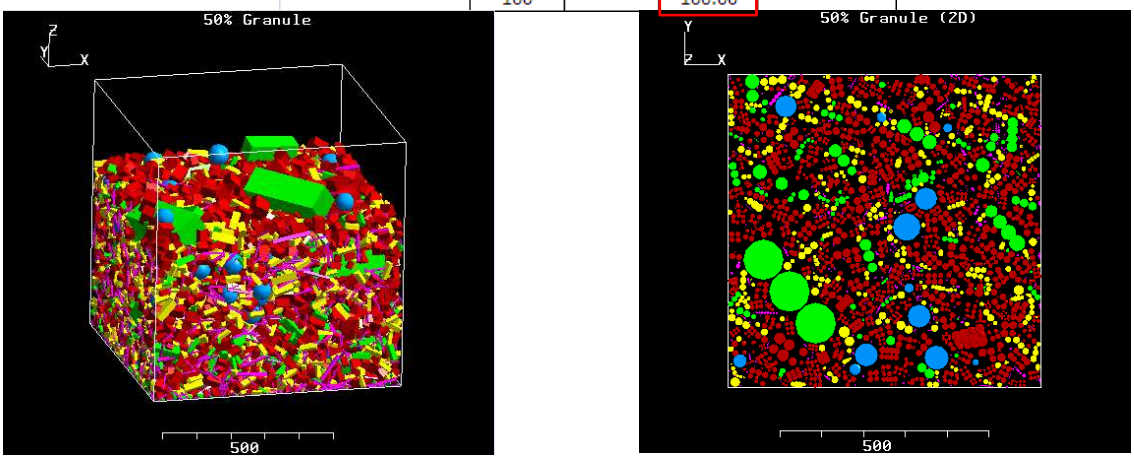
GSK 3141592 - 10% API Granule Formulation

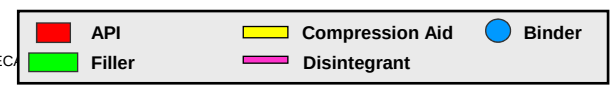
Granule 10%	w/w%	TD	v/v%	Size x50 (um)
GSK3141592 API	10	1.3	11.42	50
Filler	63.5	1.5	62.84	160
Compression Aid	20	1.6	18.55	50
Disintegrant	1.5	1.5	1.48	50
Binder	5	1.3	5.71	60
	100		100.00	



GSK 3141592 - 50% API Granule Formulation

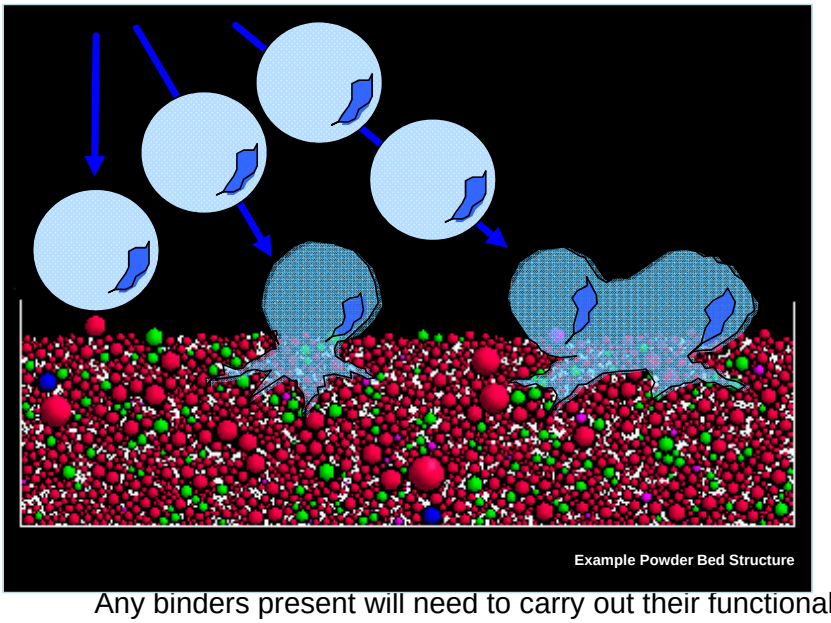
Granule 50%	w/w%	TD	v/v%	Size x50 (um)
GSK3141592 API	50	1.3	53.81	50
Filler	21	1.5	19.59	160
Compression Aid	20	1.6	17.49	50
Disintegrant	4	1.5	3.73	50
Binder	5	1.3	5.38	60
	100		100.00	





