8TH ANNUAL PTI TRAINING PROGRAM

FORMULATION AND PROCESS DEVELOPMENT FOR ORAL DOSAGE FORMS

A 5-Day Modular and Case Study Oriented Training Program

AUGUST 27-31, 2012 - NASSAU INN - PRINCETON - NJ - USA

Historical Location, Reputable Speakers & Innovative Program

GRANULATION

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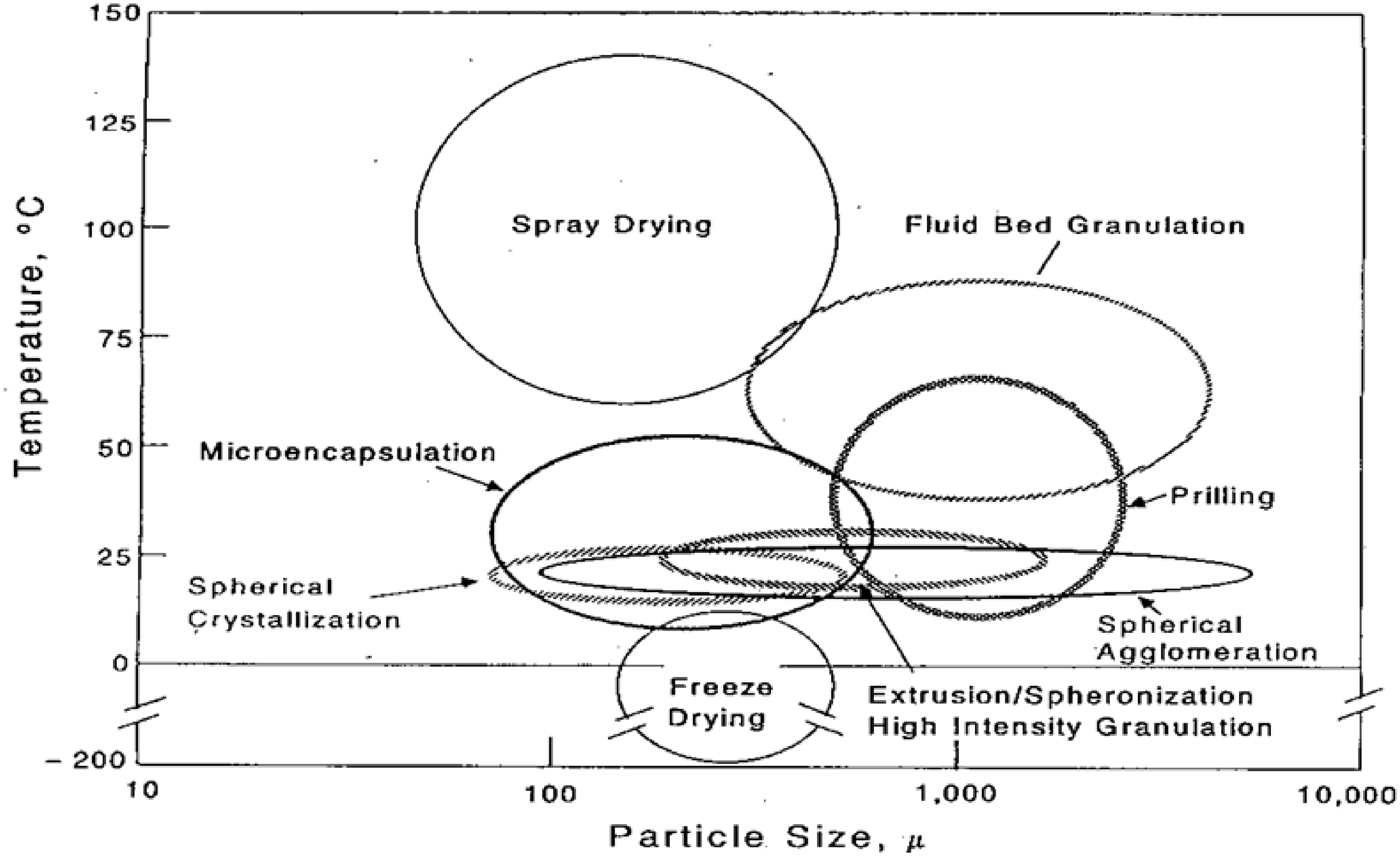
OUTLINE

- Introduction
- Roller Compaction
- Wet Granulation Mechanism & Techniques
- Granulation Equipment
- Process Control & Scale-up Issues
- Melt Granulation
- Single Pot Processing
- Extrusion and Spheronization
- Melt Extrusion
- Integrated Systems

Overall Hypothesis

- Granulation can be predicted from:
  - the raw material properties and
  - the processing conditions
    of the granulation process.

Particle Generation & Growth



Granulation Approaches

- Direct Compression
- Compression Granulation
  - Slugging
  - Roller Compaction
- Low Shear Granulation
- High Shear Granulation
- Extrusion/Spheronization
- Single Pot Systems
- Fluid Bed Granulation
- Integrated Systems

Attractive Forces Between Solid Particles

- If the particles are close enough then these surface forces can interact to bond particles:
  - *Van der Waals forces (short-range)*
  - *Electrostatic forces*
- Decreasing particle size increases surface/mass ratio and favors the bonding
- Van der Waals forces are sevenfold stronger than electrostatic forces and increase substantially when the distance between them is reduced which can be achieved by applying pressure as in dry granulation method

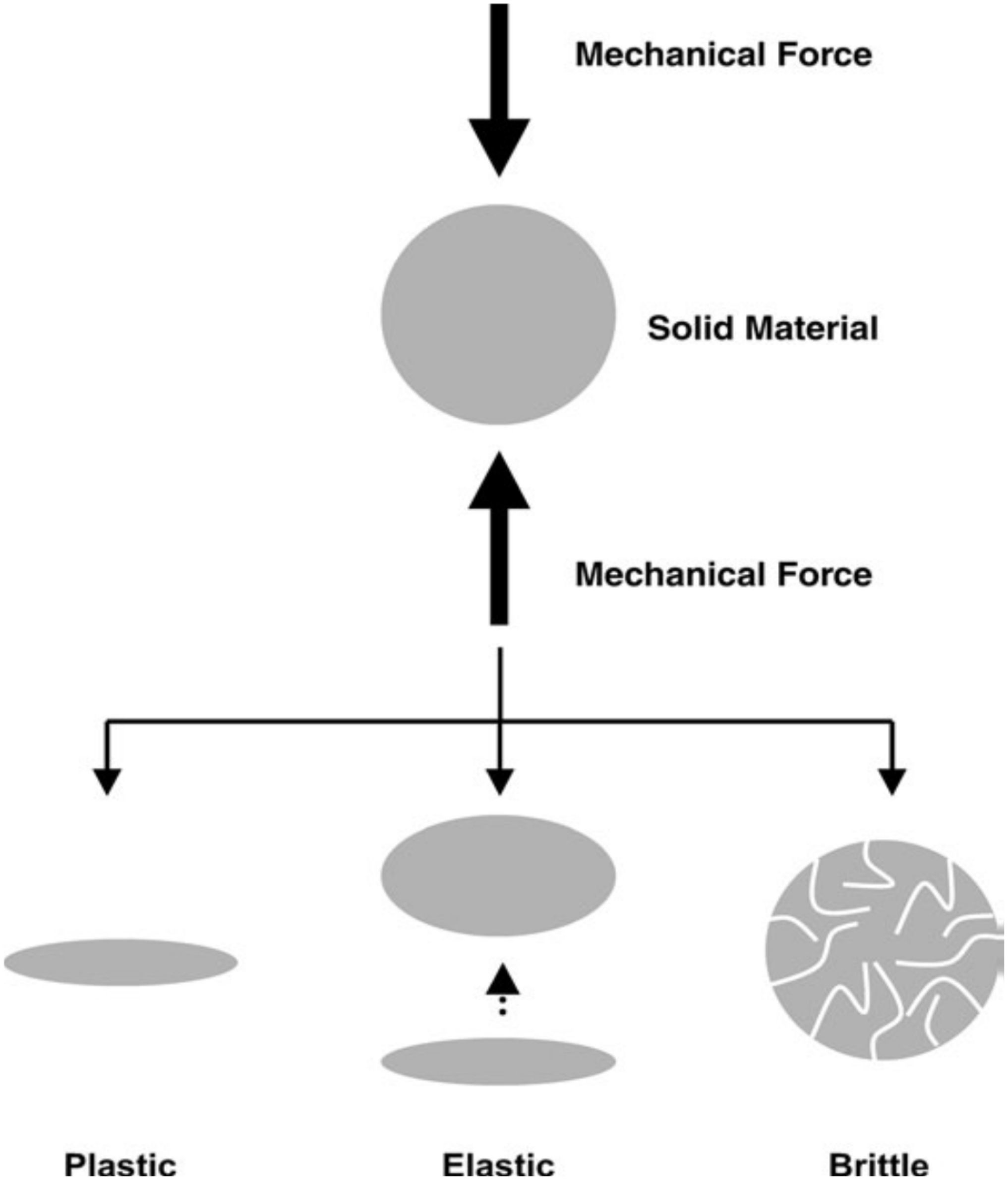
Dry Granulation

- The process of dry granulation relies on inter-particulate bond formation characterized by
  - Particle Rearrangement
  - Particles Deformation
  - Particle Fragmentation
  - Particle Bonding

Mechanical Effect on Powders

- When Pressure or Force is Applied
  - It creates stress which causes strain
  - There are three basic deformation mechanisms
    - Elastic deformation
    - Plastic deformation
    - Brittle Fracture
- Most material show a combination of at least two deformation mechanisms

Material classification on the basis of their deformation behavior in the presence of applied stress



Dry Granulation

- The process of dry granulation relies on inter-particulate bond formation characterized by
  - Particle Rearrangement
  - Particles Deformation
  - Particle Fragmentation
  - Particle Bonding

Slugging (Double Compression)

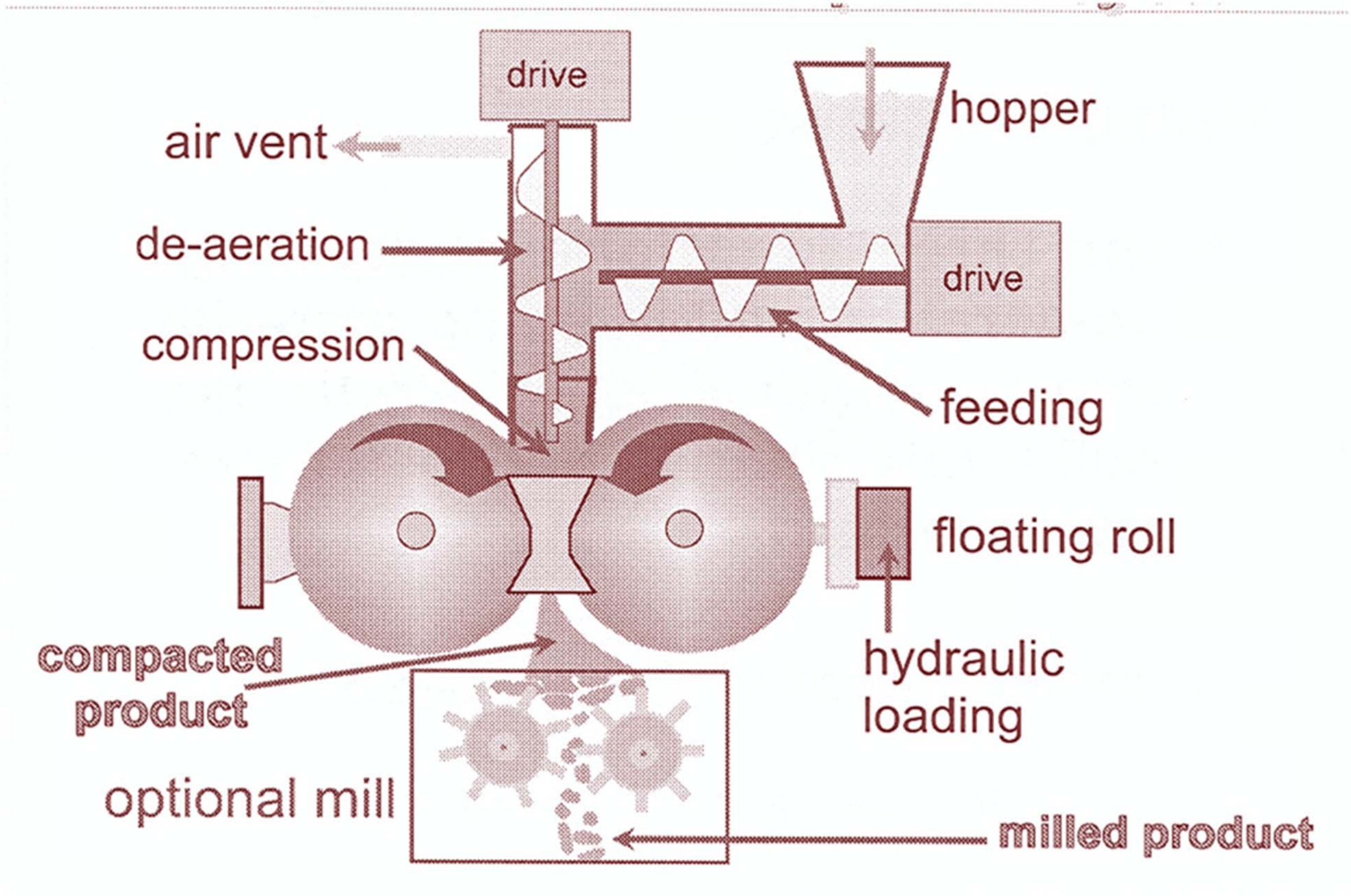
- For difficult to flow powder with a very low bulk density
- Compress powders on a tablet press into 25-50mm size tablet thus increasing density
- Milling these “slugs” to produce compacted granules
- Subjecting these compacted granules with a better density and flow property for subsequent processing.

Roll Compaction

- Provides a means for increasing bulk density and producing a coarser particle size distribution in a powder mix by compressing the material between the two rollers.

Roller Compactor

Double Screw Roll compactor- “Chilsonator”



Principles of Roll Compaction

- Essentially a three stage process:
  - Densification by removal of significant proportion of the air between particles in the augur feeder
  - Consolidation of particles as they pass between the rolls
  - Milling and classification of material after it emerges from the rolls

Dry Granulation with Roller Compaction

- The process of dry granulation relies on inter-particulate bond formation. Granule bond formation is characterized in different stages, which usually occur in the following order**:**
- ***particle rearrangement***

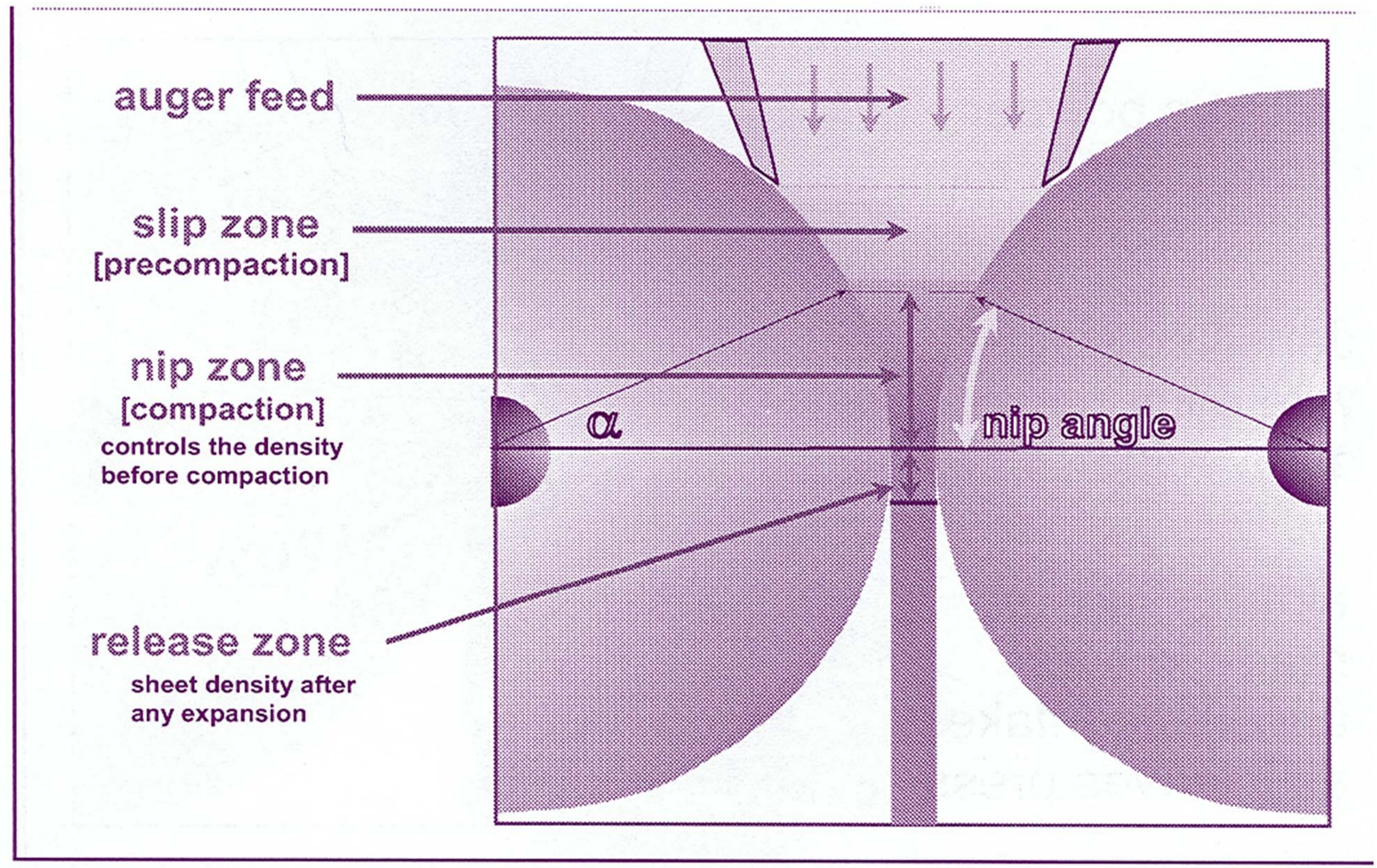
  occurs initially as powder particles begin filling void spaces. Air begins to leave the powder blend's interstitial spaces, and particles begin to move closer together. This action increases the powder blend's density.
- ***particle deformation***

  occurs as compression forces are increased. This deformation increases the points of contact between particles where bonding occurs and is described as plastic deformation
- ***particle fragmentation***

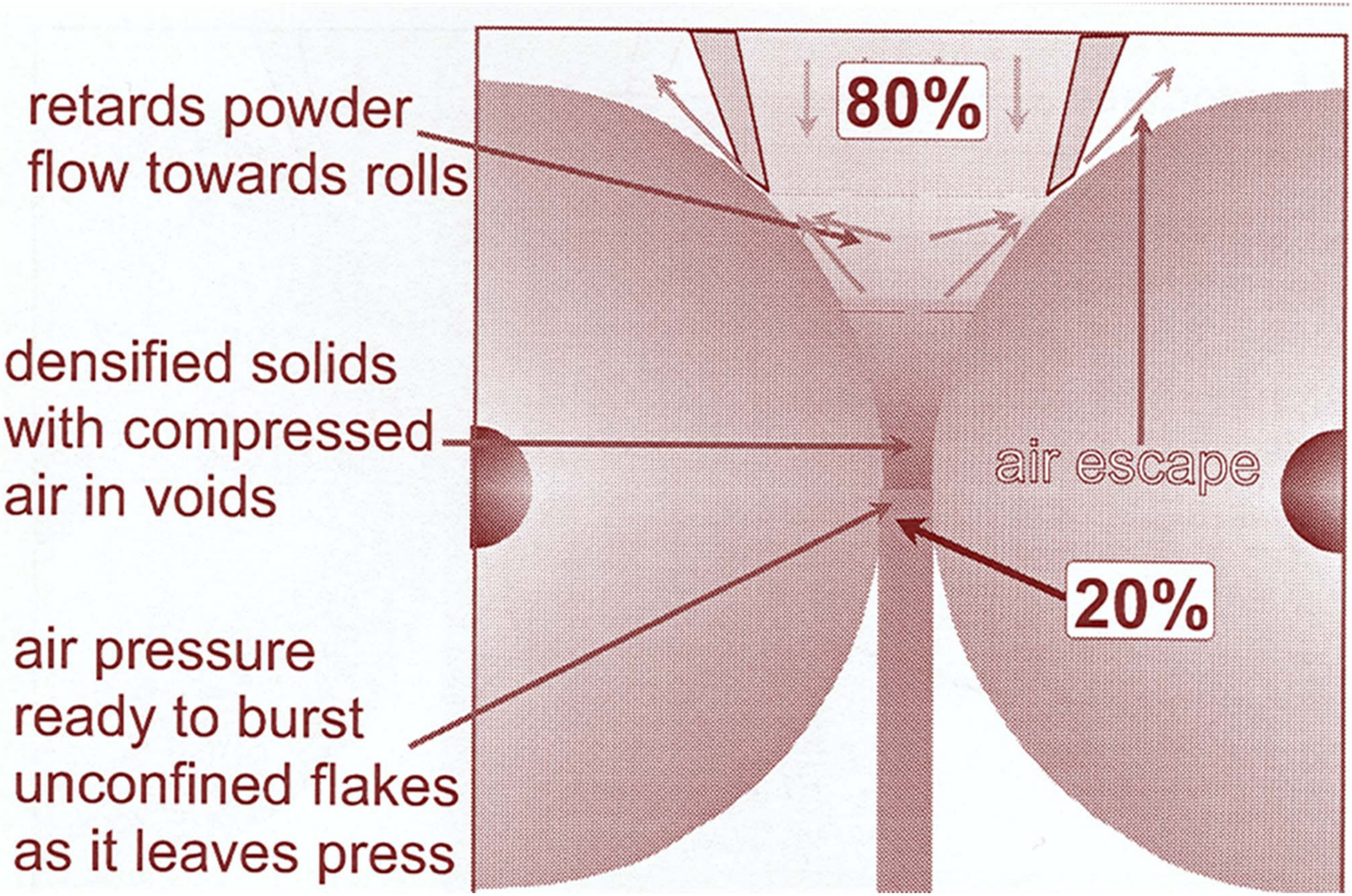
  occurs at increased compression force levels. At this stage, particle fracturing creates multiple new surface sites, additional contact points, and potential bonding sites.
- ***particle bonding***

  occurs when plastic deformation and fragmentation happen. It is generally accepted that bonding takes place at the molecular level, and that this is due to the effect of van der Walls forces