‘Rich Picture’ for High Shear Wet Granulation

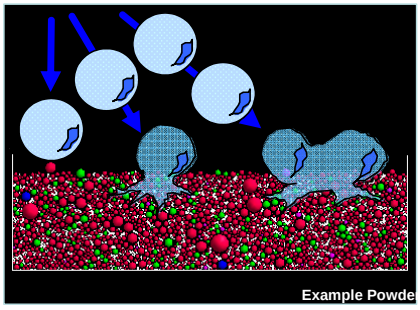
Spray water solution

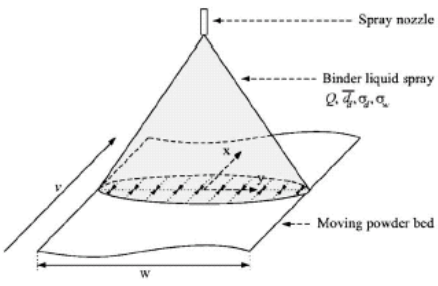


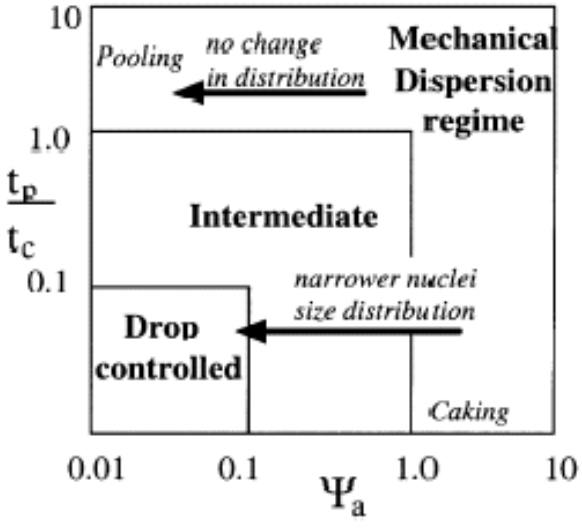
- Powder blend material ‘engulfed’ by water droplets
- Water interacts with excipient particles by hydrating them, forming gelatinous matter in some cases
- Any viscous matter formed is able to spread and ‘coat’ all other particles with which it comes into contact during further mixing.

Any binders present will need to carry out their functionality during granulation.
Any disintegrants present will need to retain their functionality for dissolution/ingestion