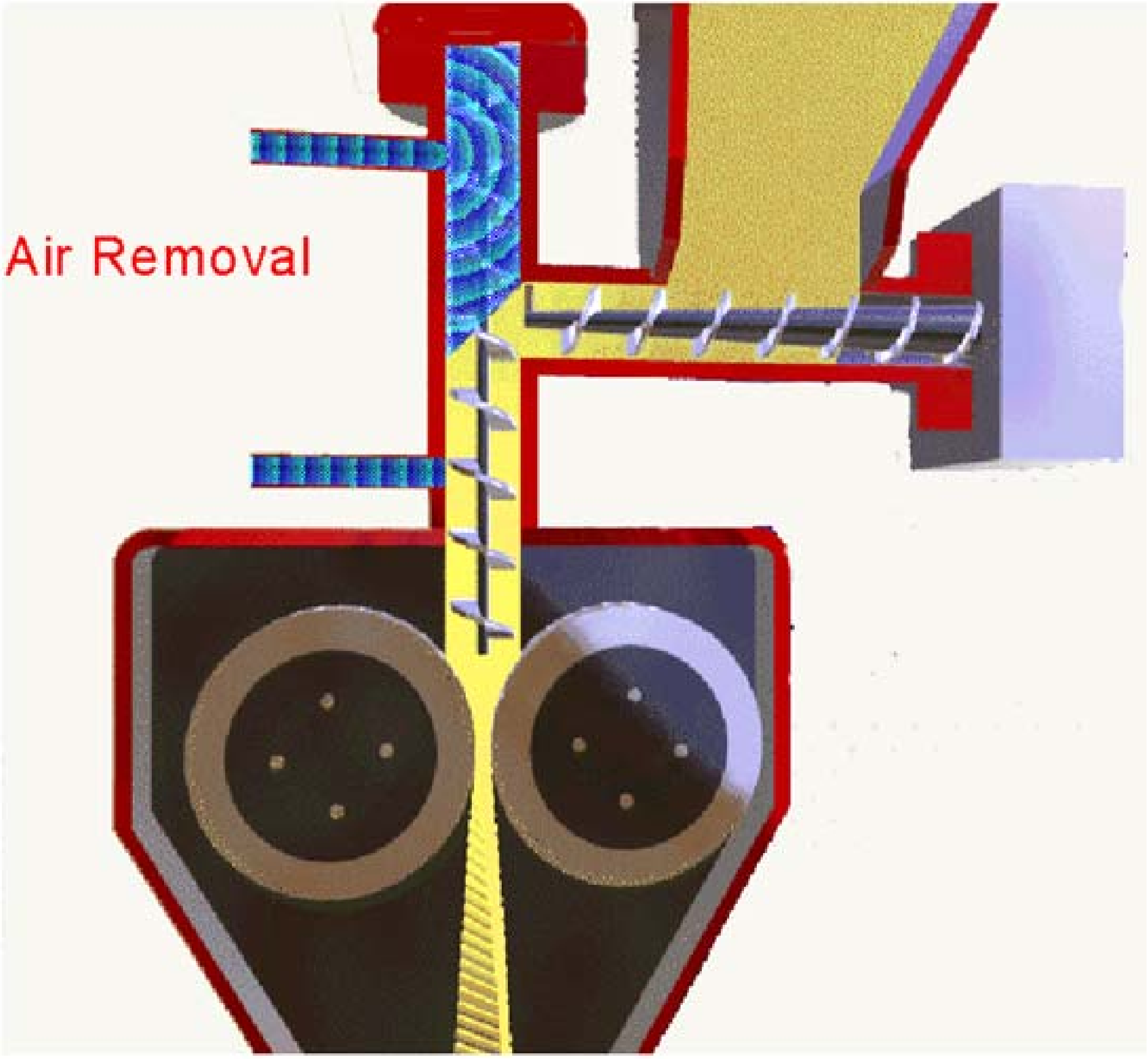
Densification Stages



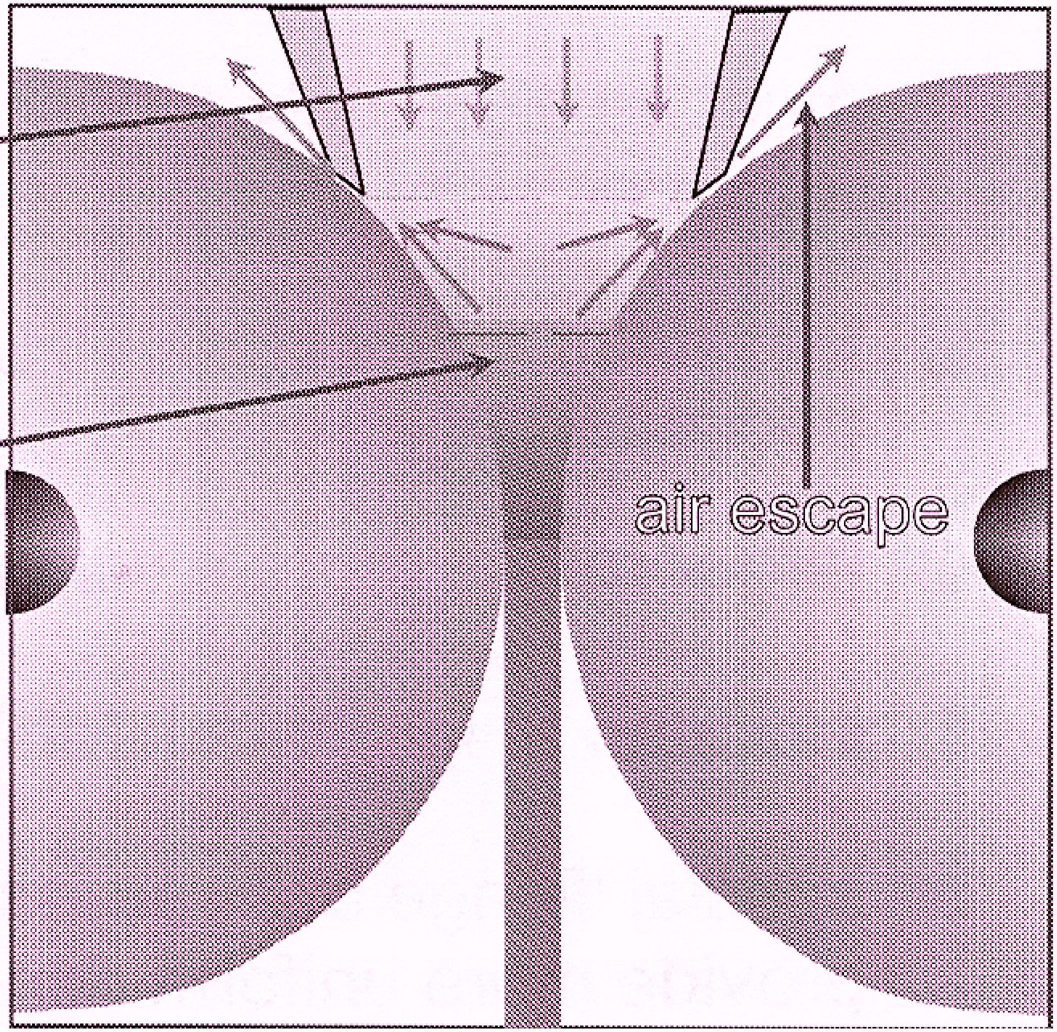
Effect of Air Content



Roller Compactor



Displacement of Air

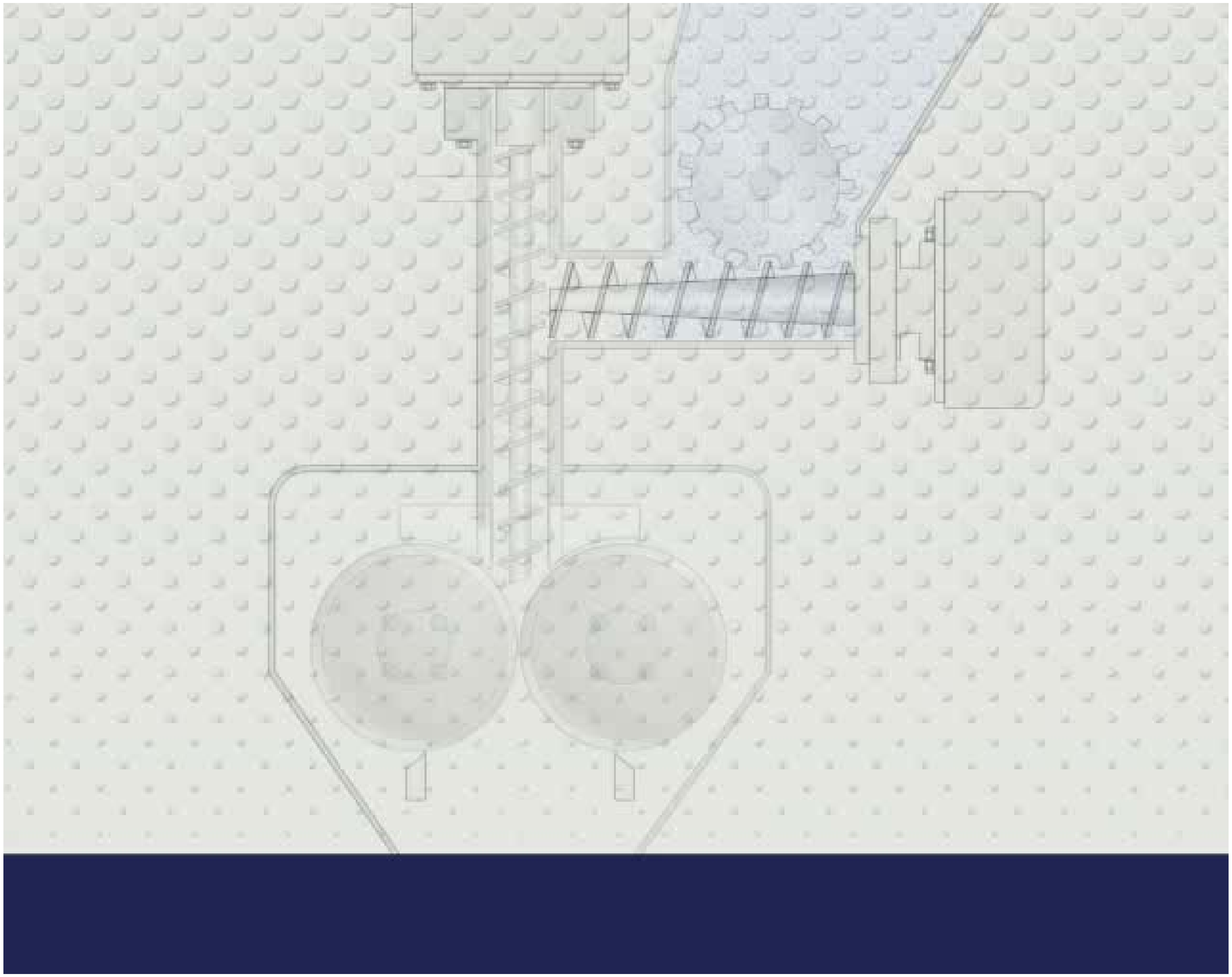


de-aeration by the auger is critical

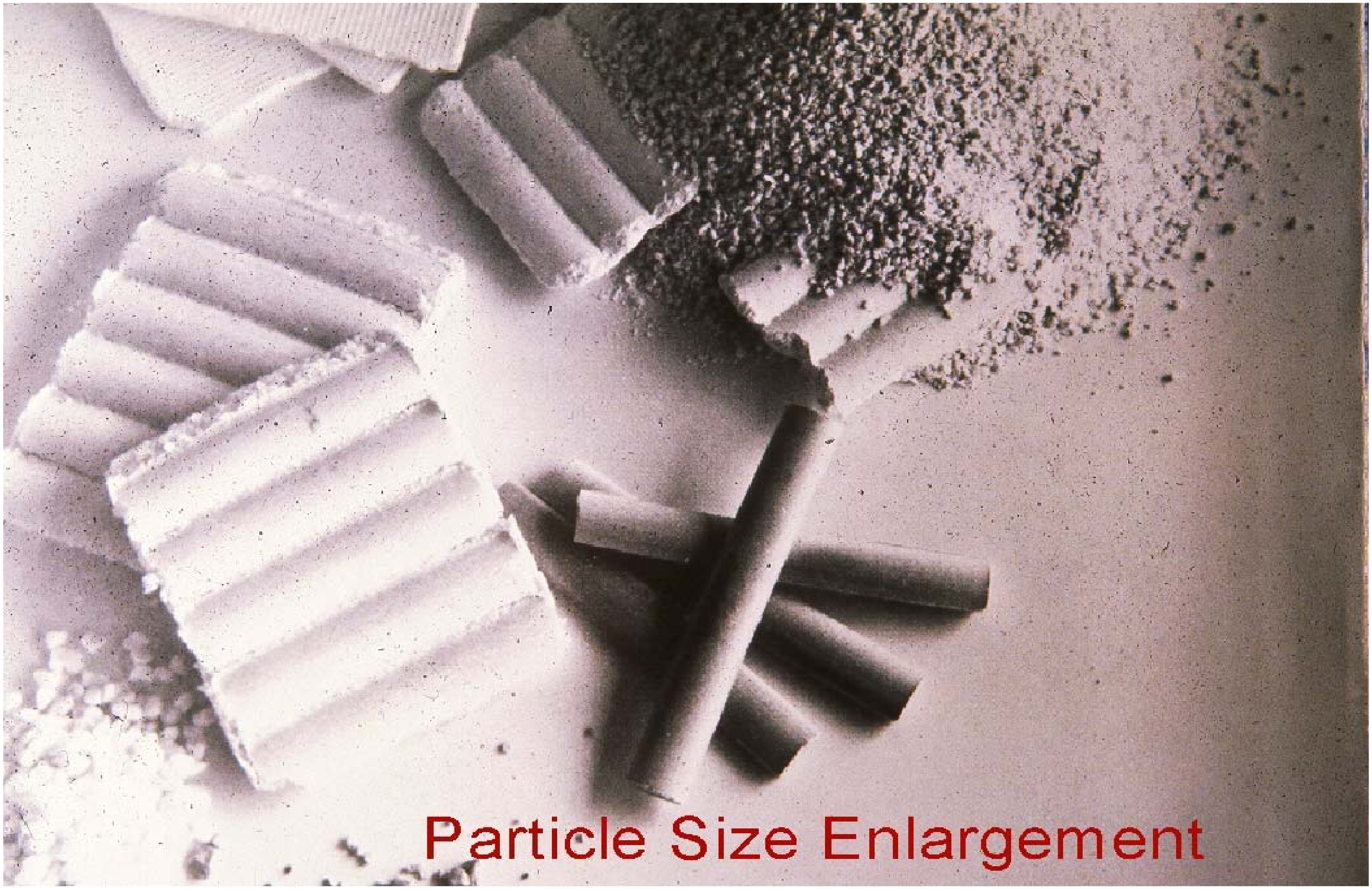
air squeezed upwards

Efficiency is measured by the volume of air removed per unit weight of material processed

Automatic Roll Gap Adjustment



Compacts from Roller Compactor

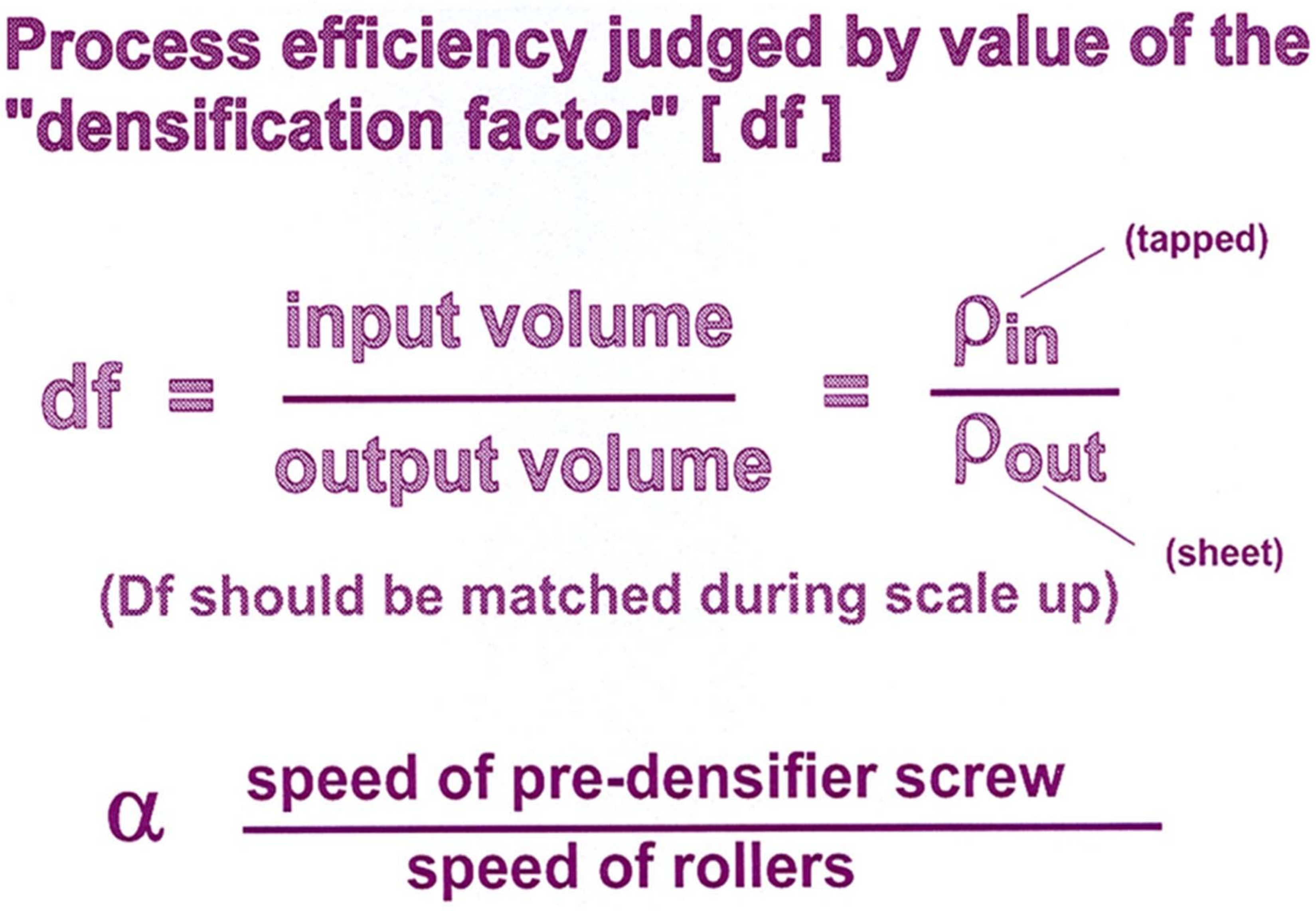


Various Designs of Rolls

Typical Roller Compaction Formulation

Components	Typical %
Active Drug Substance	As Specified
Inert (Fillers and Binder)	Sufficient to form Ribbon
Intragranular Disntegrant	0.5-4.0
Glidant	0.5-4.0
Lubricant	0.5-1.0
Extra Granular- Binder and Disintegrant	1.0-4.0
Glidant	0.5-1.0
Lubricant	0.5-1.5

Densification Factor



Process efficiency judged by value of the "densification factor" [df]

$$df = \frac{\text{input volume}}{\text{output volume}} = \frac{\overset{\text{(tapped)}}{\rho_{in}}}{\underset{\text{(sheet)}}{\rho_{out}}}$$

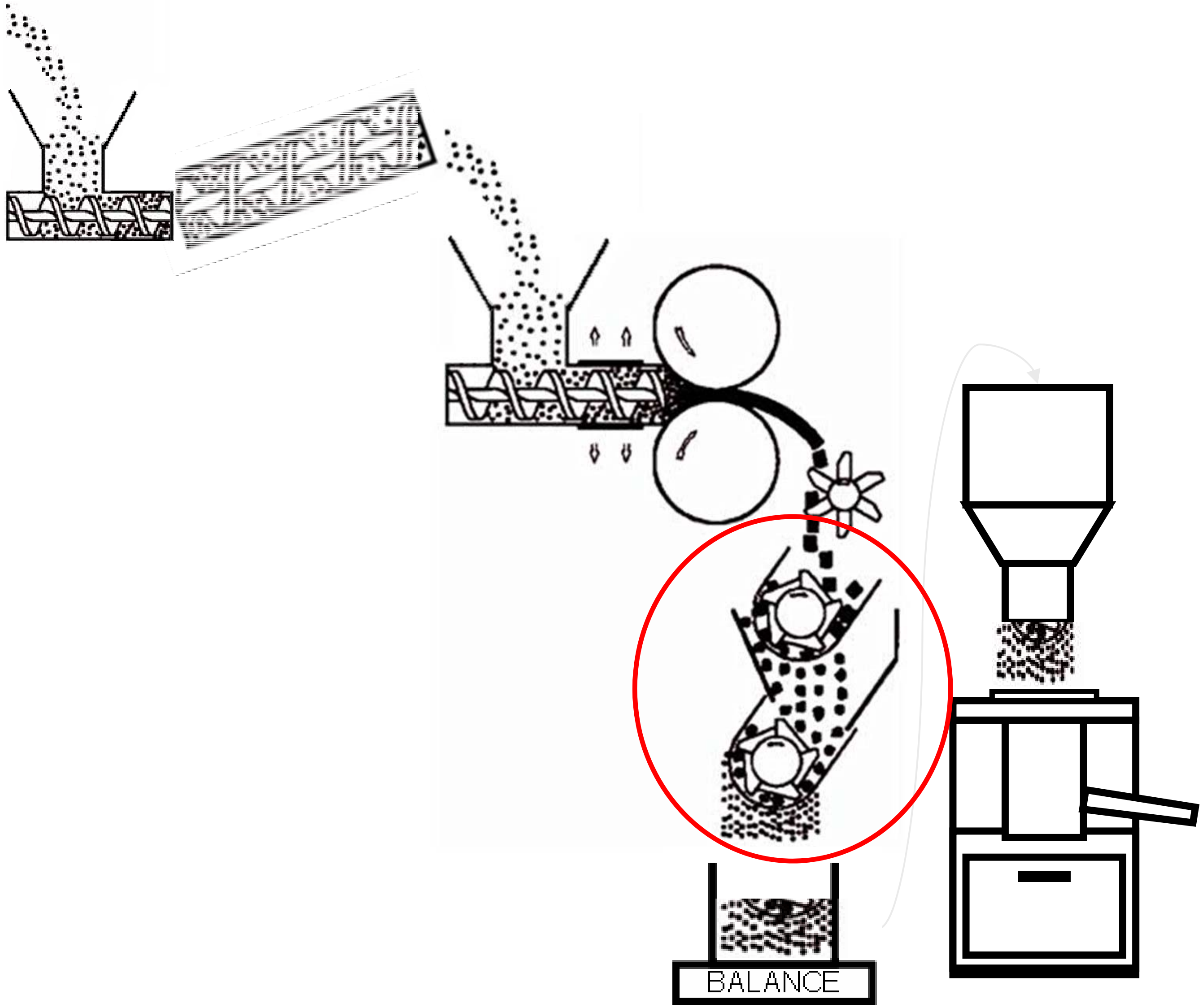
(Df should be matched during scale up)

$$\alpha \quad \frac{\text{speed of pre-densifier screw}}{\text{speed of rollers}}$$

Roll Compactor Variables

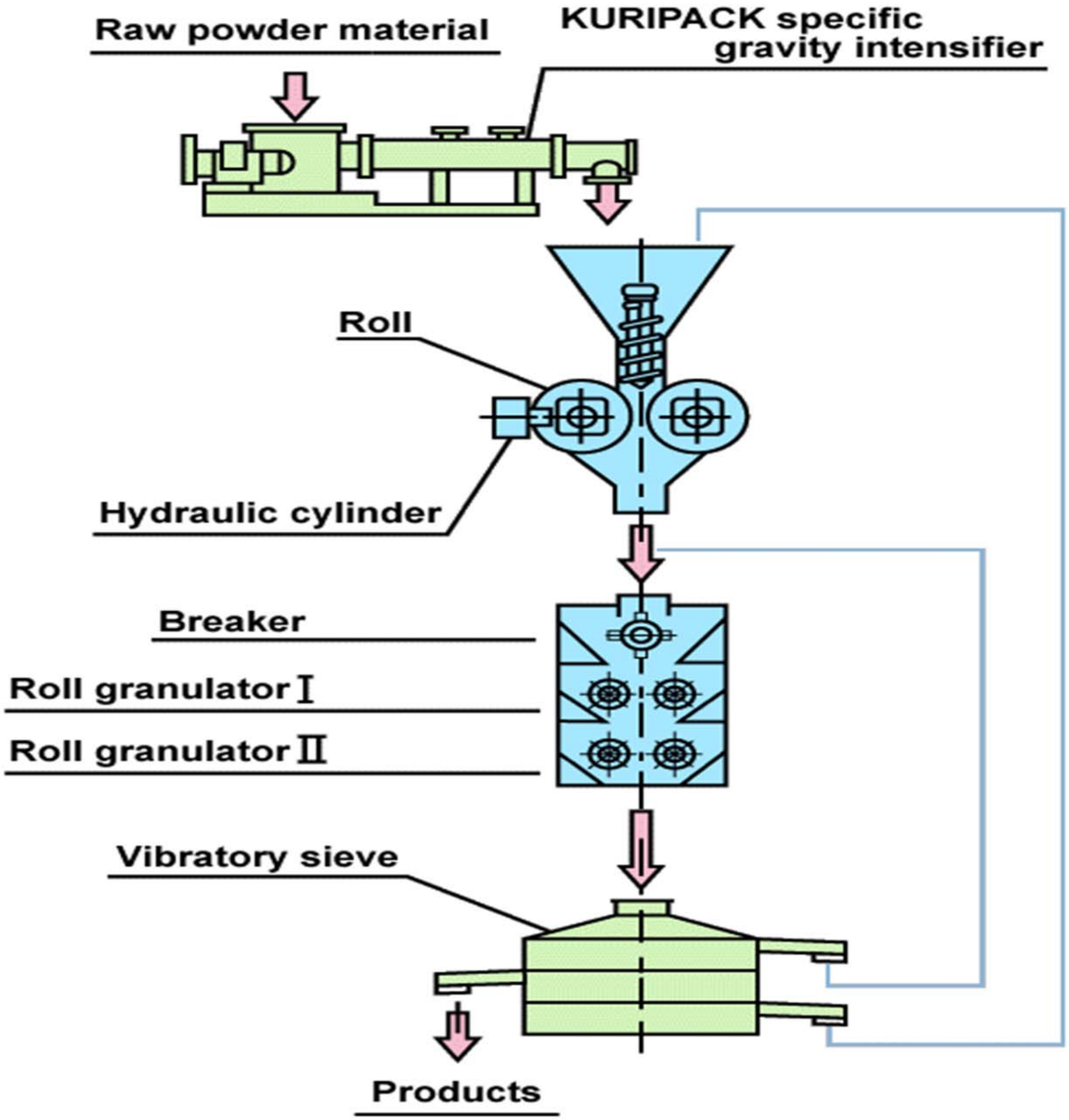
- Material feed rate (screw speed)
- Degree of de-aeration (bulk density)
- Diameter of the rolls
- Gap width between rollers
- Maximum compaction pressure
- Dwell time under load (speed of rollers)
- Degree of densification

Roller Compaction



Courtesy : Pavan Kumar Akkisetty
Purdue University

Roller Compaction Installation



Advantages of Roller Compaction

- Eliminates wet granulation/drying and degradants
- Facilitates powder flow and minimal energy usage
- Facilitates continuous manufacturing
- Produces dry product that is process scaleable

Direct Compression Vs Wet Granulation

- Metronidazole formulation was reported to be difficult direct compress because of capping.
- After wet granulating in a planetary mixer, the brittle characteristics of the formulation, induced by the drug were largely eliminated. (Itiola & Pilpel 1986)

Direct Compression vs Wet granulation

- Negative aspect of wet granulation on the dissolution profile of Naproxen Sodium was reported by Bansal et.al.1994)
- The authors hypothesized that wet granulation created a hydrated form that was less soluble.