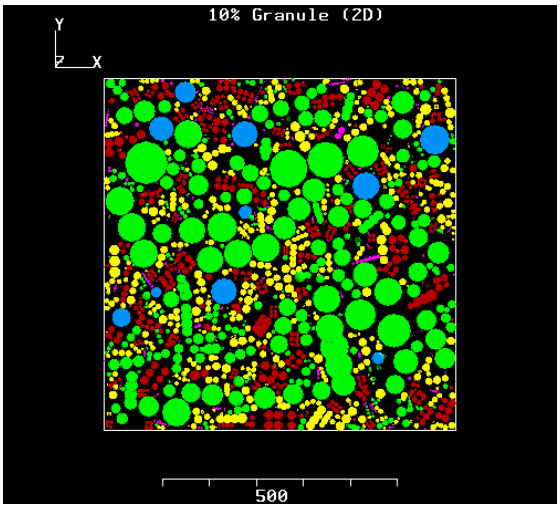
Nucleation regime map

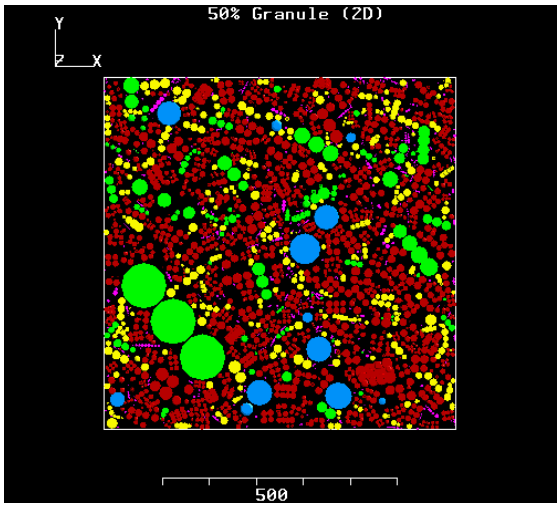






Comparing Granule Structures





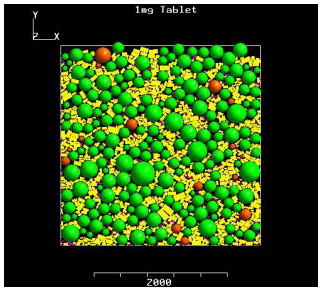
API
Filler
Compression Aid
Disintegrant
Binder

Risks to Consider:

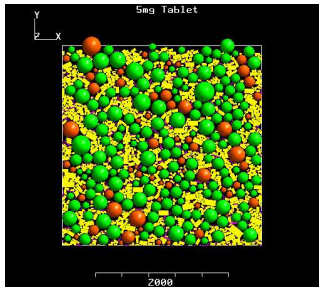
- Binder capability during Granulation
- API wettability during Granulation
- Particle Size Distribution, flow properties of dried granules
- Compressibility of final granules

Comparing Tablet Structures

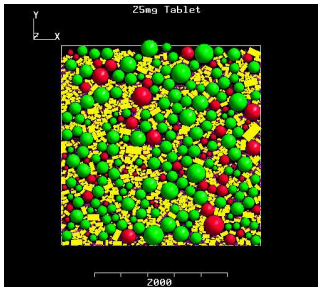
1mg



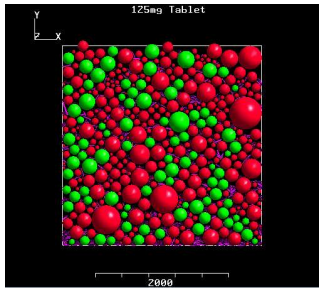
5mg



25mg



125mg



10% Granule
50% Granule
Compression Aid
Disintegrant
Filler

Risks to Consider:

- Segregation of species (granules or excipients)
- Flow of powder blend (hopper & tablet press)
- Tabletability of blend (tensile strength, compaction pressure, solid fraction)
- Coating of tablet surface

The Compaction Triangle

size, density
(homogenous blend)

powder flow

(lubrication)

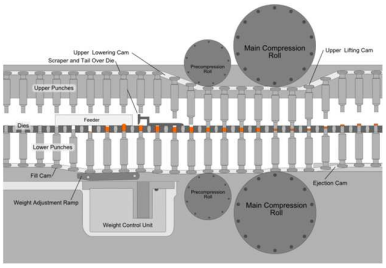
typical employed product performance relationship

breaking force (hardness)

disintegration dissolution

weight (mass)