Bonding Mechanism in Wet Granulation

- Electrostatic forces keep particles in contact long enough for another mechanism to govern the agglomeration process
- The cohesive forces that operate during the moist agglomerates are mainly due to the liquid bridges that develop between the solid particles

Binders

- **Binders are the adhesives that are added in most all types of granulation processes**
  - It provide
    - ***cohesiveness*** **essential for the bonding between particles and**
    - **promote *size enlargement* during granulation to produce granules and, thereby,**
    - **improve *flowability and density* of the powders during manufacturing.**

Common Binders in Wet Granulation

- Natural Polymers:
  - **Corn Starch, Pre-gelatinized starch**
  - **Gelatin**
  - **Acacia**
  - **Alginic Acid**
  - **Sodium Alginate**
- Synthetic Polymers:
  - **PVP**
  - **Methyl Cellulose**
  - **HPMC**
  - **Sodium - CMC**
  - **Ethyl Cellulose**
- Sugars:
  - **Glucose**
  - **Sucrose**
  - **Sorbitol**

Binder	Typical Use Level	Comments
Hydroxpropylcellulose (HPC)	2- 6%	Used with water, hydroalcoholic and neat polar organic solvents, equally effective in wet and dry addition due to high plasticity and wetting
Methylcellulose (MC)	2-10%	Used with water or hydroalcoholic solvents, dry addition typically requires higher use levels than wet addition
Hypromellose (HPMC)	2-10%	Used with water or hydroalcoholic solvents, dry addition requires higher use levels
Ethylcellulose (EC)	2-10%	Used with polar and non polar organic solvents, not soluble if water exceeds 20% of total solvent. Hydrophobic coating can slow down drug release for low soluble drugs thus best used for high dose, highly soluble drugs and moisture sensitive drugs.
Povidone (PVP)	2- 10%	Used with water, hydroalcoholic and neat polar organic solvents, dry addition requires higher use levels. Ultra low viscosity grades, allow high solution concentrations (20%)
Copovidone (PVA-PVP)	2-8%	Used with water and hydroalcoholic solvents. More thermoplastic than PVP, dry addition requires higher use levels
Pre-gelatinized starch (PGS)	5-15%	Can only be used with water, also acts as a disintegrant, effective use levels are mostly higher than other binders (8-20%)

Ref: T. Durig "Binders in Pharmaceutical Granulation Chapter4: In "Handbook of Pharmaceutical Granulation Technology" 3rd Edition , Dilip M. Parikh (Editor), 2009 Informa Health (Publisher) NY

Properties of 4% w/v binder solutions and resultant granule and tablet properties in a acetaminophen (APAP) model system

Binder Solution	Surface tension (dyn/cm)	Contact angle on APAP (°)	Work of spreading (dyn/cm)	Granule friability index	Tablet strength (N)*
HPMC	**45.2**	**27.4**	**-5.07**	**14.8**	**180**
Acacia	**50.6**	**30.3**	**-6.92**	**19.8**	**162**
Sucrose	**50.4**	**32.8**	**-8.01**	**87. 6**	**98**
PVP	**53.6**	**42.2**	**-13.9**	**26.5**	**57**
Starch	**58.7**	**47.3**	**-18.9**	**45.3**	**37**
Water	**70.3**	**59.6**	**-110**	**-**	**-**

*Diametral crushing strength for tablets compressed at 120 MPa

Ref: T. Durig "Binders in Pharmaceutical Granulation Chapter4: In "Handbook of Pharmaceutical Granulation Technology" 3rd Edition, Dilip M. Parikh (Editor), 2009 Informa Health (Publisher) NY

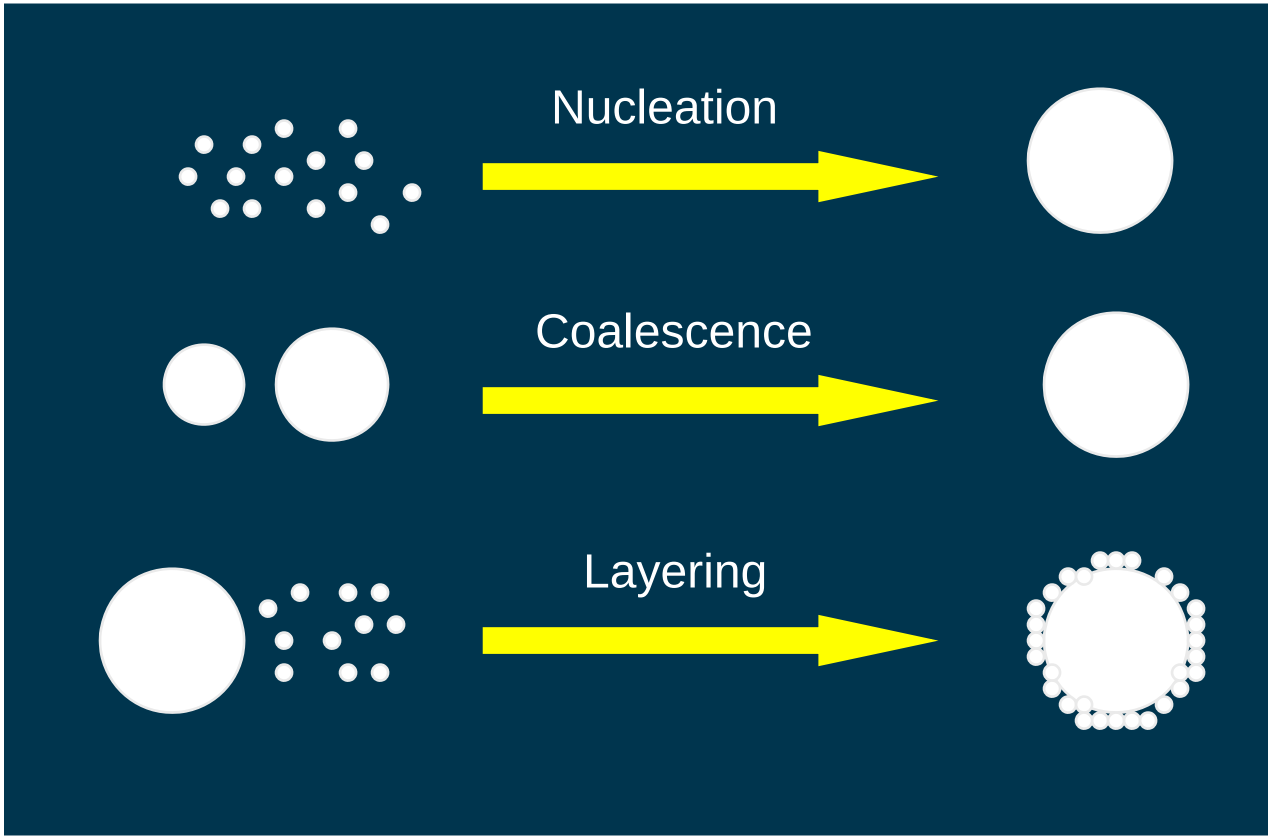
Factors Influencing Binder Efficiency

- **Drug and Excipient properties:**
  - *Particle size*
  - As particle size decreases, surface area of the powder increases resulting in :
    - Increase in Amount of granulation liquid required
    - Increase in Granule strength due to more contact points of smaller particles

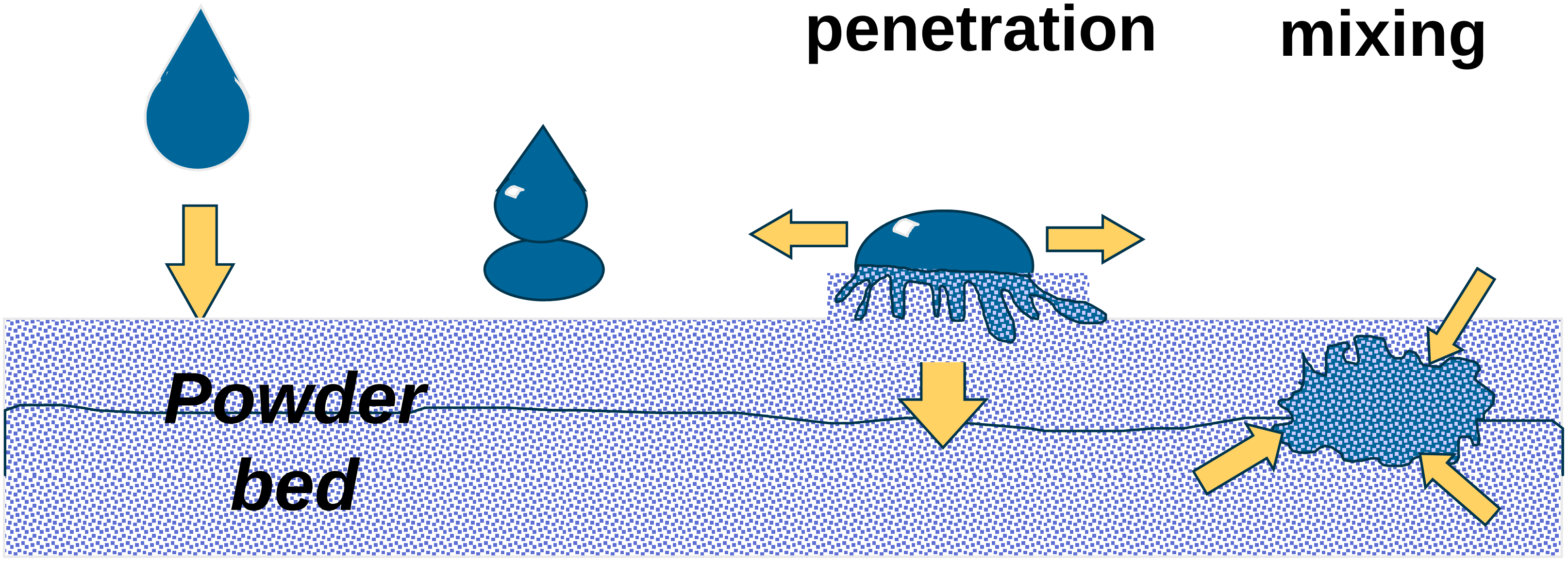
Granule Growth

- Nucleation results in formation and growth of granules by
  - Added liquid
  - Degree of consolidation
- Coalescence takes place when:
  - Presence of liquid bonds with high saturation level
    - increases surface plasticity
    - increases the contact area

Granule Growth Mechanism



Nucleation Process



Droplet formation

Droplet coalescence & overlap

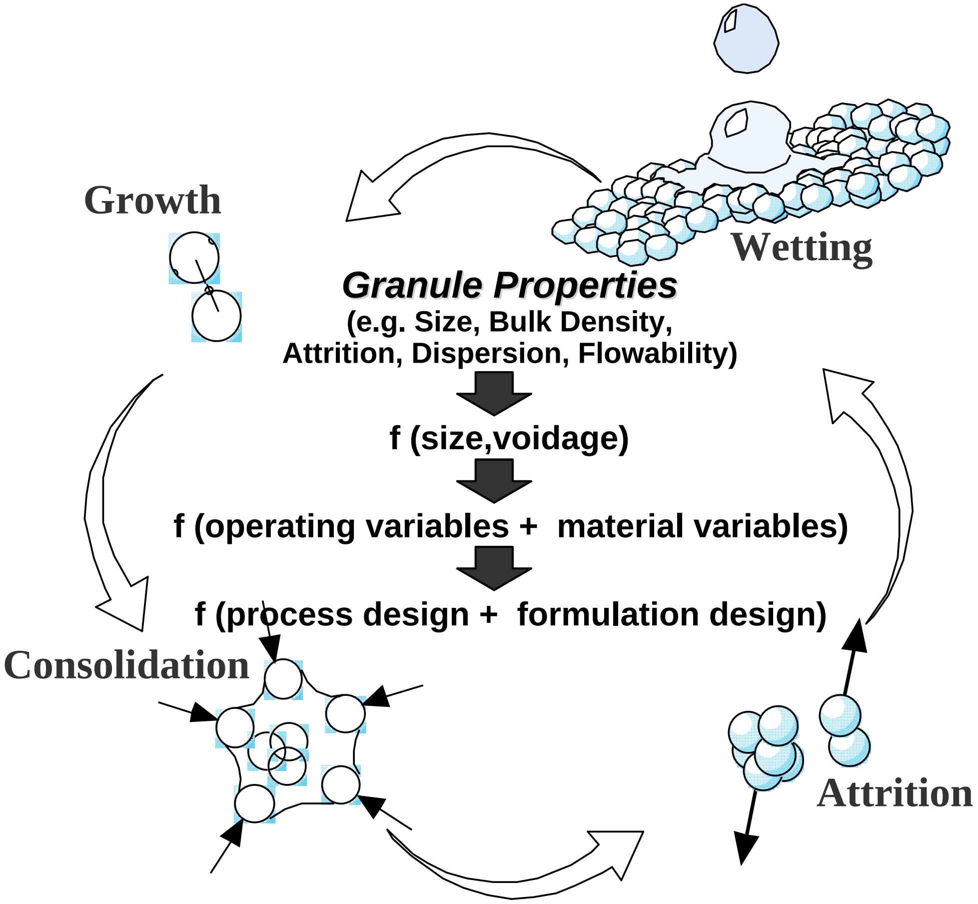
Binder dispersion by wetting & capillary penetration

Binder dispersion by mechanical mixing

Powder bed

Karen P. Hapgood, AAPS June 2003 Symposium

Granule Growth



Granule Properties
(e.g. Size, Bulk Density,
Attrition, Dispersion, Flowability)

f (size,voidage)

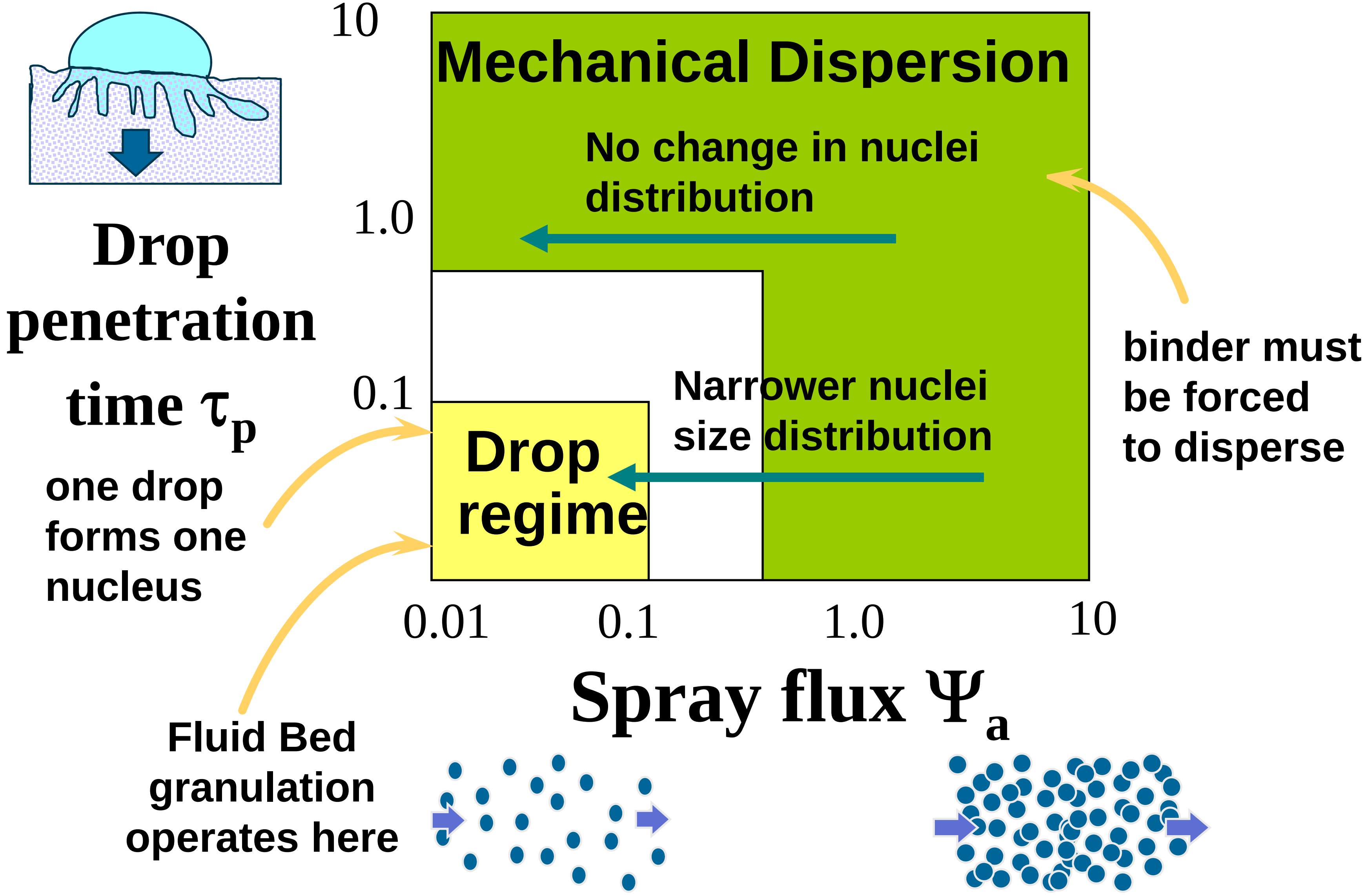
f (operating variables + material variables)

f (process design + formulation design)

- In this case growth may proceed by the layering of particles from the degradation on the surface of larger agglomerates
- If the strength of agglomerates can not withstand the agitation and collisions they become crush

Ennis, B.J. “theory of Granulation: An Engineering Perspective” Handbook of Pharmaceutical Granulation 2nd Edition, Editor: D.M. Parikh, Taylor and Francis Publisher (2005)

Nucleation Regime Map



Drop penetration time τ_p

10

1.0

0.1

Mechanical Dispersion

No change in nuclei distribution

Narrower nuclei size distribution

Drop regime

0.01

0.1

1.0

10

Spray flux Ψ_a

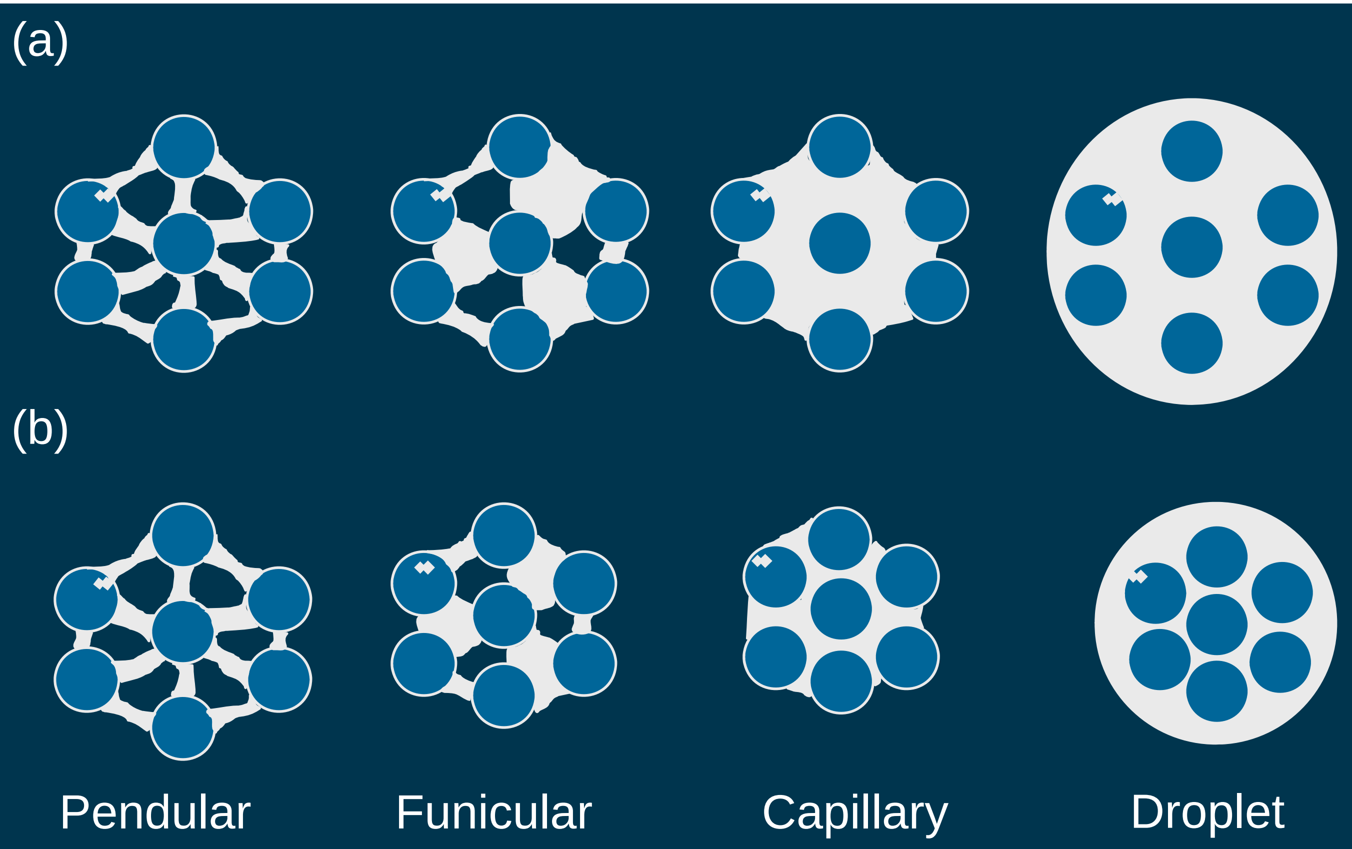
binder must be forced to disperse

one drop forms one nucleus

Fluid Bed granulation operates here

Karen P. Hapgood, AAPS June 2003 Symposium

Granulation and liquid bridges



Liquid bridging state of agglomerates undergoing (a) binding liquid addition and (b) densification.

Factors Influencing Binder Efficiency

- Drug and Excipient properties:
  - Particle Size
  - Solubility
- Binder and solvent system properties:
  - Mechanical properties of the binder
  - Binder-substrate interaction
  - Binder solution viscosity and surface tension
  - Solvent properties

Factors Influencing Binder Efficiency

- Drug and Excipient properties:
- Particle size
  - As particle size decreases, surface area of the powder increases as a result:
    - Amount of granulation liquid required increases
    - Granule strength increases due to more contact points of smaller particles

Factors Influencing Binder Efficiency

- Drug and Excipient properties:
  - Solubility:
    - Increasing the excipient solubilities in the granulating solvent decreases the solvent requirement and form tighter particle size distribution and reduced friability
    - Changing the proportion of water soluble excipients alter the granule properties.
    - Drug solubility in the granulating solvent can affect distribution in different granule fractions: high solubility have a higher tendency to migrate during drying, forming crust and creating drug-rich fines when milled

Factors Influencing Binder Efficiency

- ❑ Binder and Solvent System Properties:
  - ➢ Mechanical properties of the binder
    - ▪ Mechanical and film forming properties determine strength and deformation behavior of a binder matrix. PVP forms weak films but has high deformability aiding consolidation during compaction
  - ➢ Binder-substrate Interactions
    - ▪ Spreading coefficient : positive spreading coefficient results in dense non-friable granules while negative spreading coefficient leads to the formation of porous granules.
    - ▪ PVP and HPMC has positive spreading coefficient over lactose, while lowest spreading coefficient with acyclovir.

Factors Influencing Binder Efficiency

- Binder and Solvent System Properties:
  - Viscosity and Surface Tension
    - Increased binder solution viscosity increases the granule size and decreases the amount of binder required to initiate the granule growth {Hooraert et.al. 96, (1998) ,116}
    - But very high viscosity may pose problems with distribution and hence non-uniform granulation
    - Decreasing surface tension decreases the capillary suction pressure , decreases friction resistance to consolidation resulting in granule consolidation rate increase {Iveson et.al. Powder Tech. 99 (1998)}
    - Decreasing the surface tension decreases the liquid requirements to attain overwetting .{Pepin et.al. J.Pharm.Sci. 90(3), 322}

Factors Influencing Binder Efficiency

- Binder and solvent system properties:
  - Solvent Properties:
    - water, alcohol, hydro-ethanol solvents widely used
    - Changing the solvent system can affect the formulation excipients wettability and influence binder distribution.

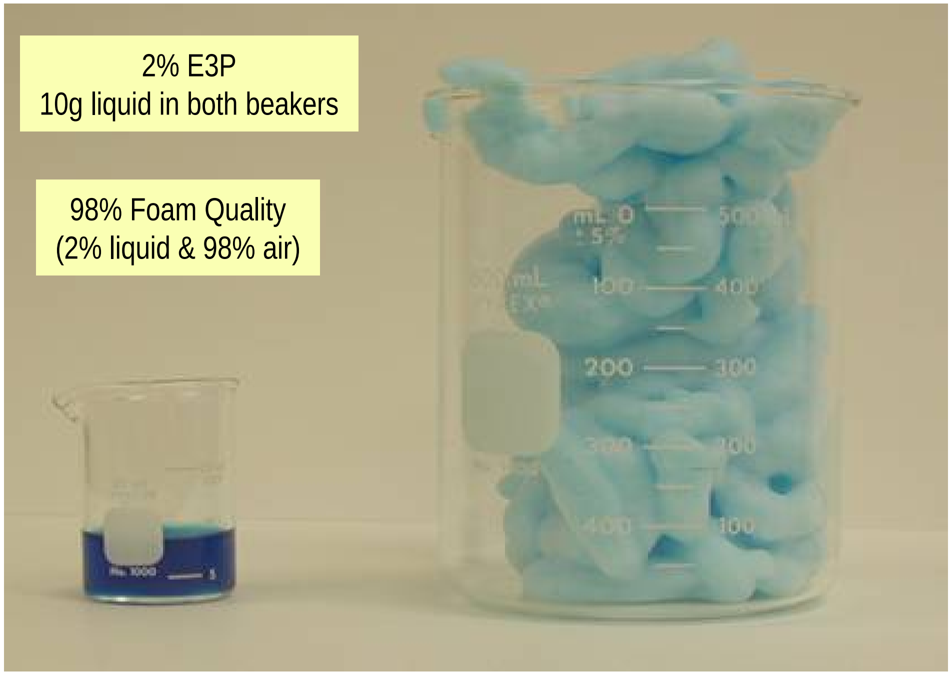
Foam Technology by Dow Chemicals

What’s New? – Foam Binder

Courtesy: Paul Sheskey-Dow Chemicals

What is Foam Granulation?

- ❑ A process where air is incorporated into a binder solution that is subsequently used in granulation:
  - ➢ uses conventional binders and granulation equipment
  - ➢ uses a foam generator
  - ➢ shaving foam consistency
- ❑ Taking advantage of the tremendous increase in liquid surface area and volume
  - ➢ improved liquid/binder distribution within the powder mass over conventional spray techniques
- ❑ Liquid is the continuous phase. Air is the discontinuous phase.
- ❑ Foam is introduced without the use of any nozzles.

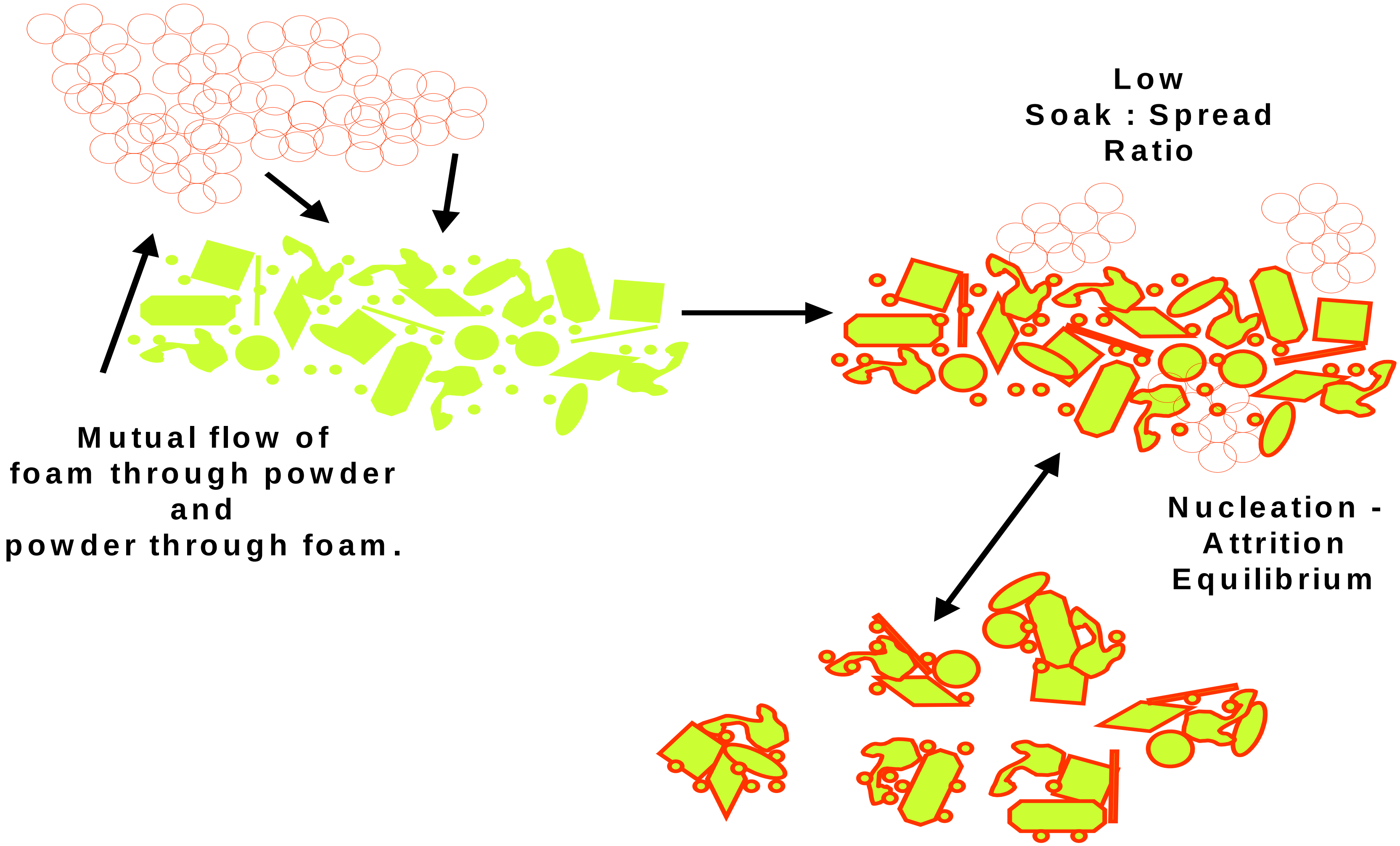

2% E3P
10g liquid in both beakers

98% Foam Quality
(2% liquid & 98% air)

Foam does not survive the granulation, the foam is designed to break, the granules are not more porous than granules prepared conventionally.

Courtesy: Paul Sheskey-Dow Chemicals

Nucleation During Foam Granulation



Low
Soak : Spread
Ratio

Mutual flow of
foam through powder
and
powder through foam.

Nucleation -
Attrition
Equilibrium

Courtesy: Paul Sheskey-Dow Chemicals

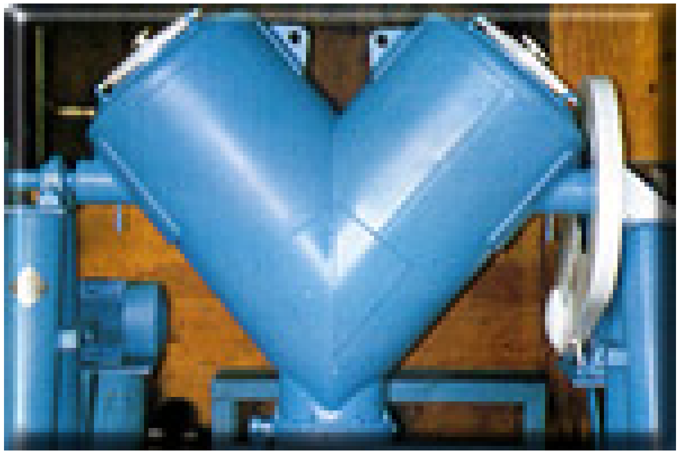
Wet Granulation Equipment

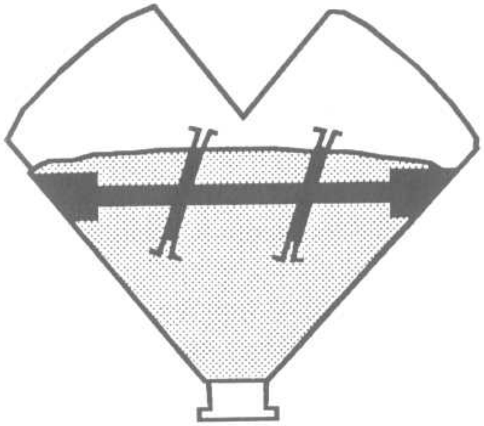
- ❑ Low Shear Mixer
  - ➢ Planetary, Twin shell or double cone, orbiting screw, sigma blade
- ❑ High Shear Mixers
  - ➢ Bottom Driven/fixed bowl (Fielder, Powerex)
  - ➢ Top driven /Removable bowl (Collette, Glatt)
  - ➢ Horizontal (Loedige)
- ❑ Continuous Granulators

Low Shear Granulator

Planetary Mixer

Low Shear Granulator





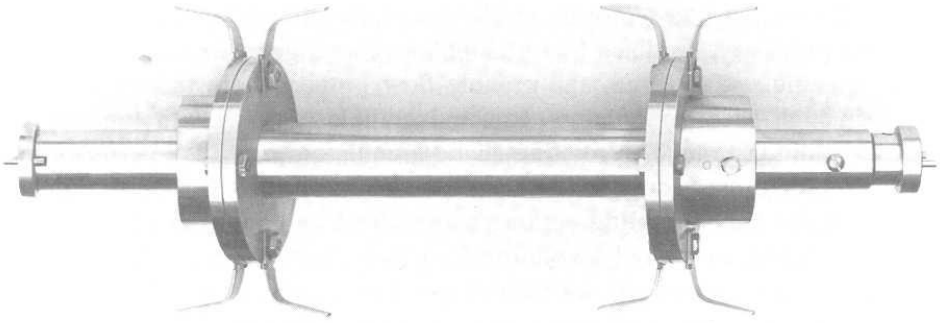
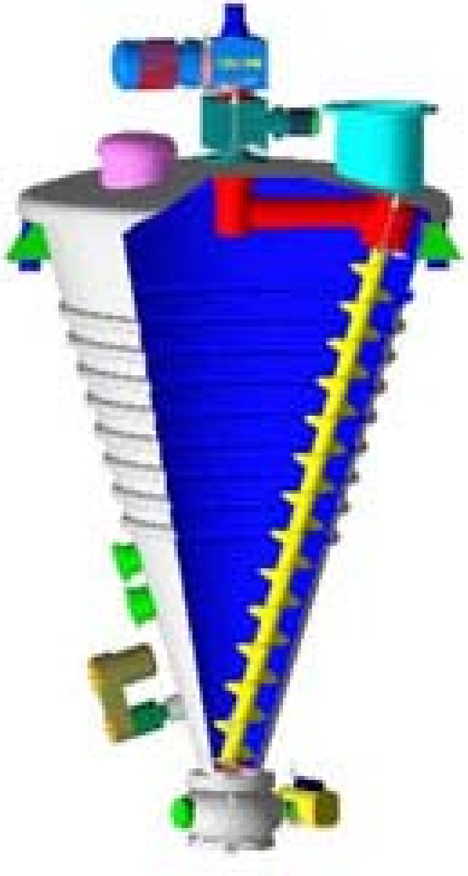


Figure 9 Intesifire bar with discs for liquid distribution

Twin Shell Mixer with a intensifying Bar

Orbiting Screw (Nauta) Mixer



Low Shear Granulator for Viscous Materials

Sigma Blade Mixer

Typical Process Steps in High Shear Granulation

1. Binder Distribution
    - ☐ -Mixing of powders
    - ☐ -Liquid addition
    - ☐ -Distribution of binder solution
2. Massing Phase
    - ☐ -Densification
    - ☐ -Controlled granule growth
3. End point determination

High Shear Mixer

Premixing of the solids

↓

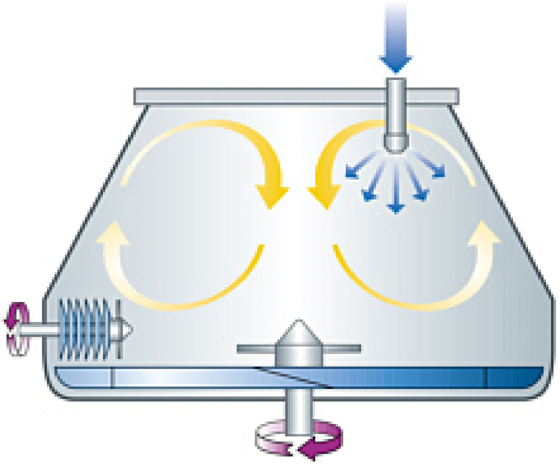
Liquid addition stage

↓

Wet massing stage

↓

Drying



High Shear Mixer

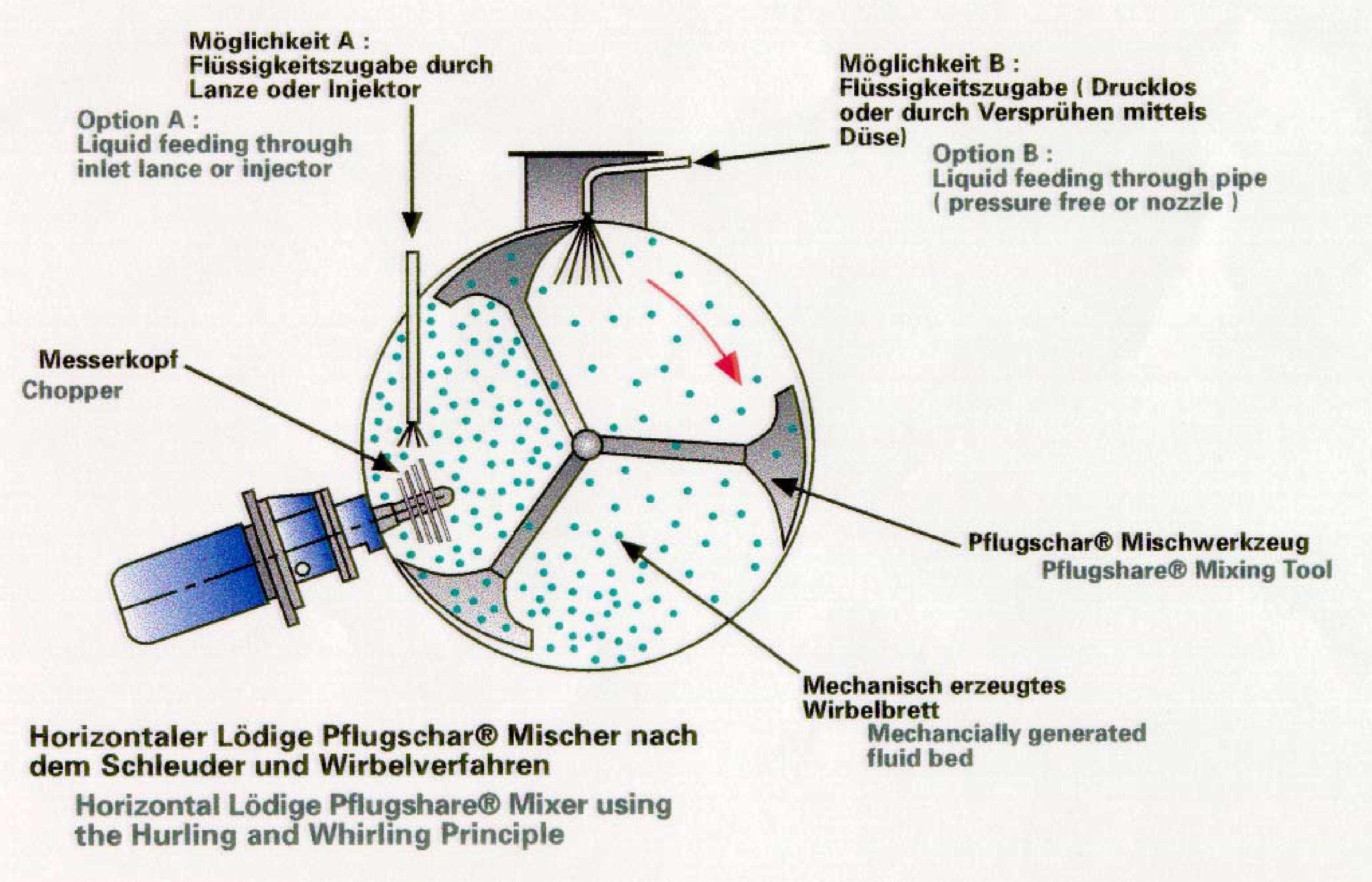
Bottom Driven High Shear Mixer

Top Driven High Shear Mixer/Granulator

Horizontal High Shear Granulator

Courtesy Loedigie

Horizontal High Shear Granulator



Horizontaler Lödige Pflugschar® Mischer nach dem Schleuder und Wirbelverfahren

Horizontal Lödige Pflugshare® Mixer using the Hurling and Whirling Principle

Process Variables in High Shear Granulation

- ❑ Major
  - ➢ Binder quantity
  - ➢ Impeller speed (Radial Velocity)
  - ➢ Massing time
  - ➢ Percent Load on motor (Power Consumption)
- ❑ Minor
  - ➢ Chopper blade
  - ➢ Concentration of binder solution
  - ➢ Temperature of Binder Solution
  - ➢ Method of adding Solution

Effect of Mechanical Dispersion

- Doubling impeller speed or doubling mixing time increases the number of impeller rotations per unit fluid added
  - improved mechanical dispersion distributes the granulating liquid
  - Fewer coarse granules in the product
- Mechanical dispersion is the most efficient way to minimize coarse granule formation when <u>liquid distribution in the spray zone</u> (spray flux) is high

Mixer Controls

- Binder addition rate controls granule density
- Impeller and chopper speed control granule size and granulation rate
- End point controls the mix consistency and reproducibility

Granulation End Point Determination

- Hand-O-Meter
  - Subjective, operator dependent & not reproducible

Granulation End Point Determination

- Hand-O-Meter
  - Subjective, operator dependent & not reproducible
- Off-line Measurement (particle size)
  - Retrospective rather than prospective measurement
- Boots-Diosna Probe (vibration)
  - Online measurement, intrusive
- Current Approaches and PAT

Granulation End Point Determination

Assessment of wet Mass Rheology

- **Electrical Methods:** Ammeters for motor current and power consumption. Motor load can be used to measure rehological properties of wet mass
- **Mass Properties : Temperature Changes**
- **Torque Measurement: on the shaft**

Torque and Power Signals

- Torque and Power signals are affected by
    - Granulate and binder viscosity
    - Impeller speed
    - Binder addition Rate

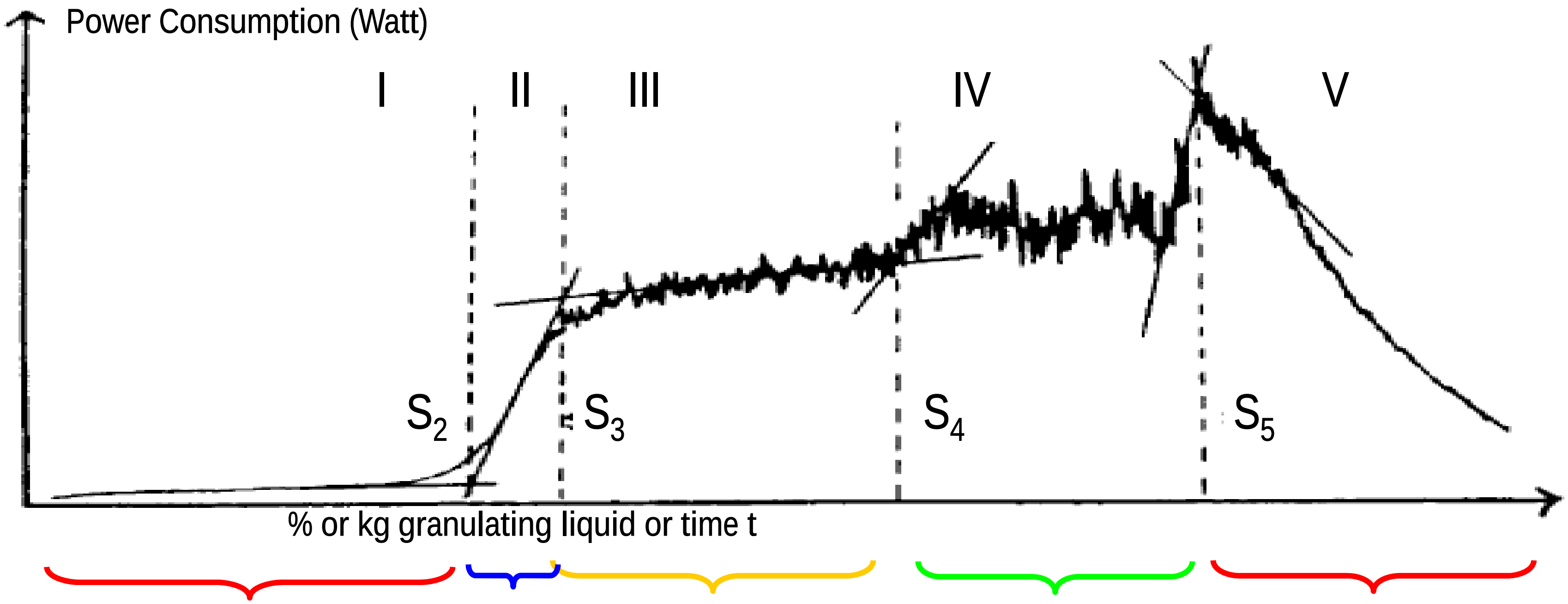
Mixer Controls and Process End Point

- Power Consumption Measurement
  - Measured by a watt transducer or a power cell.
  - Power is proportional to load and reflects system performance and signal is affected by number of factors such as product formulation, equipment or process variables
  - Measurement is inexpensive, it does not require extensive mixer modifications and is well correlated with granule growth.
  - Wear and tear of the granulator could also affect the power consumption signal
  - Power consumption profile for a granulation process is formulation specific

Torque

- ❑ **Direct Impeller Torque measurements require installation of strain gages on the impeller shaft or on the coupling between the motor and impeller shaft.**
- ❑ **Since the shaft is rotating, a device called slip ring is used to transmit the signal to the stationary data acquisition system.**
- ❑ **Impeller torque is an excellent in-line measure of the load on the main impeller and was shown to be more sensitive to high frequency oscillations than power consumption**
- ❑ **It is Independent of all drive train efficiencies and electrical conditions**
- ❑ **Very easy and direct to calibrate**

Granulation End Point



STAGE 1
Baseline

STAGE 2
Dry Powder Mixing
Agglomerates formed in this stage are weak and break upon drying

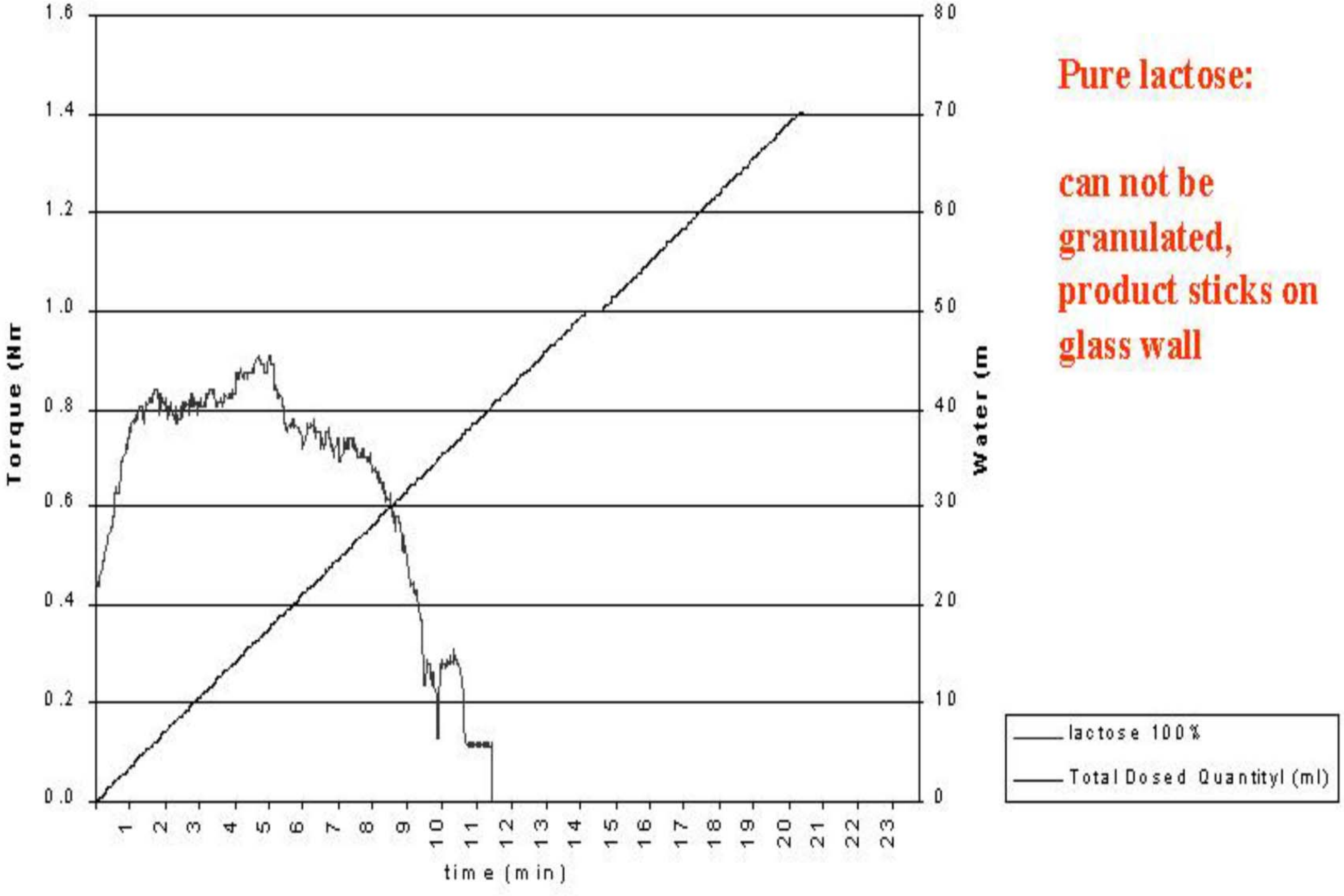
STAGE 3
Binder Addition
Densification initiated.
Liquid bridges are increased without significant changes in the cohesive force

STAGE 4
Wet Mixing
Densification completed.
Pore spaces begin to fill completely with liquid