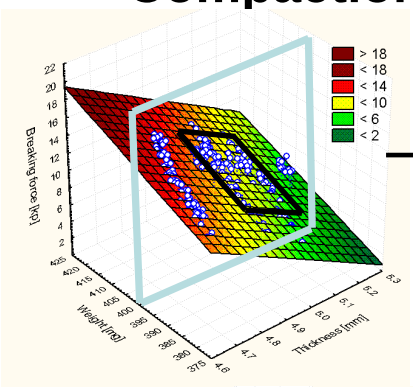
thickness

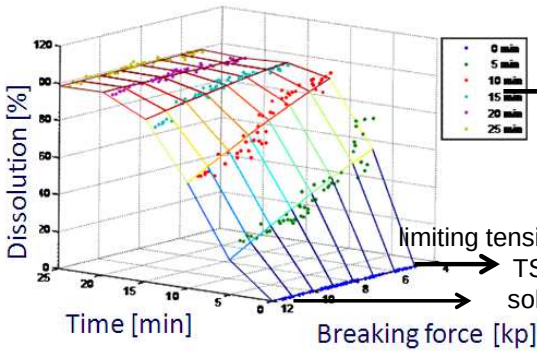


determined by:
fill depth,
powder bulk density
powder flow

determined by:
punch separation
(cylindrical height)
weight (mass)
…

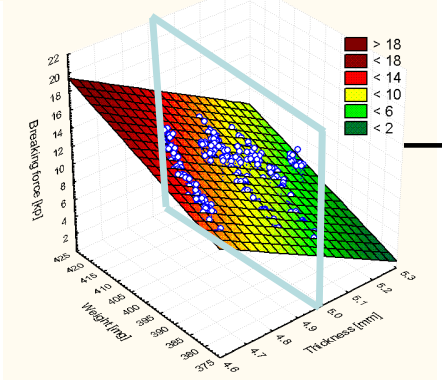
Compaction – Design Space Development

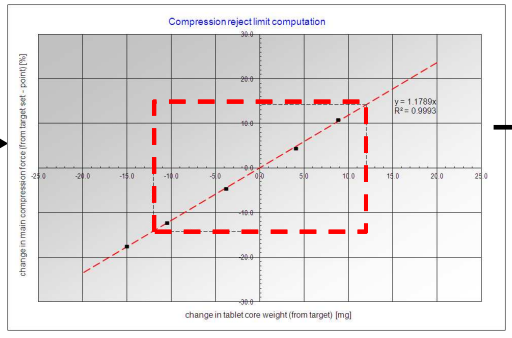




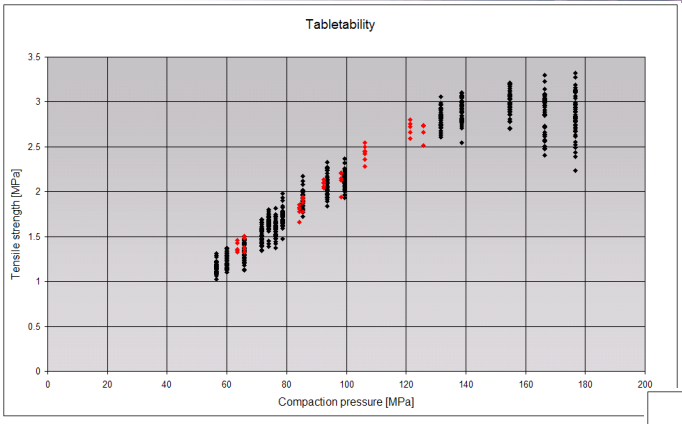
IPC limits breaking force to assure dissolution

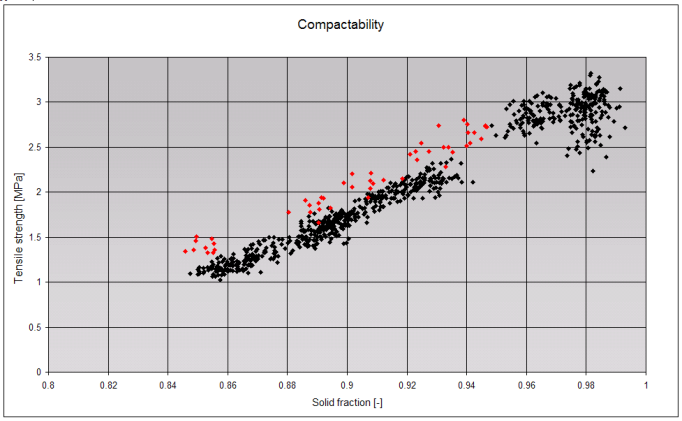
limiting tensile strength ~ 1.7 MPa
TS = 1.6 MPa
solid fraction ~ 0.95
SF = 0.93