STAGE 5
Over Wetting
A slurry is formed when too much water is added

Source: http://irs.ub.rug.nl/ppn/16190985X

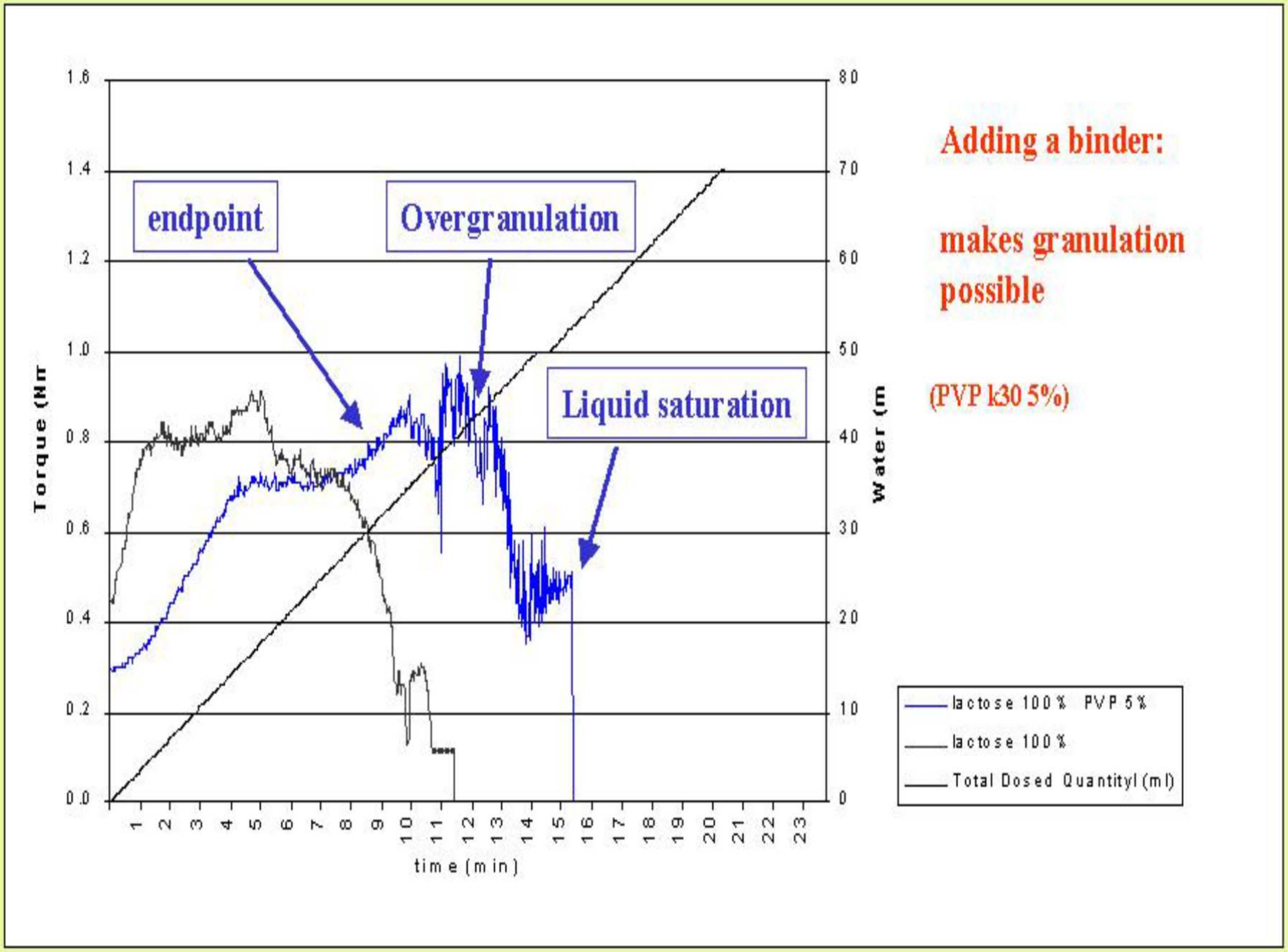
Torque Measurement Effect of Lactose



Pure lactose:

can not be granulated, product sticks on glass wall

Binder Addition allows for Granulation

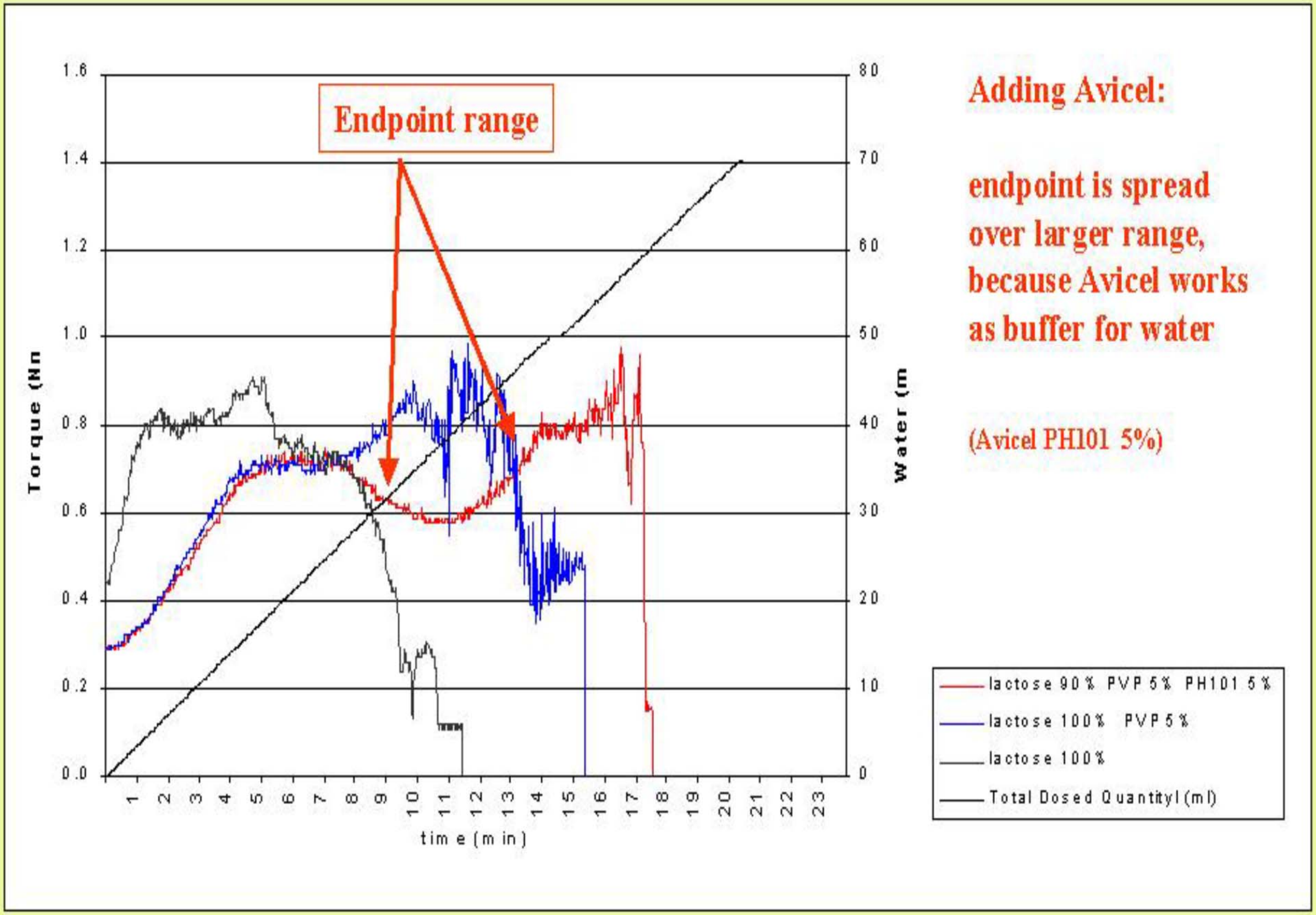


Adding a binder:

makes granulation possible

(PVP k30 5%)

Torque Measurement –
Extending Granulation Endpoint



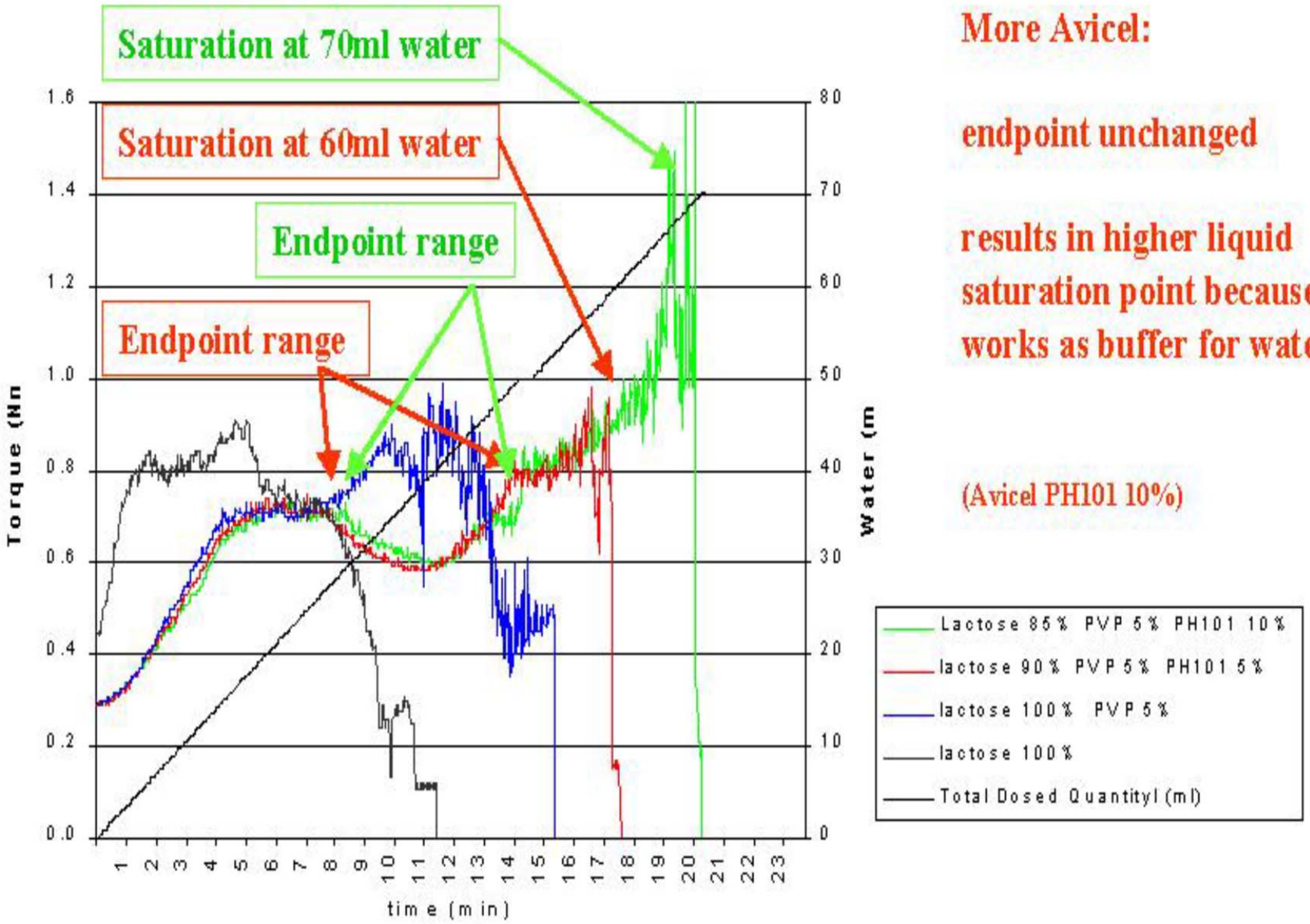
Endpoint range

Adding Avicel:

endpoint is spread over larger range, because Avicel works as buffer for water

(Avicel PH101 5%)

Torque Measurement –
Extending Granulation Endpoint



More Avicel:

endpoint unchanged

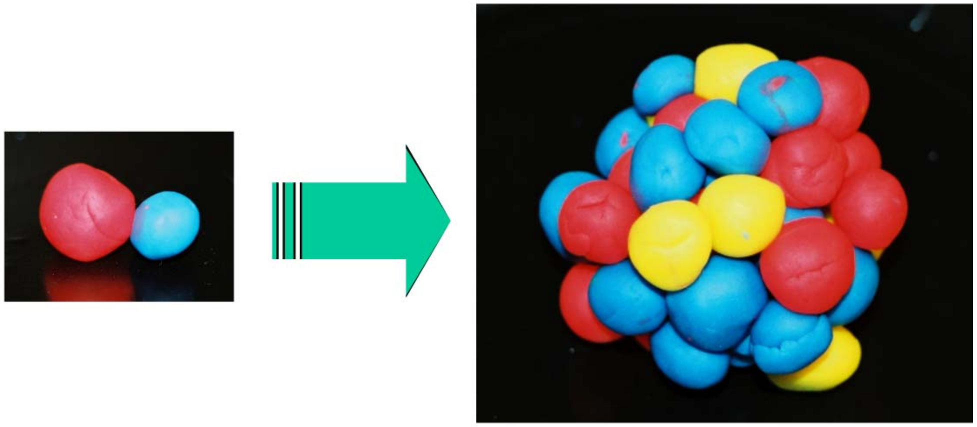
results in higher liquid saturation point because Avicel works as buffer for water

(Avicel PH101 10%)

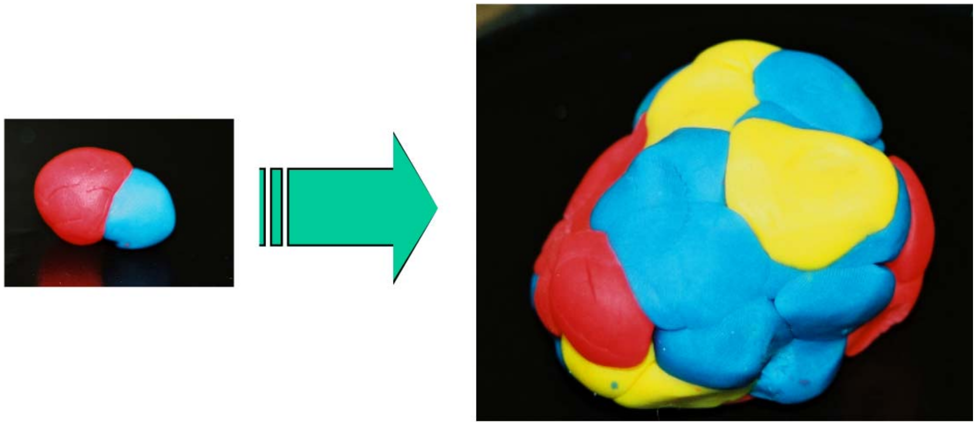
Wet Granulation Vs Slugging Vs Roller Compaction

- Active drug with low bulk density, highly water soluble, needle shape crystal,poor flow, sticky
- Wet granulation was not feasible due to extreme high solubility forming pockets highly wetted area.
- Slugging produced uneven flow and inconsistent granule blend
- Compactor provided the ideal method.

Granule Structures Resulting from (a) Low and (b) High Deformability Systems



a) Fluid Bed



b) High
Shear mixer

Characterization of Wet Granulation

- Raw Material Characterization
  - Wettability of the solid by the liquid
  - Solid Solubility and degree of swelling in binder liquid
  - Powder particle size distribution
  - Binder Concentration and viscosity
- Process Characterization
  - Torque/power consumption
  - Acoustic and vibration
  - NIR
  - Liquid penetration Mechanism
  - Granule formation
- Wet Mass Characterization
  - Mixture torque Rheometer
  - Ram extruder
  - Triaxial Compression
- Granule Characterization
  - Particulate level (shape, size, crystallinity, electrostatic charge, porosity, strength)
  - Bulk level (surface area, moisture content, density, flow, compactability)

Scale-up of High Shear Granulation Process

Common Issues in Scale-Up

- The lab trials do not effectively bracket what will be seen in scale-up
- The process used for the formulation was developed in a conservative manner
- The formulators do not have a feel for how production equipment works
- Questionable assumptions regarding the production equipment were made (both set-up and selection of process variables)

Process Scale-up Using Power Number Correlations

Concept of Similarity

- Geometric Similarity – all corresponding dimensions have the same ratio
- Kinematic Similarity – all velocities at corresponding points have the same ratio
- Dynamic Similarity – all forces at corresponding points have the same ratio

Dimensionless Groups

- Wet granulation process cannot be described (so far) adequately by mathematical equations, hence the dimensionless groups have to be determined by dimensional analysis.
- Dimensionless groups are Process variables and dimensionless constants

Dimensionless Numbers

- Power Number
- Specific amount of granulation liquid
- Fraction of volume loaded with particles
- Froud number (centrifugal/gravitational energy)
- Geometric number (ratio of characteristic lengths)

Dimensionless groups

Power Number – relates to the drag force acting on the unit area of the impeller to the inertial stress	$Np = \dfrac{\Delta P}{\rho N^{3} R^{5}}$
Reynolds Number –Inertial force to the viscous force	$\mathrm{Re} = \dfrac{\rho N R^{2}}{\eta}$
Froudes Number - ratio of the centrifugal acceleration to the gravitational constant (g) N=Rotation speed in rpm R=Diameter of the impeller g=Gravitation constant	$Fr = \dfrac{R N^{2}}{g}$

Dimensionless Spray Flux Y_a~1

Dimensionless spray flux Ψ_a describes liquid distribution in the spray zone quantitatively (Litster et. al., 2001)

V is the volumetric flowrate (m^3/s)

d_d is the drop size of the spray (m)

v is the powder surface velocity (m/s)

W is the width of the spray(90° to powder flow) (m)

$$\Psi_a = \frac{3\dot{V}}{2 d_d v w}$$

Assumptions: no drop overlap, even spray density, simple drop areas: volume relation

Spray Flux and Scale-up

- Dimensionless spray flux (liquid distribution in the spray zone) is a useful tool to scale-up liquid distribution)
- Spray flux tends to increase on scale-up
  - Nucleation mechanism may change as spray flux increases
- Multiple nozzles allow independent scale-up of liquid distribution

What’s New?- Process Control

- ❑ **Near Infrared Measurement(NIR)**
- ❑ **Other Process Control/Scale up /Process Modeling approaches**
  - ➢ Neural Networks [Generalized regression neural networks(GRNN)]
  - ➢ Fuzzy logic
  - ➢ Self Organizing Maps(SOM)
  - ➢ Population Balance Modeling (PBM)

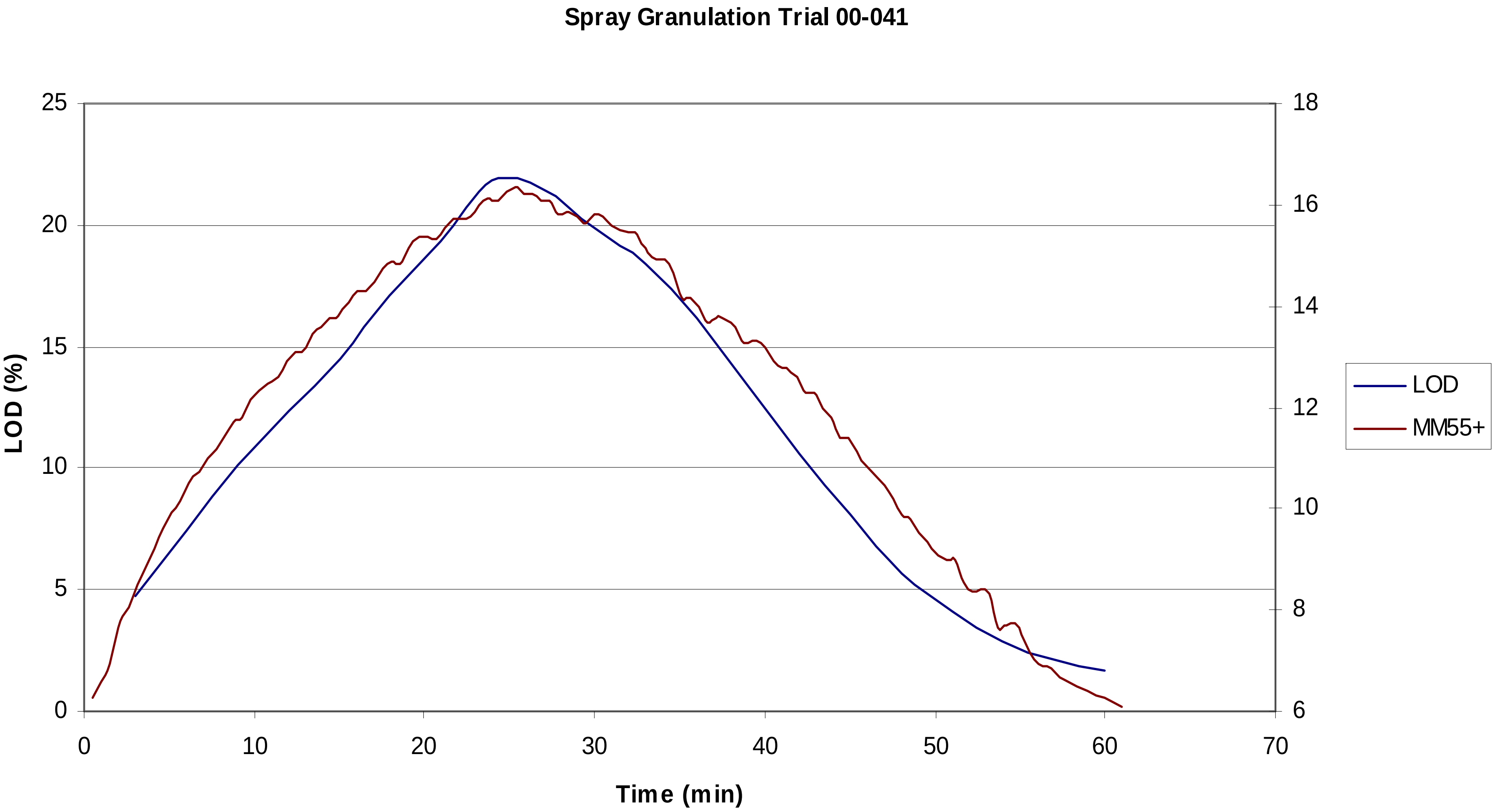
NIR

Near-Infrared Detector model M55+, NDC (Infrared Engineering)

The sensor ‘looks’ through the sight glass in the product container.

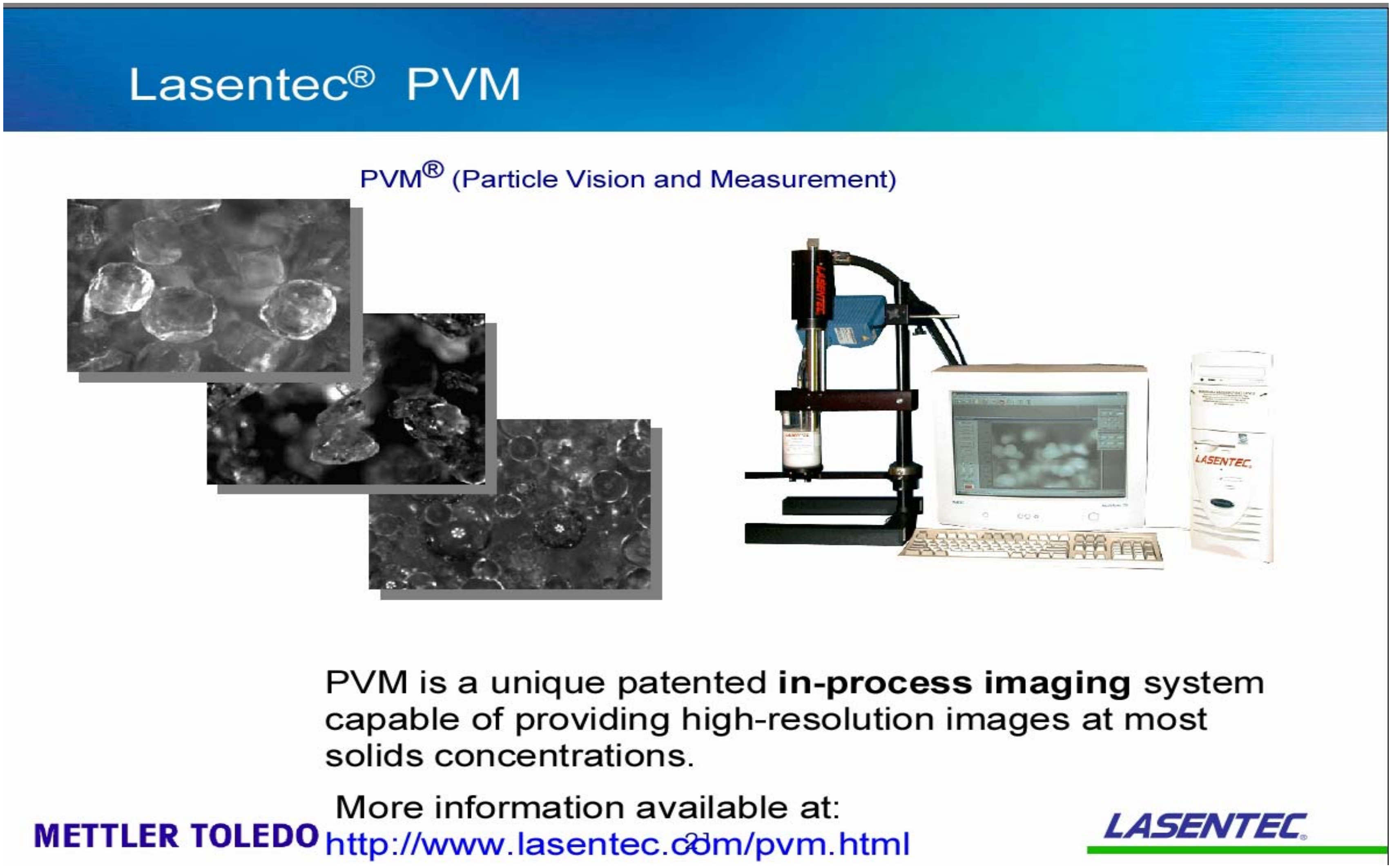
Note: a sparging device was used in the GPCG-15 to keep the surface of the window clear

Comparison NIR with LOD



The actual LOD sample data points are shown. The differences in absolute terms comparing to the NIR data are not insignificant.

Particle Vision and Measurement



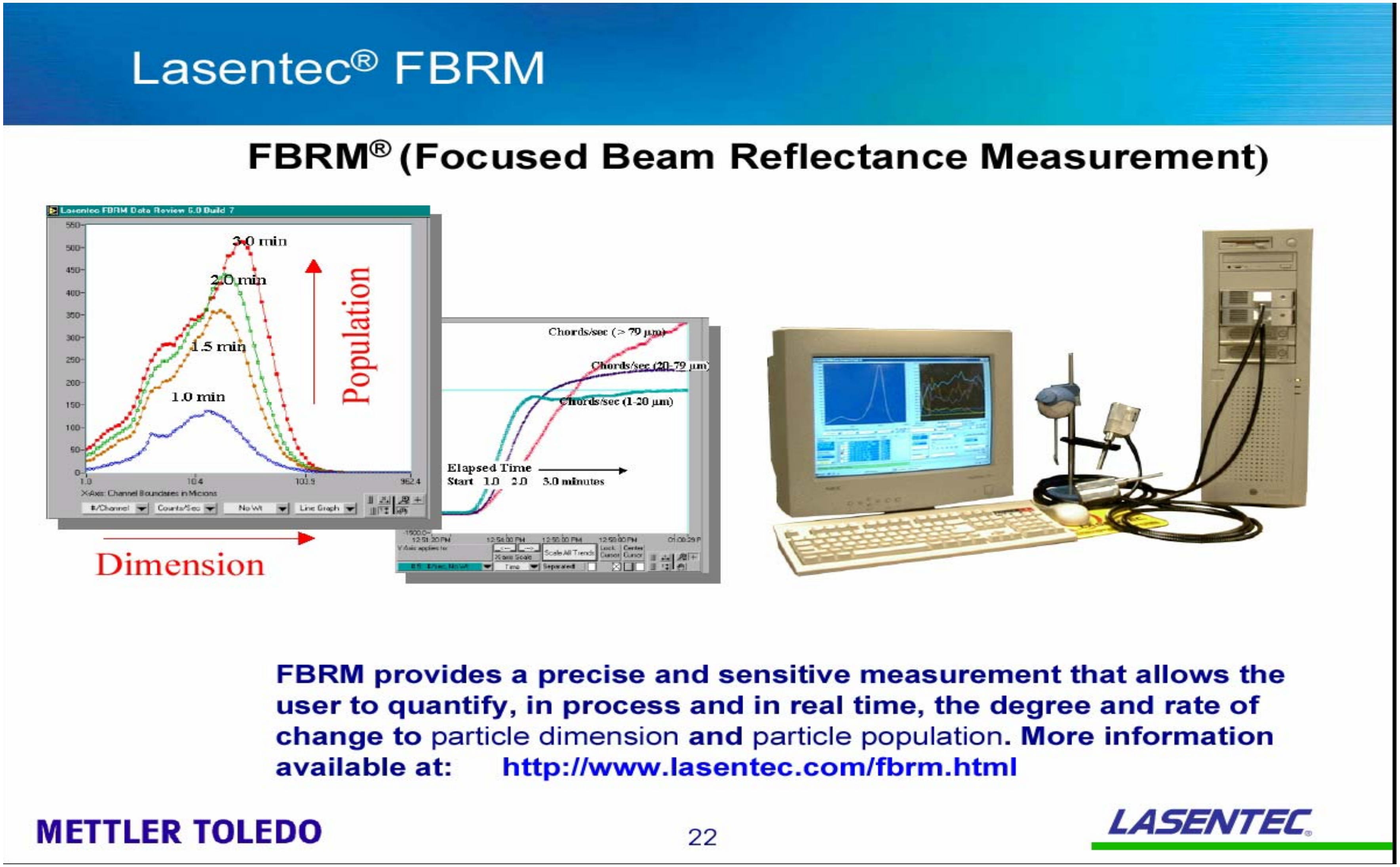
Lasentec® PVM

PVM® (Particle Vision and Measurement)

PVM is a unique patented **in-process imaging** system capable of providing high-resolution images at most solids concentrations.

More information available at:
http://www.lasentec.com/pvm.html

Focused Beam Reflectance Measurement



Lasentec® FBRM

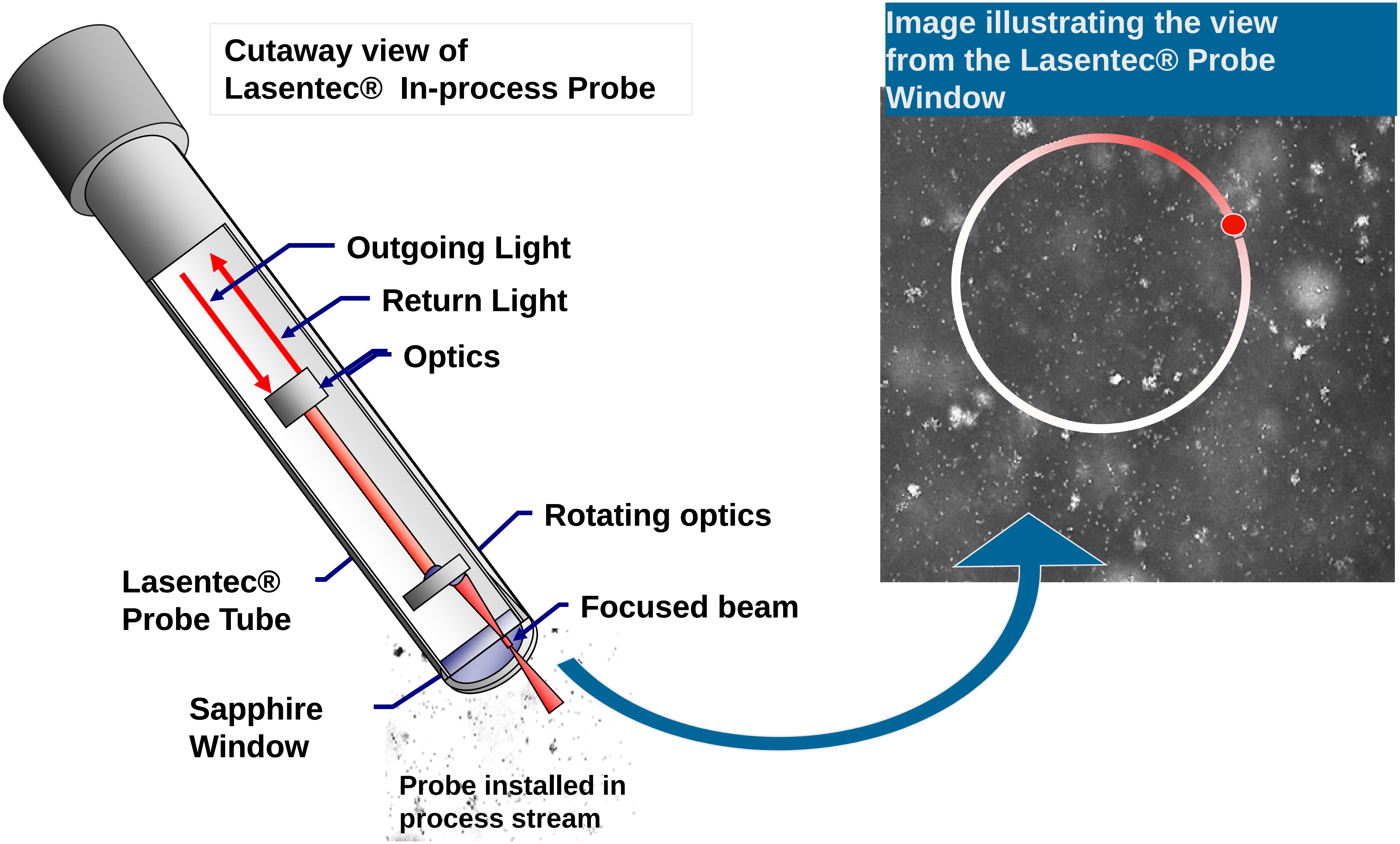
FBRM® (Focused Beam Reflectance Measurement)

FBRM provides a precise and sensitive measurement that allows the user to quantify, in process and in real time, the degree and rate of change to particle dimension **and** particle population**. More information available at: http://www.lasentec.com/fbrm.html**

METTLER TOLEDO

LASENTEC

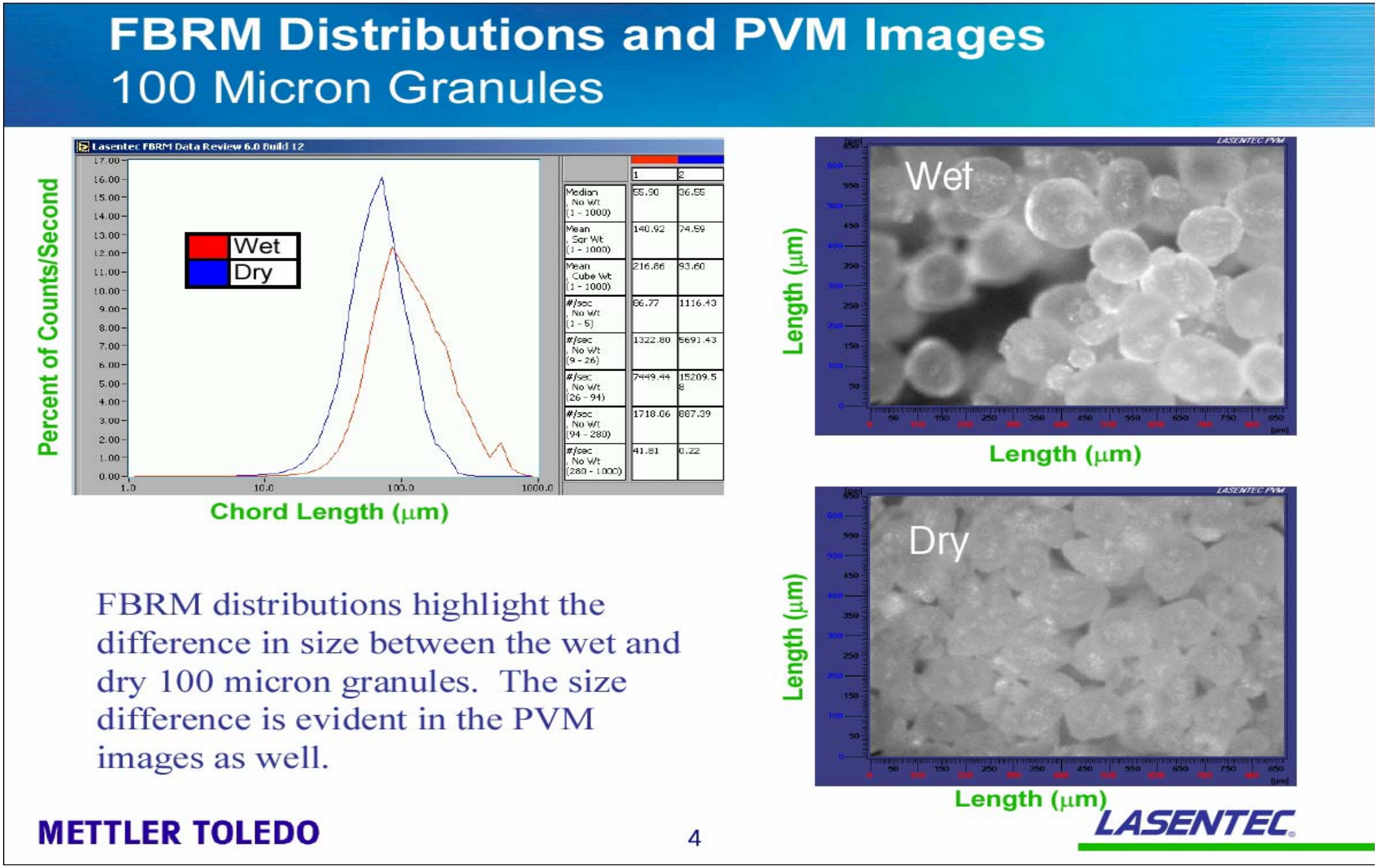
How does Lasentec® work?1



Cutaway view of Lasentec® In-process Probe

Image illustrating the view from the Lasentec® Probe Window

Focused Beam Reflectance Measurement



FBRM Distributions and PVM Images

100 Micron Granules

Lasentec FBRM Data Review 6.0 Build 12

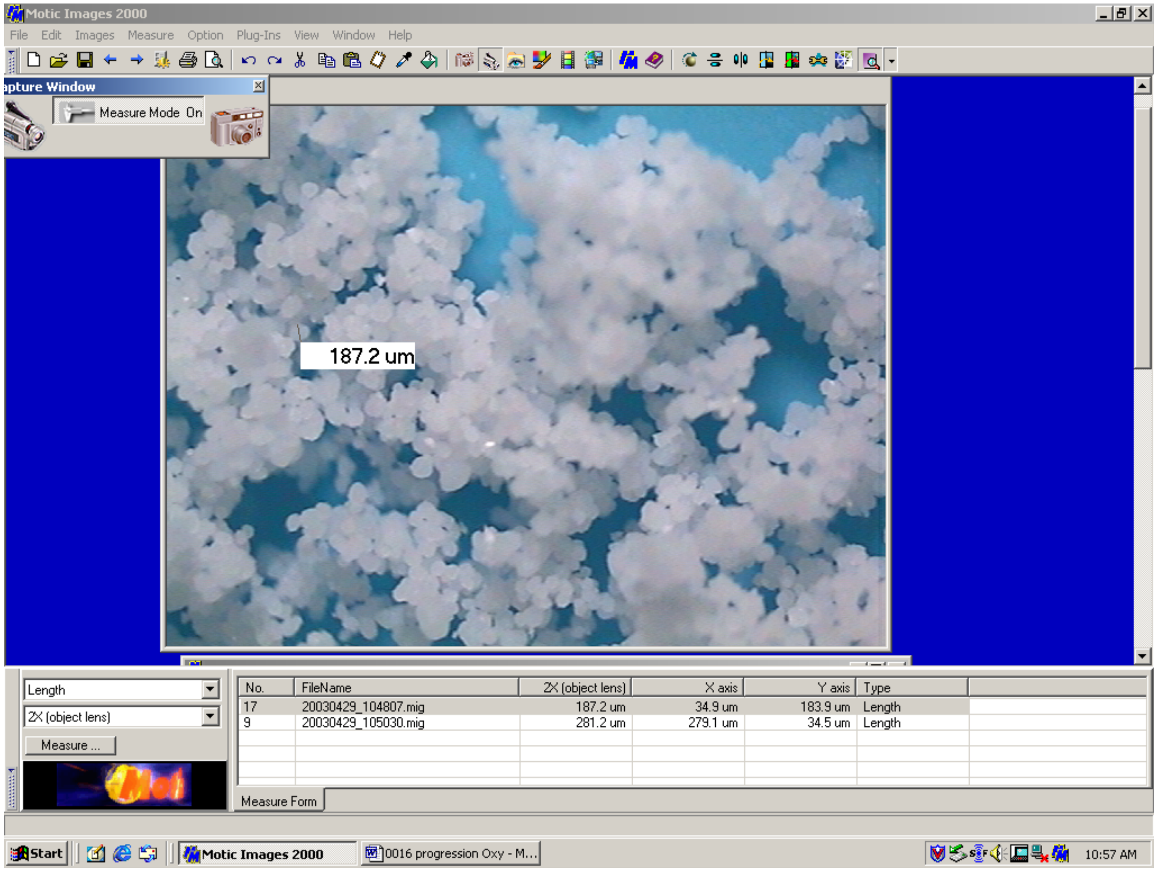
	1	2
Median , No Wt (1 - 1000)	55.90	36.55
Mean , Sqr Wt (1 - 1000)	140.92	74.59
Mean , Cube Wt (1 - 1000)	216.86	93.60
#/sec , No Wt (1 - 5)	86.77	1116.43
#/sec , No Wt (9 - 26)	1322.80	5691.43
#/sec , No Wt (26 - 94)	7449.44	15209.58
#/sec , No Wt (94 - 280)	1718.06	887.39
#/sec , No Wt (280 - 1000)	41.81	0.22

FBRM distributions highlight the difference in size between the wet and dry 100 micron granules. The size difference is evident in the PVM images as well.

METTLER TOLEDO

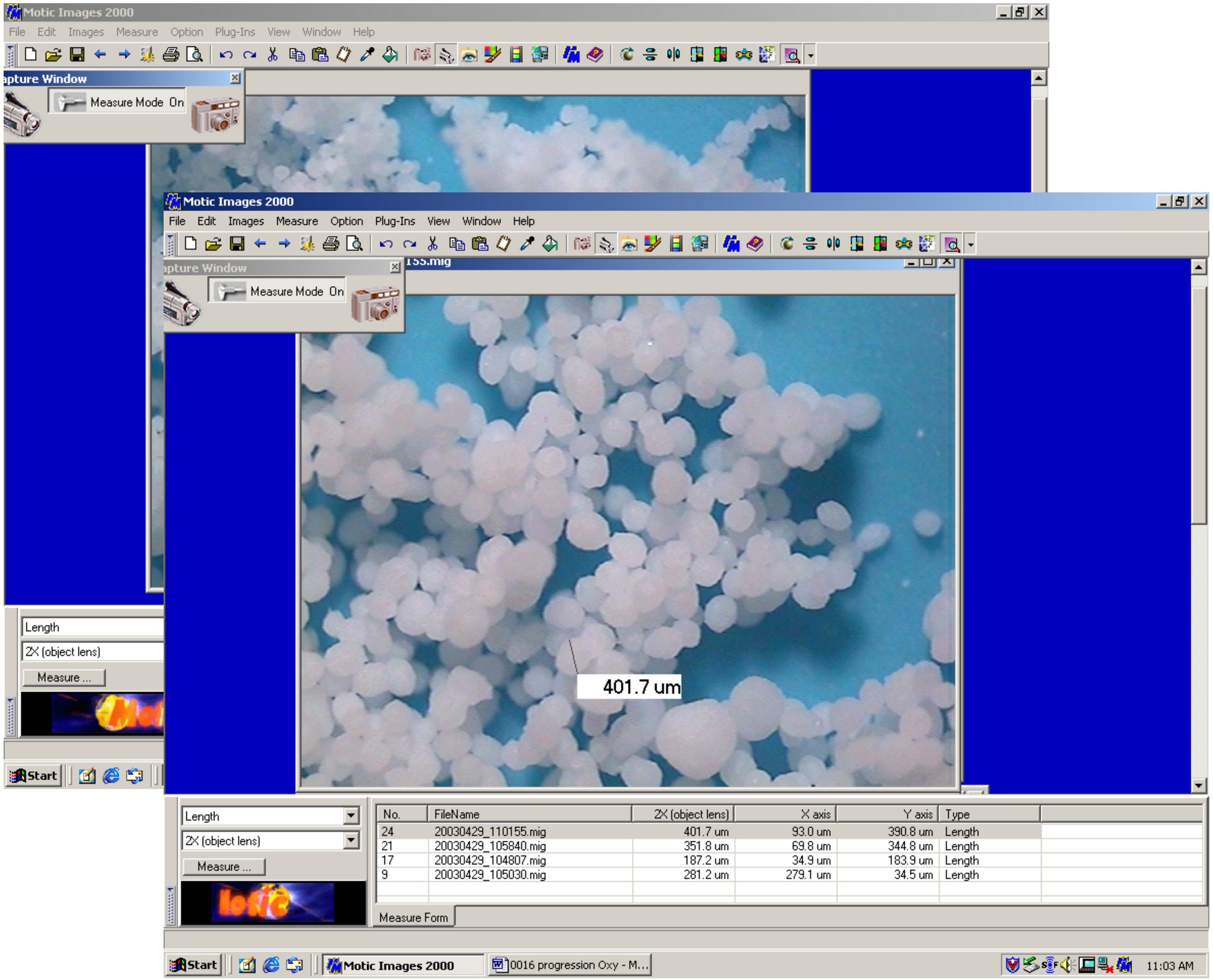
LASENTEC

Image Analysis by Stereoscope and Software



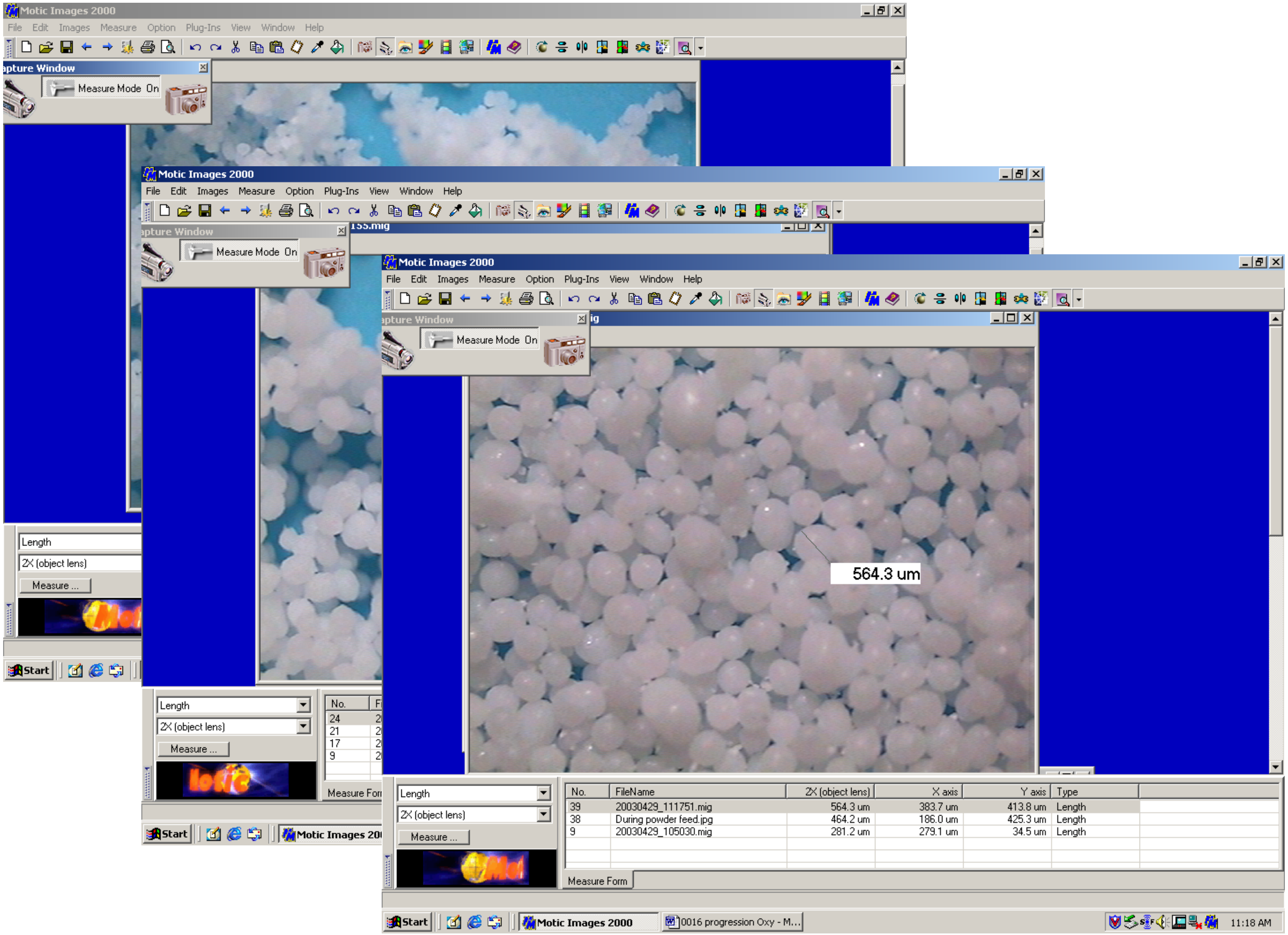
No.	FileName	2X (object lens)	X axis	Y axis	Type
17	20030429_104807.mig	187.2 um	34.9 um	183.9 um	Length
9	20030429_105030.mig	281.2 um	279.1 um	34.5 um	Length

Image Analysis by Stereoscope and Software



No.	FileName	2X (object lens)	X axis	Y axis	Type
24	20030429_110155.mig	401.7 um	93.0 um	390.8 um	Length
21	20030429_105840.mig	351.8 um	69.8 um	344.8 um	Length
17	20030429_104807.mig	187.2 um	34.9 um	183.9 um	Length
9	20030429_105030.mig	281.2 um	279.1 um	34.5 um	Length

Image Analysis by Stereoscope and Software

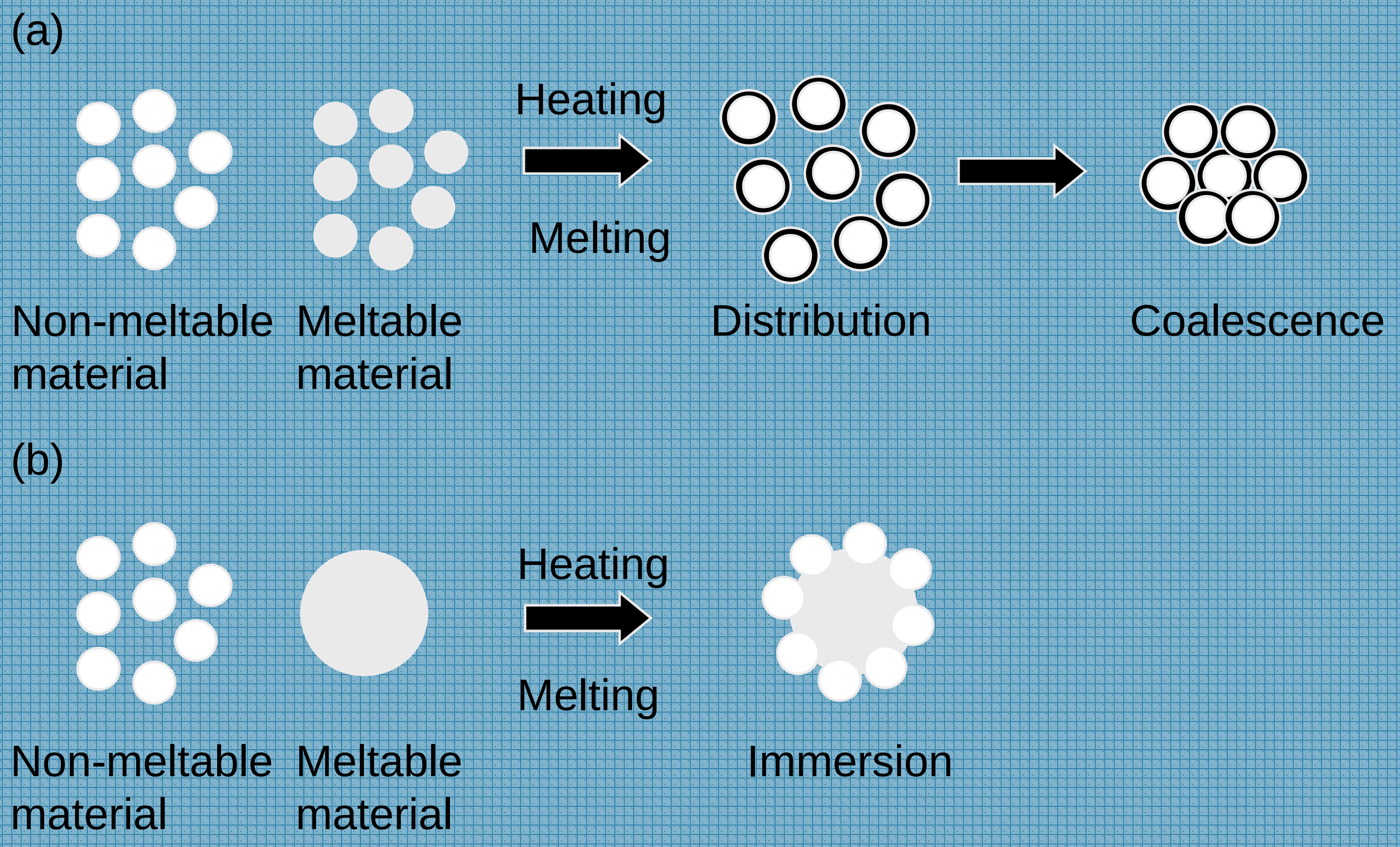


No.	FileName	2X (object lens)	X axis	Y axis	Type
39	20030429_111751.mig	564.3 um	383.7 um	413.8 um	Length
38	During powder feed.jpg	464.2 um	186.0 um	425.3 um	Length
9	20030429_105030.mig	281.2 um	279.1 um	34.5 um	Length

Melt Granulation

- Process by which the solid fine particles are bound together into granules by agitation, kneading and layering in the presence of molten binding liquid

Melt Granulation



(a)

Non-meltable material

Meltable material

Heating

Melting

Distribution

Coalescence

(b)

Non-meltable material

Meltable material

Heating

Melting

Immersion

Modes of melt agglomeration: (a) distribution and (b) immersion.