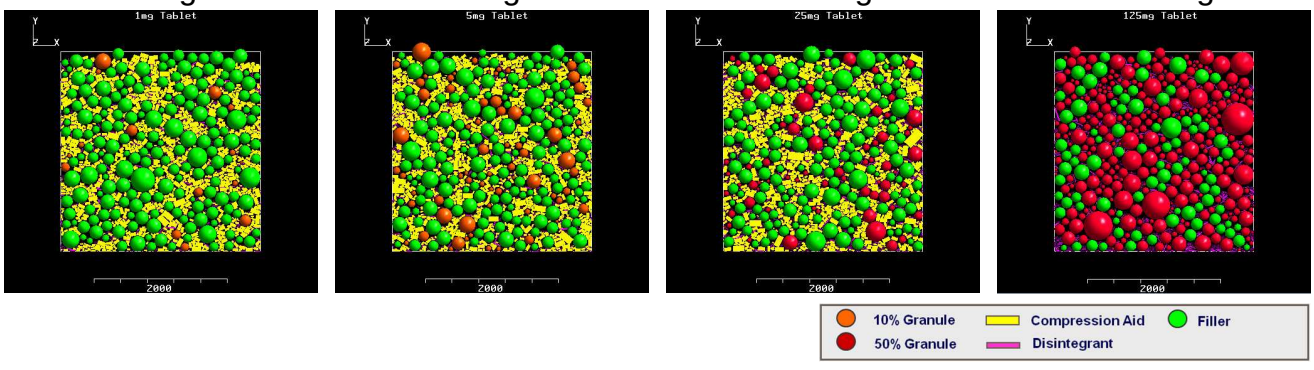
compression force control to assure weight (uniformity)





Comparing Tablet Structures

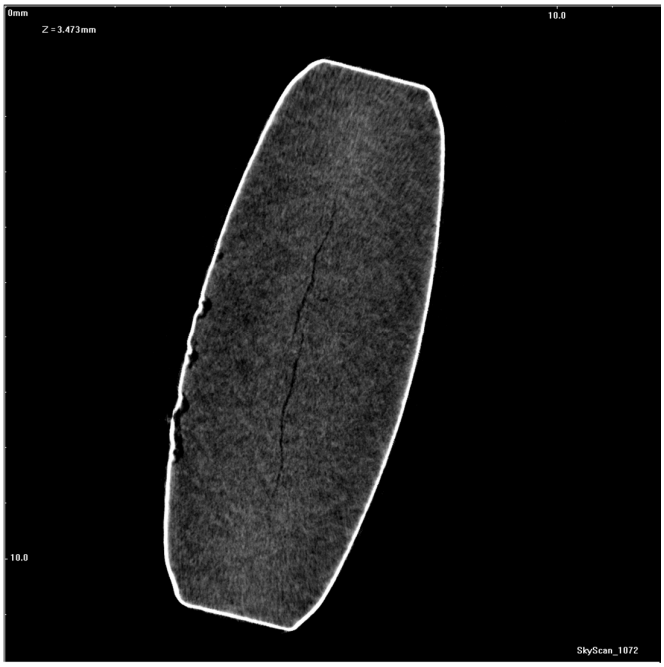
1mg 5mg 25mg 125mg



Risks to Consider:

- Segregation of species (granules or excipients)
- Flow of powder blend (hopper & tablet press)
- Tabletability of blend (tensile strength, compaction pressure, solid fraction)
- Coating of tablet surface

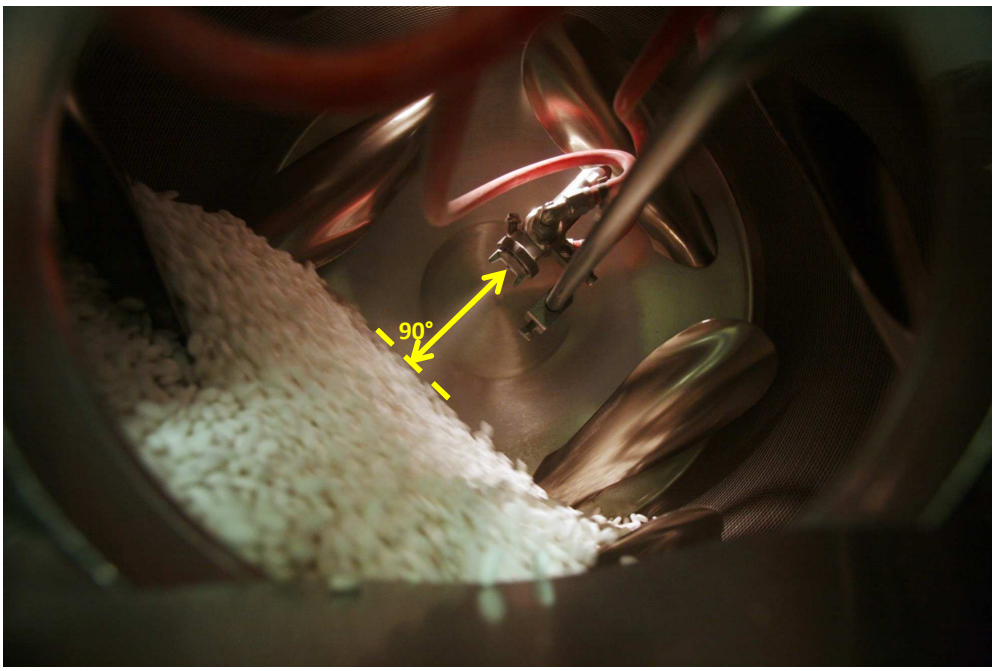
not all mechanical failure is visible to the naked eye



- Tablet debossing = 150 µm

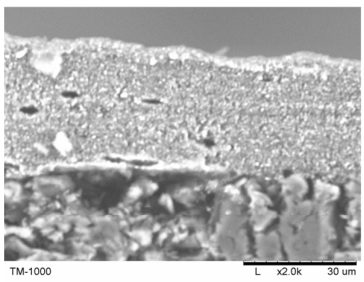
Film Coating

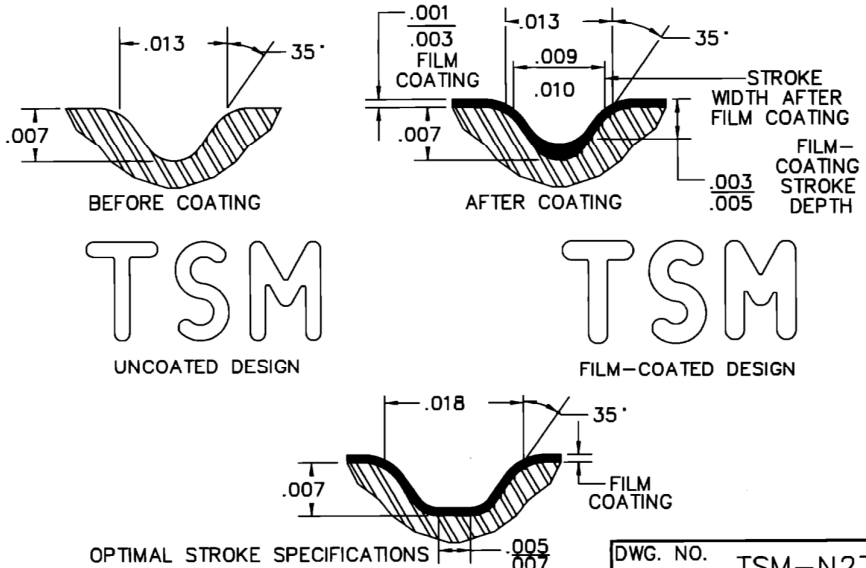
- Quality:
  - (1) film coat amount
  - (2) environmental conditions of film formation