Melt Granulation – Advantages

- Avoids aqueous solvents for moisture sensitive drugs
- Avoids use of organic solvents for processing effervescent and hygroscopic materials thus avoiding special explosion protected area and equipment requirement
- Eliminates the drying step hence shorter processing time
- Release rate of a drug can be controlled by varying the composition of the meltable materials

Melt Granulation – Disadvantages

- Process can not be applied to the heat sensitive materials

Melt granulation Binders
Typical melting range (ºC)

Hydrophilic meltable binder

Gelucire 50/13	35-44
Poloxamer 188	~50.9
Polyethylene glycol	
• 2000	42-53
• 3000	48-63
• 6000	49-63
• 8000	54-63
• 20000	53-66
Stearate 6000 WL1644	46-58

Hydrophobic meltable binder

Beeswax	56-60
Carnauba wax	75-83
Cetyl palmitate	47-50
Glyceryl behenate	67-75
Glyceryl monostearate	47-63
Glyceryl palmitostearate	48-57
Glyceryl stearate	54-63
Hydrogenated castor oil	62-86
Microcrystalline wax	58-72
Paraffin wax	47-65
Stearic acid	46-69
Stearic alcohol	56-60

Melt Granulation

- Equipment most commonly used
    - High Shear Mixers
    - Fluid Bed Processors
    - Melt Extruders

Single Pot System

- Single pot providing in one apparatus:
  - Mixing
  - Granulating
  - Drying
  - Blending

Single Pot System

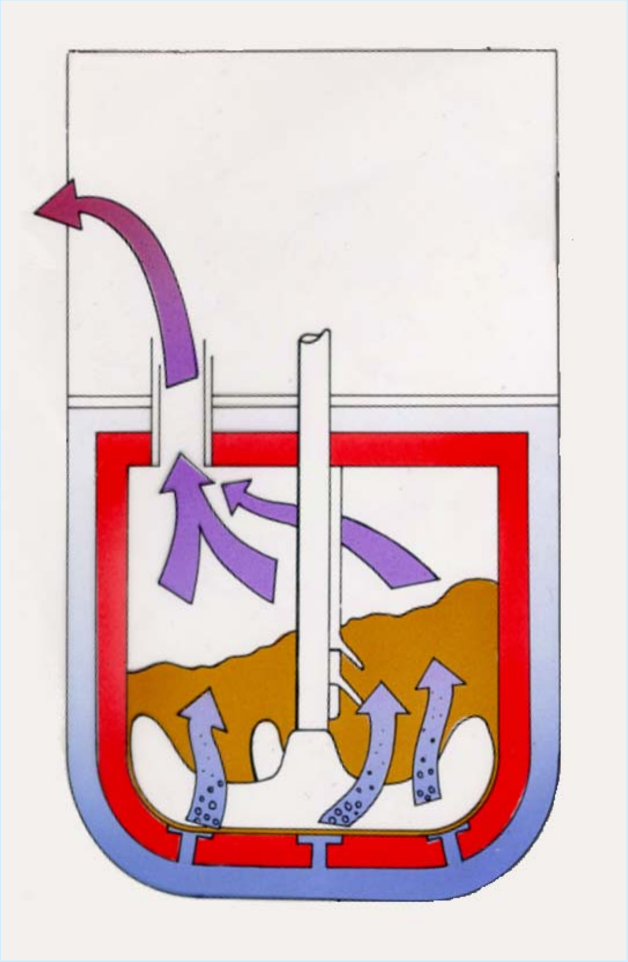
- Procedure for producing granulation is similar to the high shear mixer
- All the process variables are similar to high shear mixer
- It is the drying step that will be carried out in the same unit that distinguishes the single pot system

Single Pot System

- Drying in single pot system
  - Vacuum Drying
  - Gas Assisted Vacuum Drying
  - Microwave –Vacuum Drying

Vacuum Drying

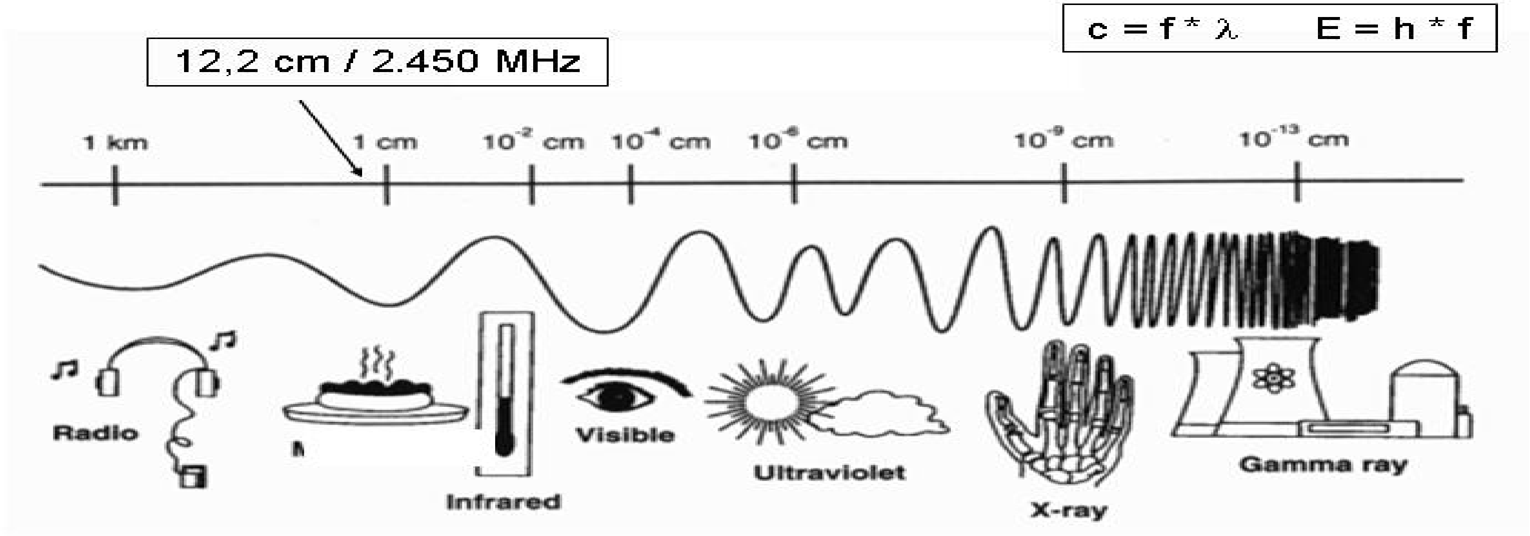
- During vacuum drying, inert gas is passed through the product in order to:
- improve the transport of moisture from the granules to the vacuum system
- increase the partial pressure drop across the vessel
- improve the heat transport through the bed
- mix the product gently when it becomes dry and fragile
  - Result : faster evaporation, reduced drying time



Microwave Vacuum Drying

- Provides fastest drying rates in the family of single pot system
- Microwave drying is based on the absorption of electromagnetic radiation by dielectric material
- Microwaves are a form of electromagnetic energy similar to radio waves
- Pharmaceutical processors generally use 2450 MHz frequency

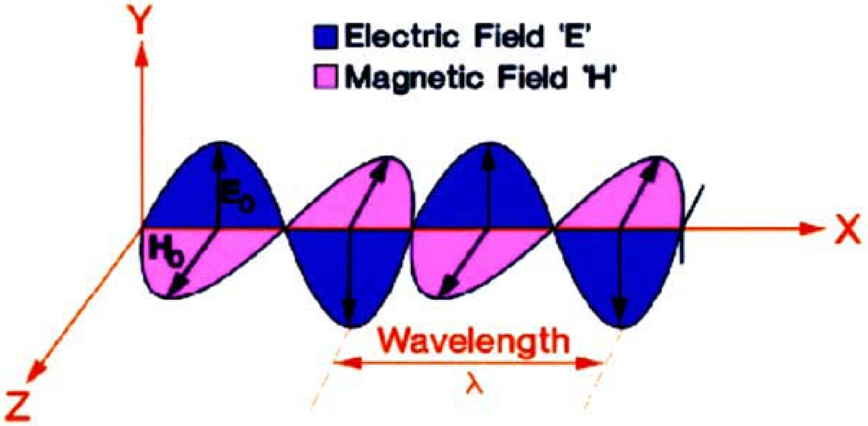
Electromagnetic Spectrum



12,2 cm / 2.450 MHz

$c = f * \lambda$ $E = h * f$

AN ELECTROMAGNETIC WAVE IN FREE SPACE



For microwave at 2.45 GHz

$$C = f\lambda$$

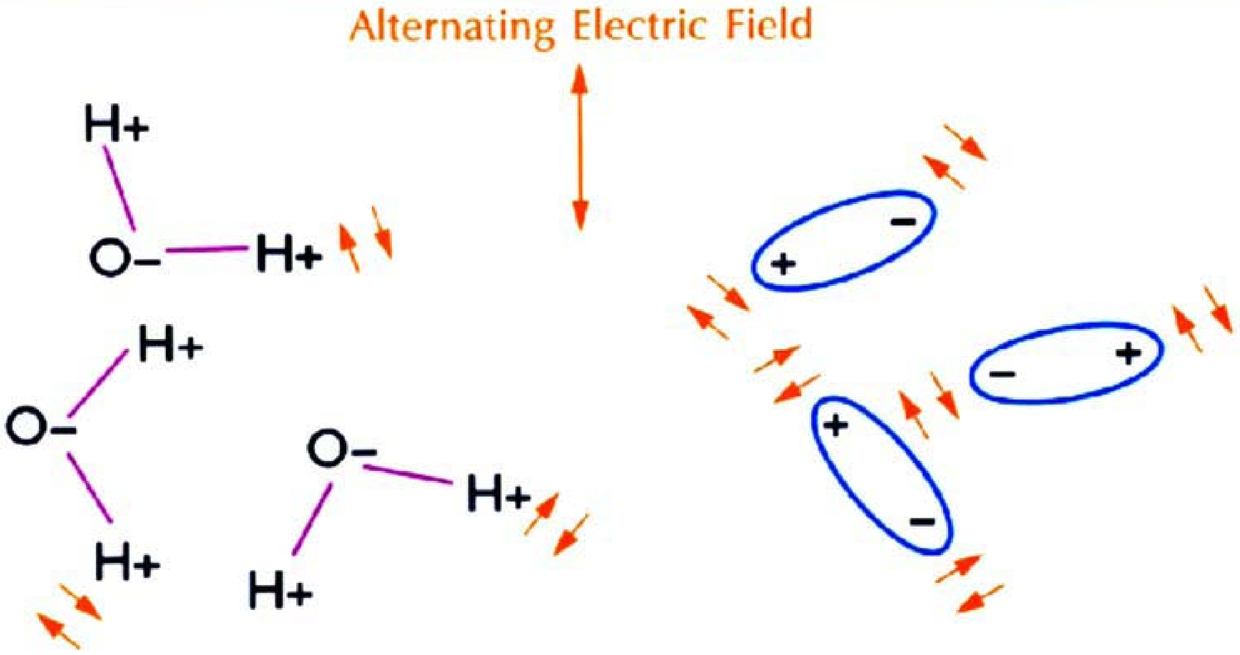
$$\lambda = \frac{3\times10^8}{2.45\times10^9} = 0.1224\ \text{m}$$

$$\approx 12\tfrac{1}{4}\ \text{cm}$$

Single Pot Processing-Microwave Drying

- In the rapidly alternating electric field generated by microwaves, polar materials orient and reorient themselves according to the direction of the field
- The rapid change in the field at 2450 MHz, the orientation of the field changes 2450 million times per second and causes rapid re-orientation of the molecules, resulting in friction and heat creation

MICROWAVES `COUPLE' ENERGY INTO DIELECTRICS



Water

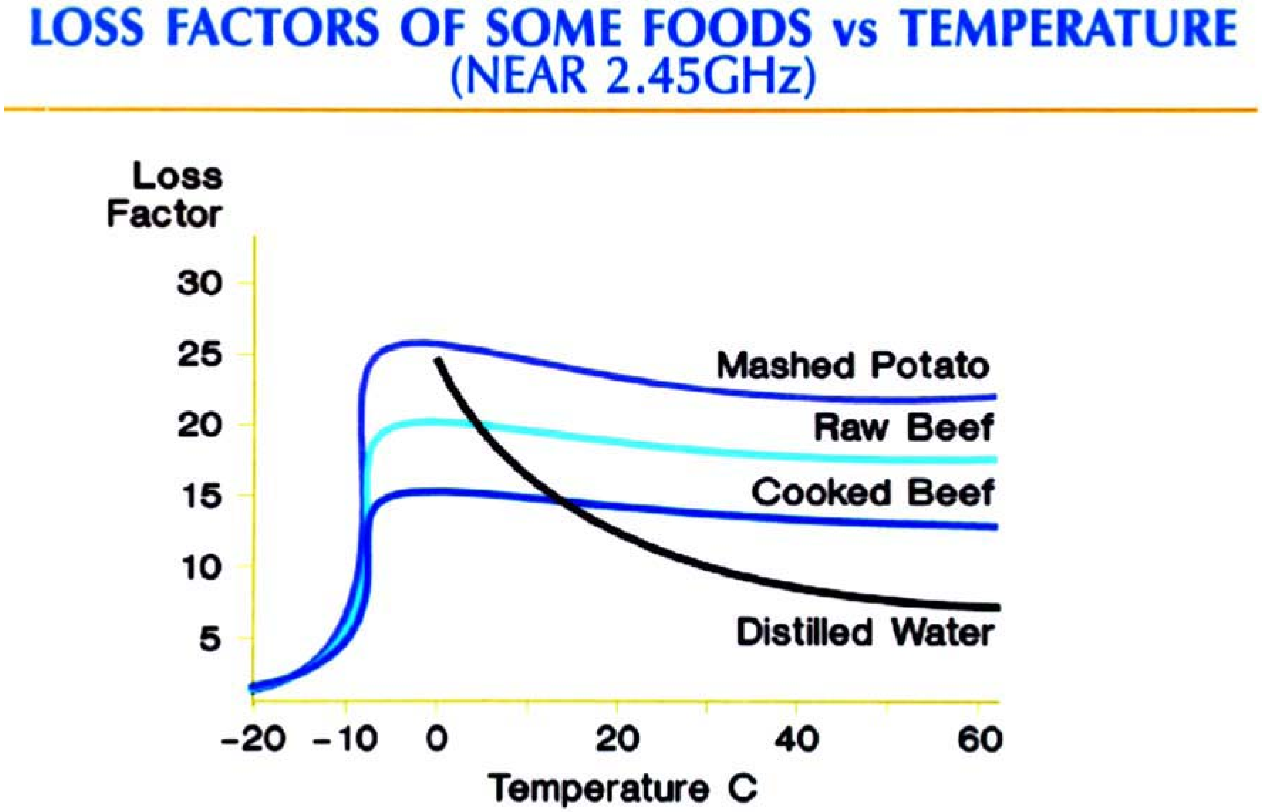
Molecular Polarisation

Microwave–Vacuum Drying

“Loss Factor”

- Amount of microwave energy is proportional to the relative measure of how easily a material absorbs microwave energy called loss factor
- Various pharmaceutical materials have low loss factors and absorb very little microwave energy
- Granulating solvents (water, ethanol, IPA etc.) on the other hand have a high loss factors and heat up readily in the presence of electromagnetic field and evaporate and removed by vacuum

Loss Factor


LOSS FACTORS OF SOME FOODS vs TEMPERATURE
(NEAR 2.45GHz)
Loss Factor
30
25
20
15
10
5
Mashed Potato
Raw Beef
Cooked Beef
Distilled Water
-20
-10
0
20
40
60
Temperature C

Loss Factors of Commonly Used Excipients

Commonly used excipients	
Cornstarch	0.41
Avicel	0.15
Carbonate	0.08
Manitol	0.06
Calcium Phosphate	0.06
Calcium Carbonate	0.03
Lactose	0.048
Polypropylene	0.0027
Teflon	0.0003

Commonly used solvents	
Methanol	13.6
Water	12.0
Ethanol	8.6
Isopropanol	2.9
Acetone	1.25
Ice	0.003

Microwave Vacuum - One Pot Processor (Top Driven)

- ❑ Through-the-wall design:
- ❑ Substantial reduction in GMP floor space needed
- ❑ Clear separation between production area and technical area
- ❑ No maintenance interventions needed in production area

Courtesy: Collette

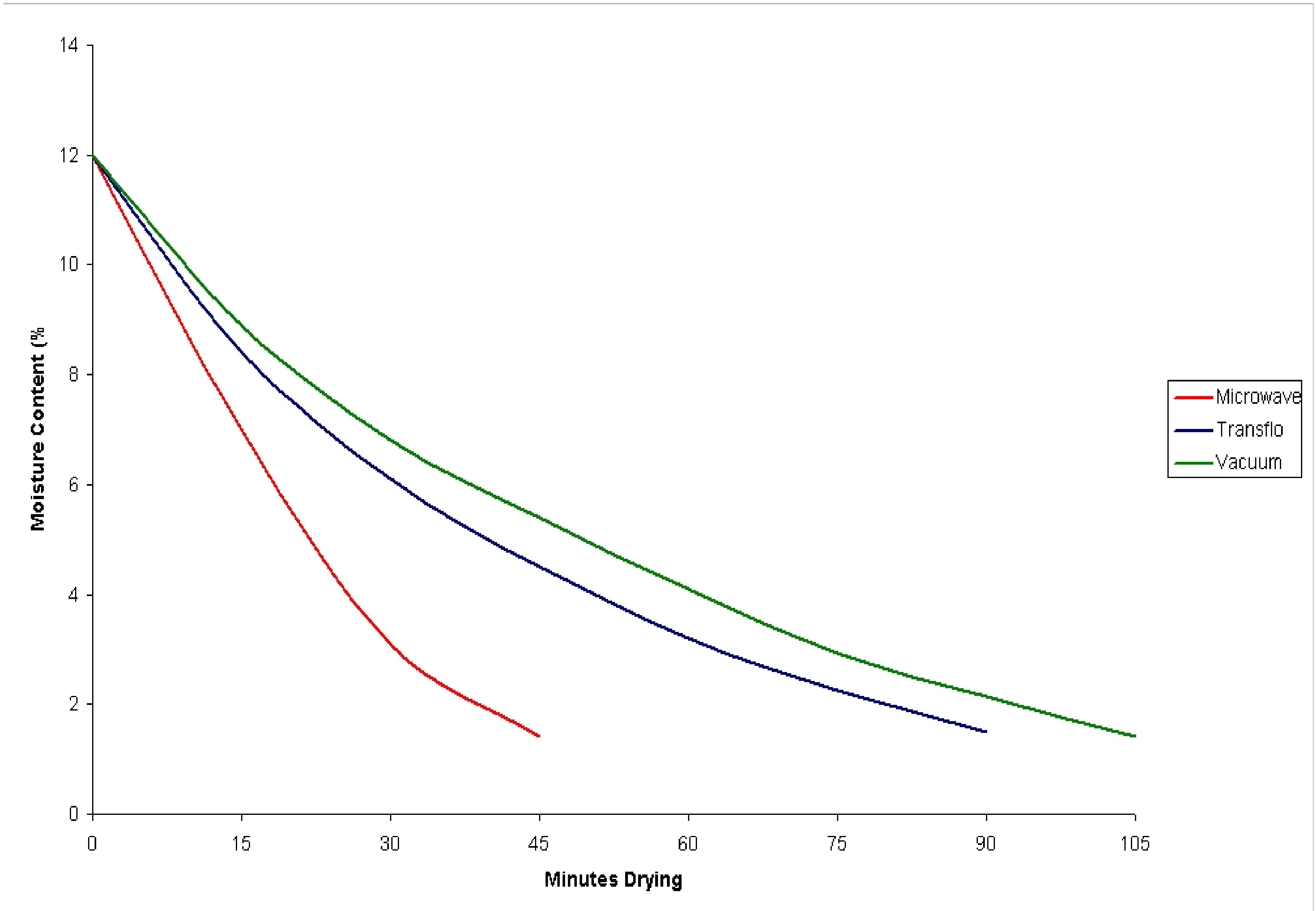
Microwave Vacuum - One Pot Processor (Top Driven)

Courtesy: Bohle

Microwave Vacuum One-Pot Processor (Bottom Driven)

Courtesy :Fielder

One Pot System –
Drying Times with Various Options



Extrusion

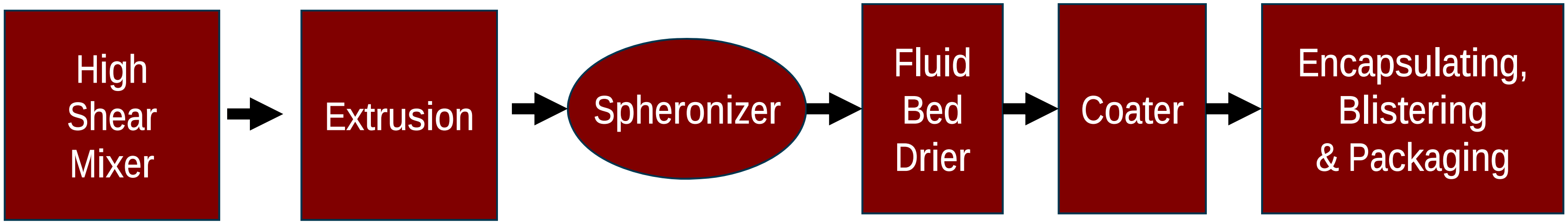
- Extrusion is method of applying pressure to a mass until it flows through an orifice or defined opening.
- Orifice defines the cross sectional geometry, extrudate length is usually the only variable dimension which is dependent on materials physical characteristic

Extrusion/Spheronization

- Most common method for making multi-particulate dosage forms
- Involves following steps
- Dry powder mix
- Wet Granulation
- Extrusion thru an Extruder
- Spheronization
- Drying
- Coating with functional coat

Extrusion Spheronization Process Flow

The Process



High Shear Mixer

Extrusion

Spheronizer

Fluid Bed Drier

Coater

Encapsulating, Blistering & Packaging

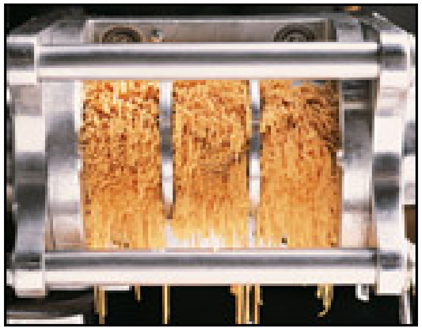
Types of Extruders

- Axial: A screw extruder where material is extruded in the same direction as it being transported by screws
- Dome extruder: A screw extruder with dome shaped extrusion area
- Radial Extruder: A screw extruder where material is extruded radially to the direction as it is being transported by screws.
- Basket Extruders:Extruder using oscillating or circular blades to wipe material through a perforated screen.