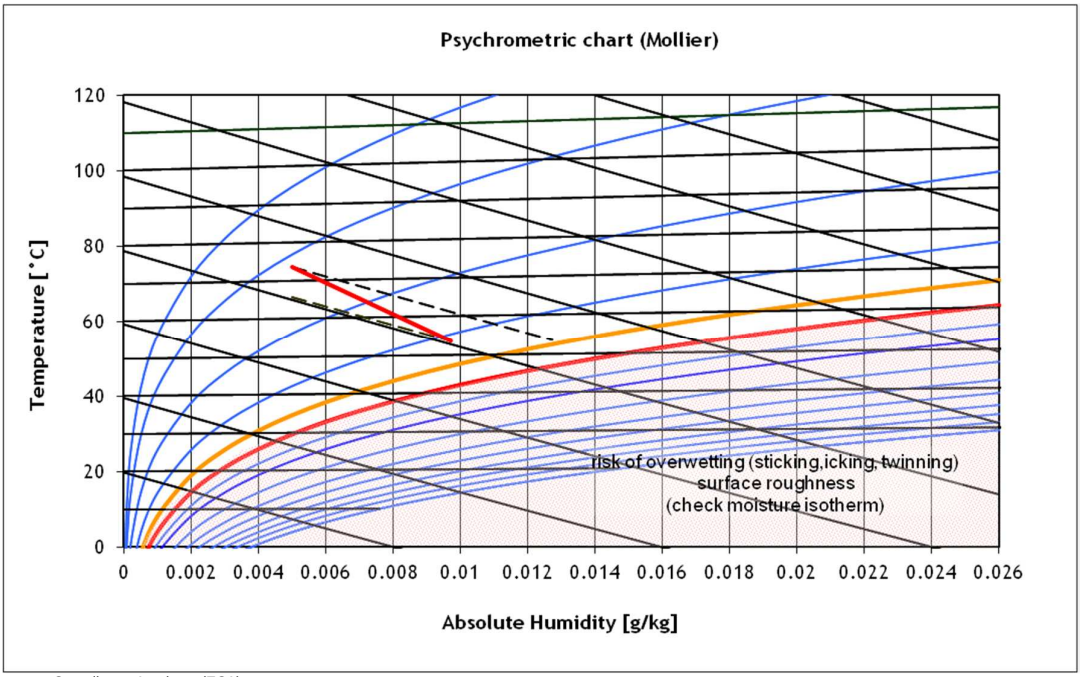
Tooling Design

FIGURE 27. GUIDELINES FOR FILM COATING





Psychrometric chart



The importance of Micro - Structure
Structure - Property - Performance Relationship

WHAT?

WHY?

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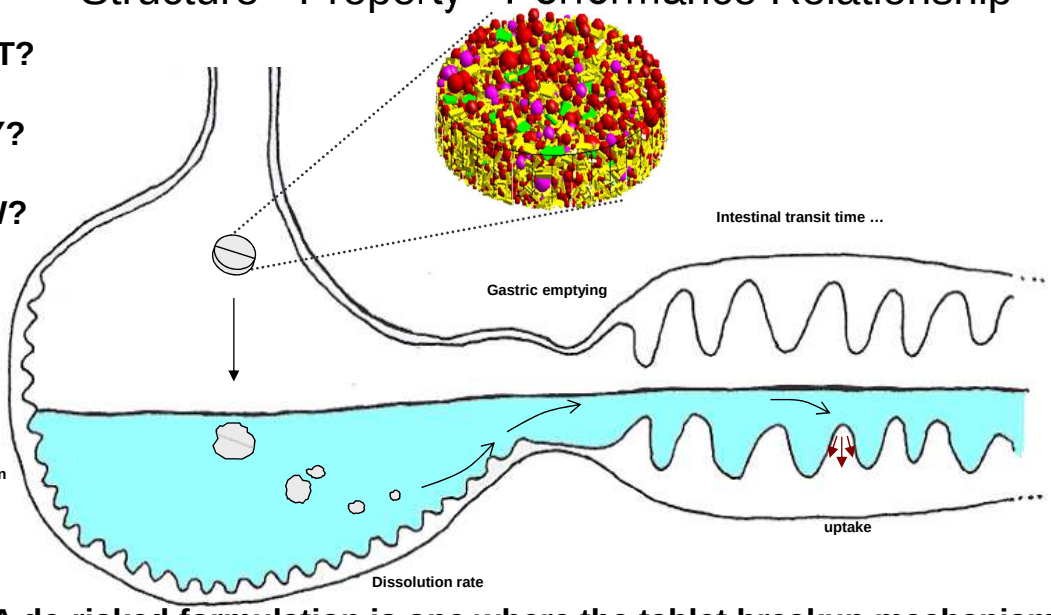

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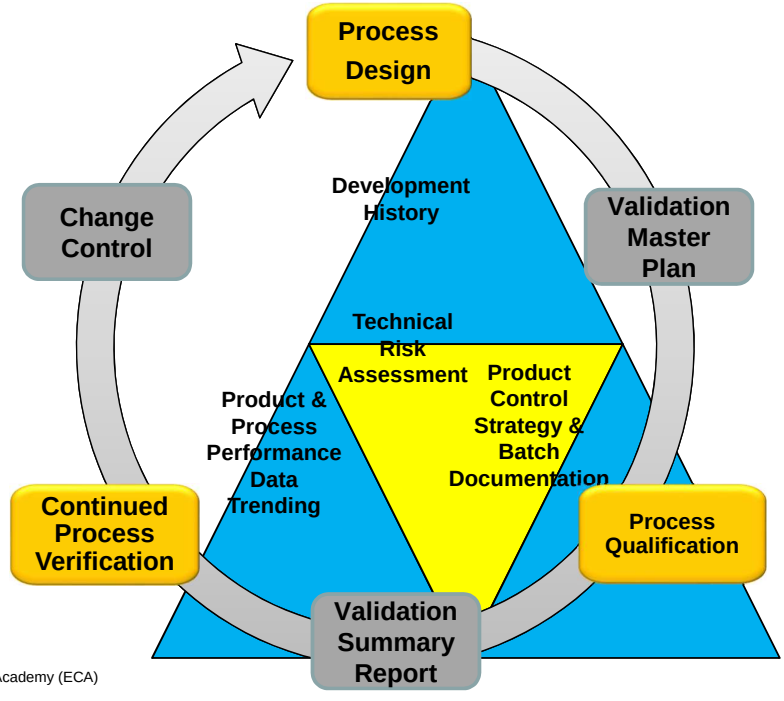
Product Quality Lifecycle Management



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Concluding Remarks

- Putting together a robust design space requires knowledge of the key product & process parameters that will affect the quality of a dosage form.

- By adopting a Materials Science approach we can begin to do two things:
  - 1. Have a greater understanding of the functionality of our raw materials, with the knowledge that this functionality may change depending on the dosage from in which they are incorporated.
  - 2. Make greater use of the phase volumes, size and shape of our excipients in 3D models to aid with tablet breakdown mechanism hypotheses.

- This approach will help to de-mystify our dosage forms, identify the correct Drug Product CQAs, and ultimately enable us to more readily ***demonstrate*** our scientific understanding of our dosage forms in our filings.