Types of Extruders

Axial

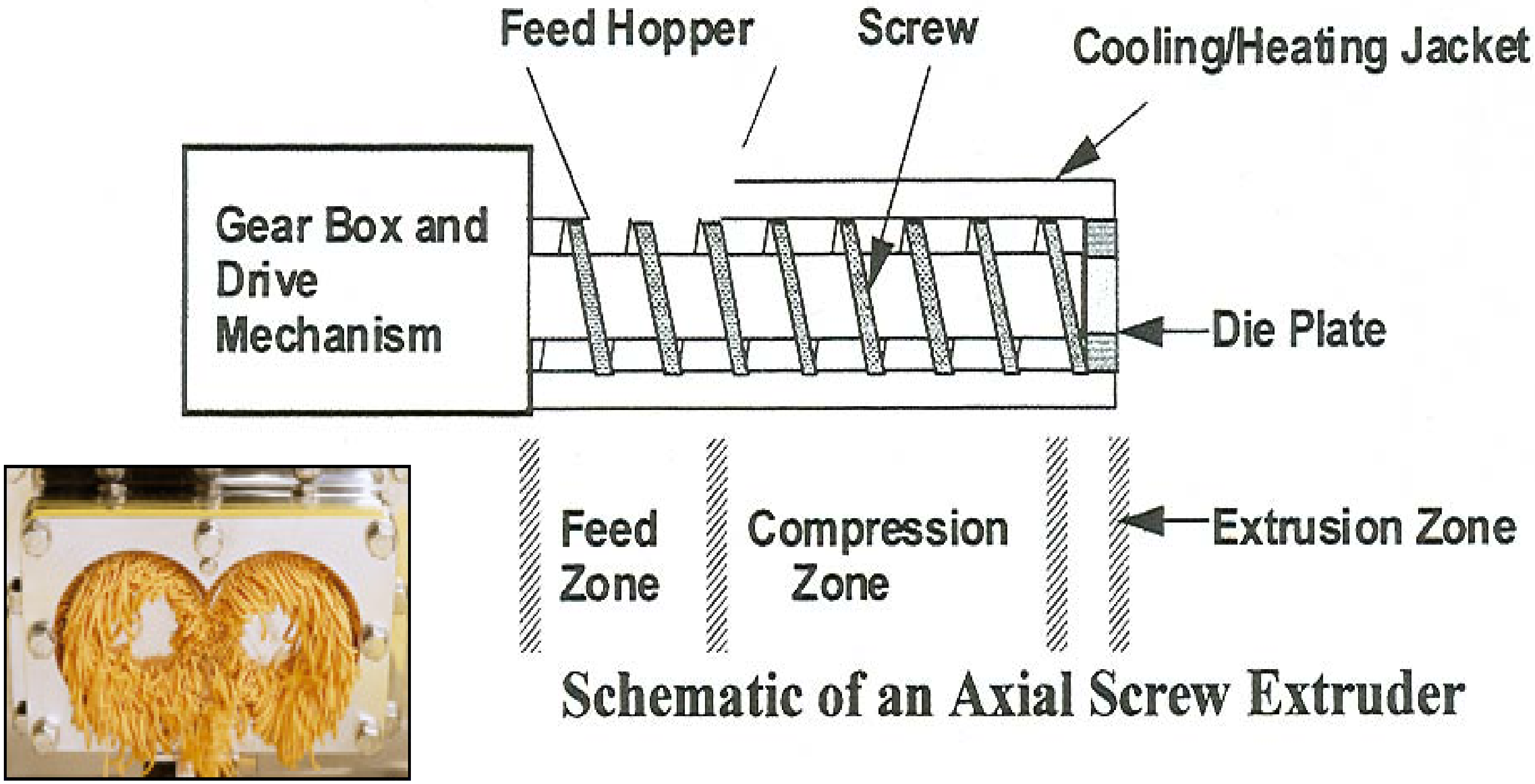
Dome



Radial

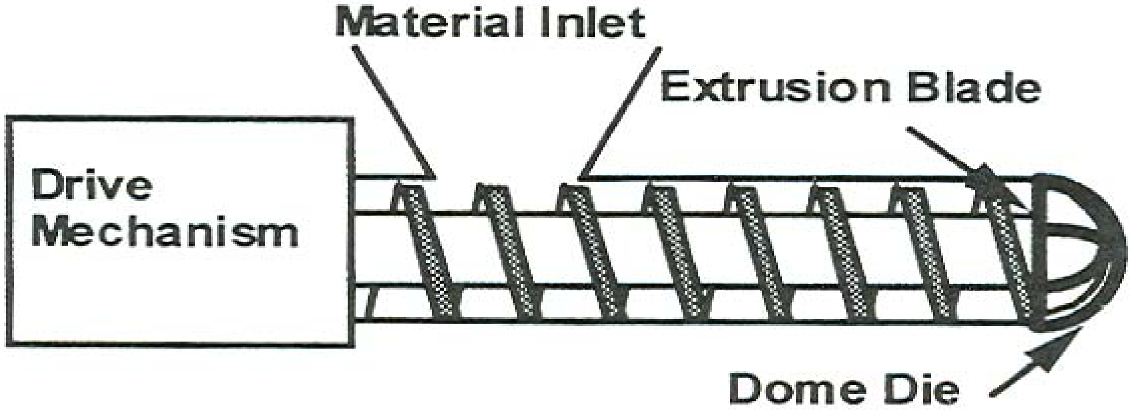
Basket

Axial Screw Extruder

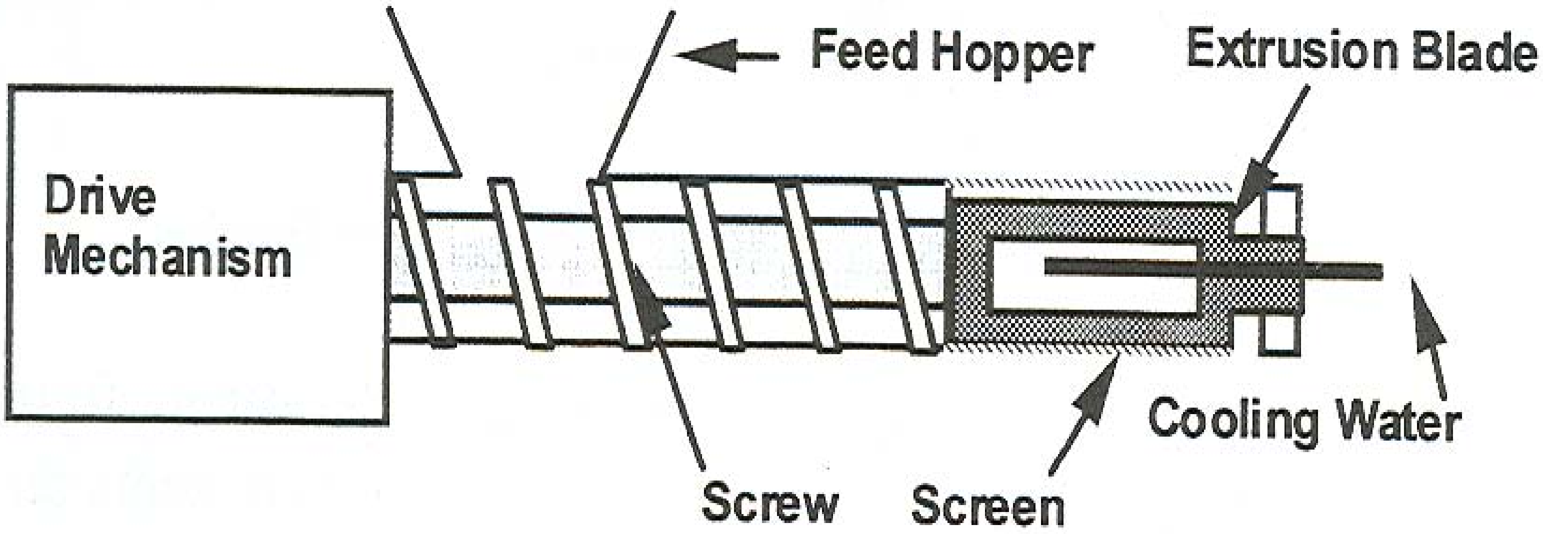


Schematic of an Axial Screw Extruder

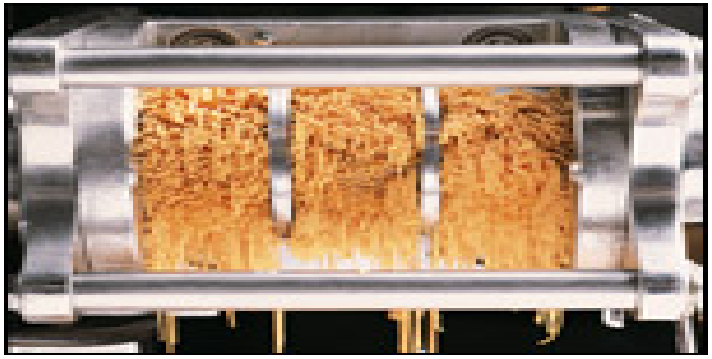
Dome Type Extruder



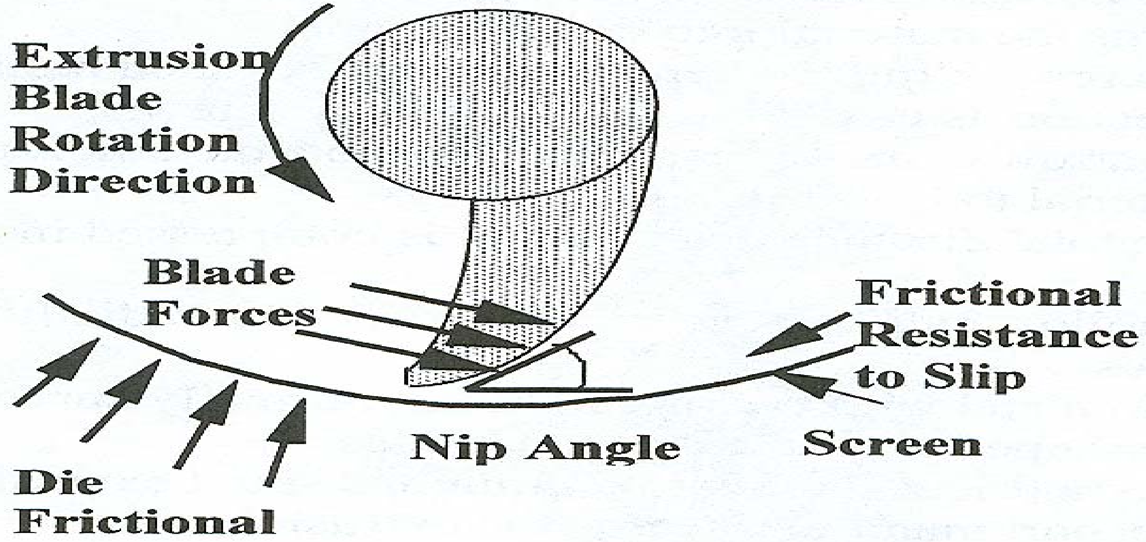
Radial Extruder



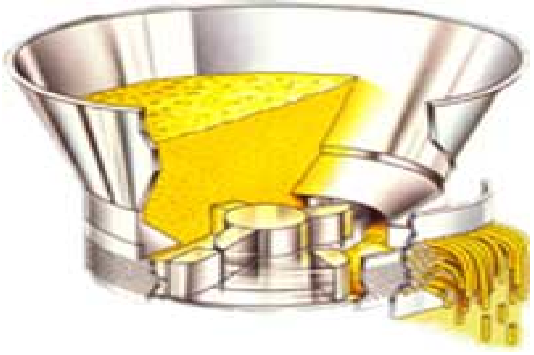
Schematic of Radial Extruder



Basket Extruder

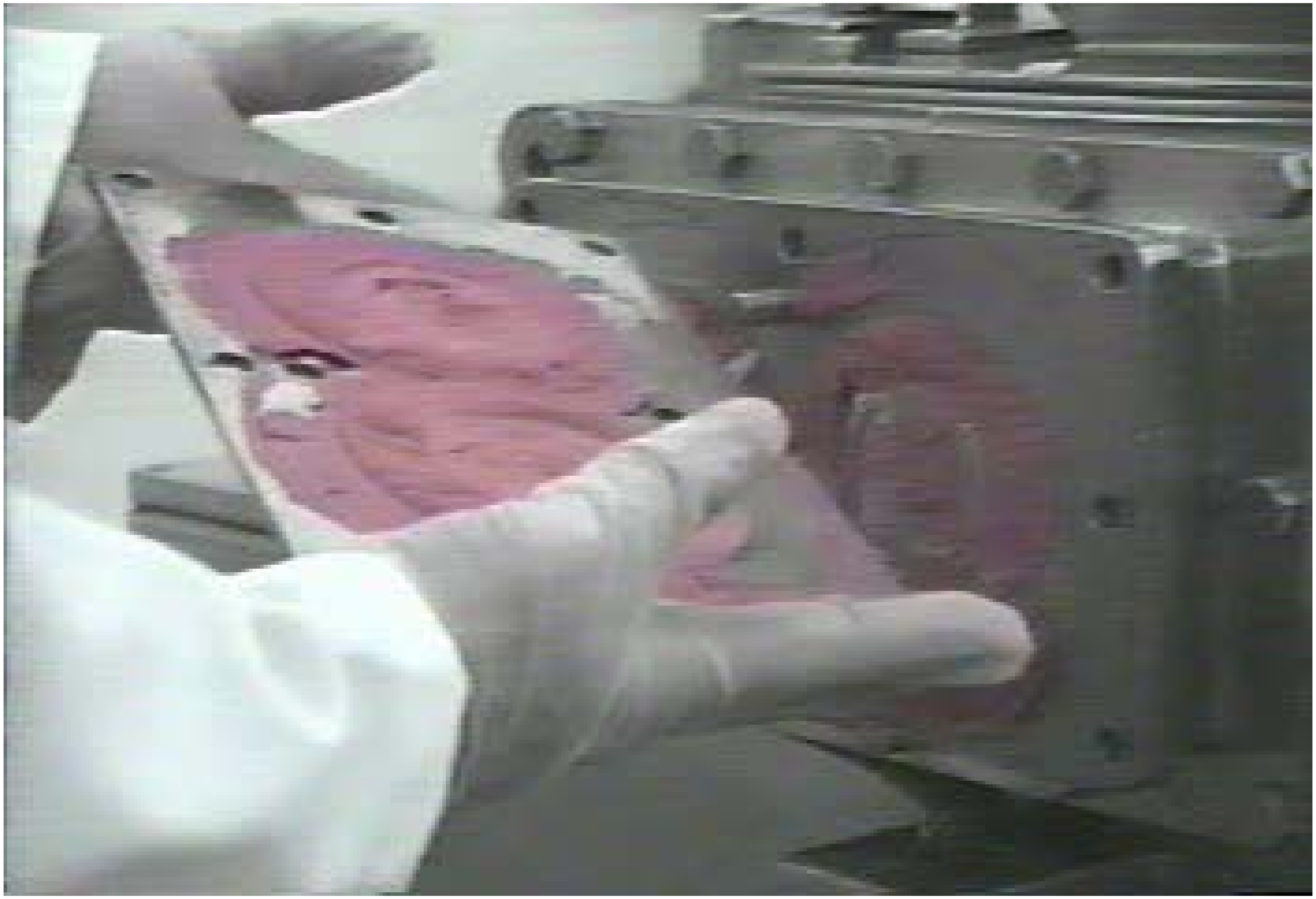


Forces For Basket Type Extrusion

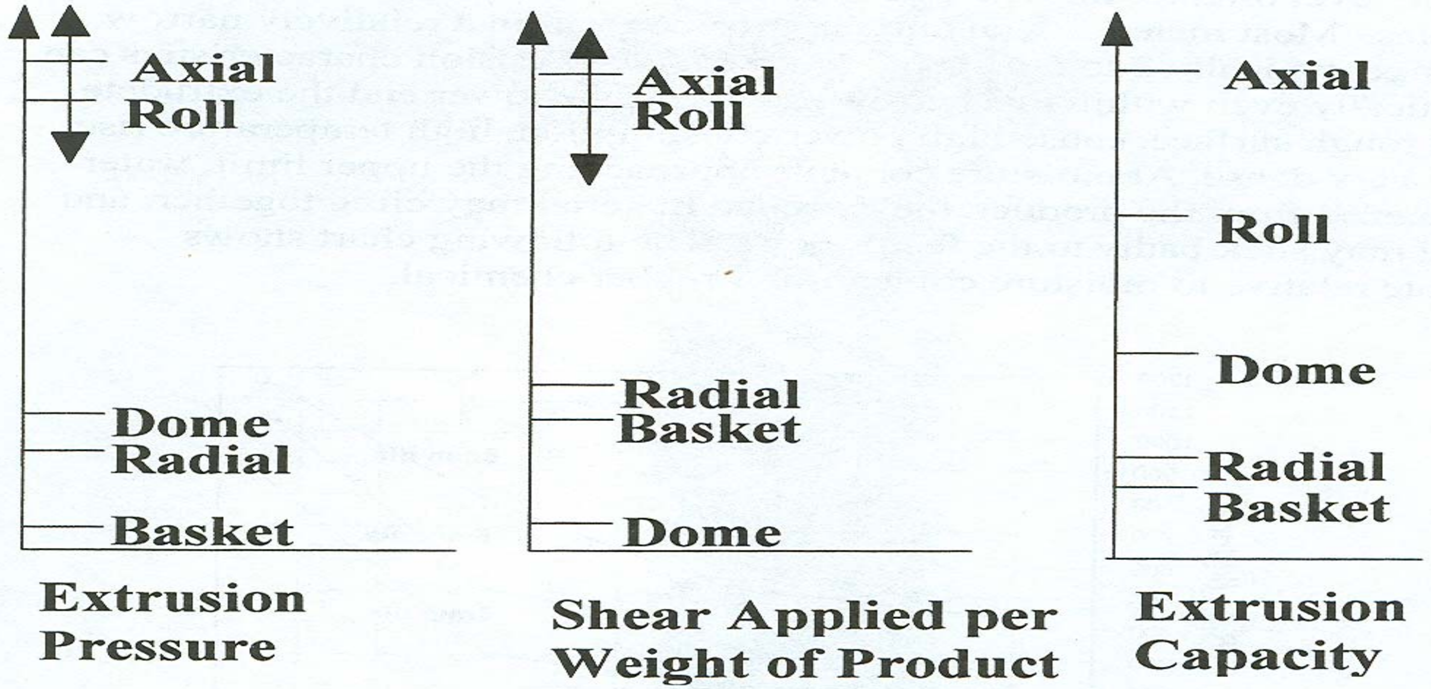


Axial Extruder in Action

Dome Extruder in Action

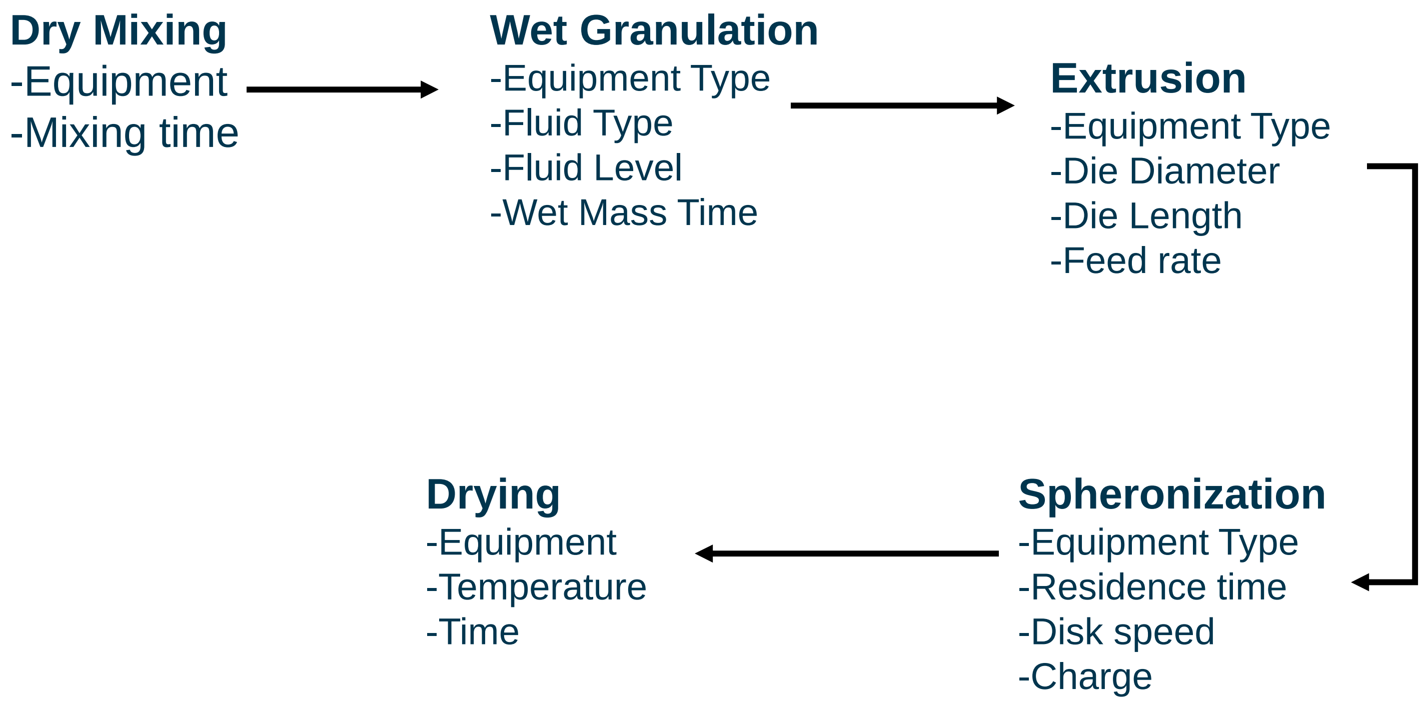


Comparison Between Types of Extruders and Pressure, Shear and Capacity



Comparison of Pressure, Shear and Capacity for Various Extrusion Techniques

Extrusion/Sphronization
Process Flow Chart and Variables



Dry Mixing
-Equipment
-Mixing time

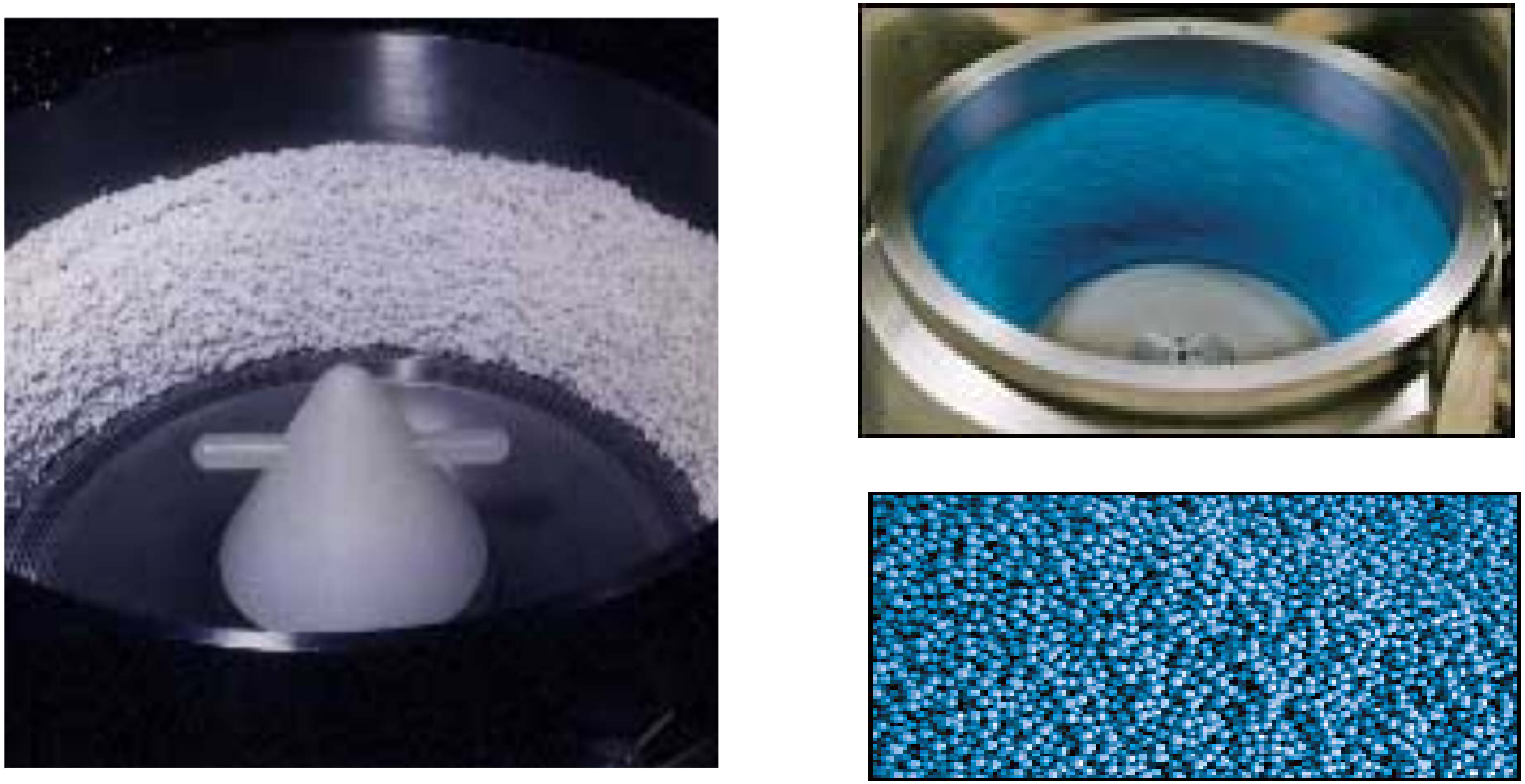
Wet Granulation
-Equipment Type
-Fluid Type
-Fluid Level
-Wet Mass Time

Extrusion
-Equipment Type
-Die Diameter
-Die Length
-Feed rate

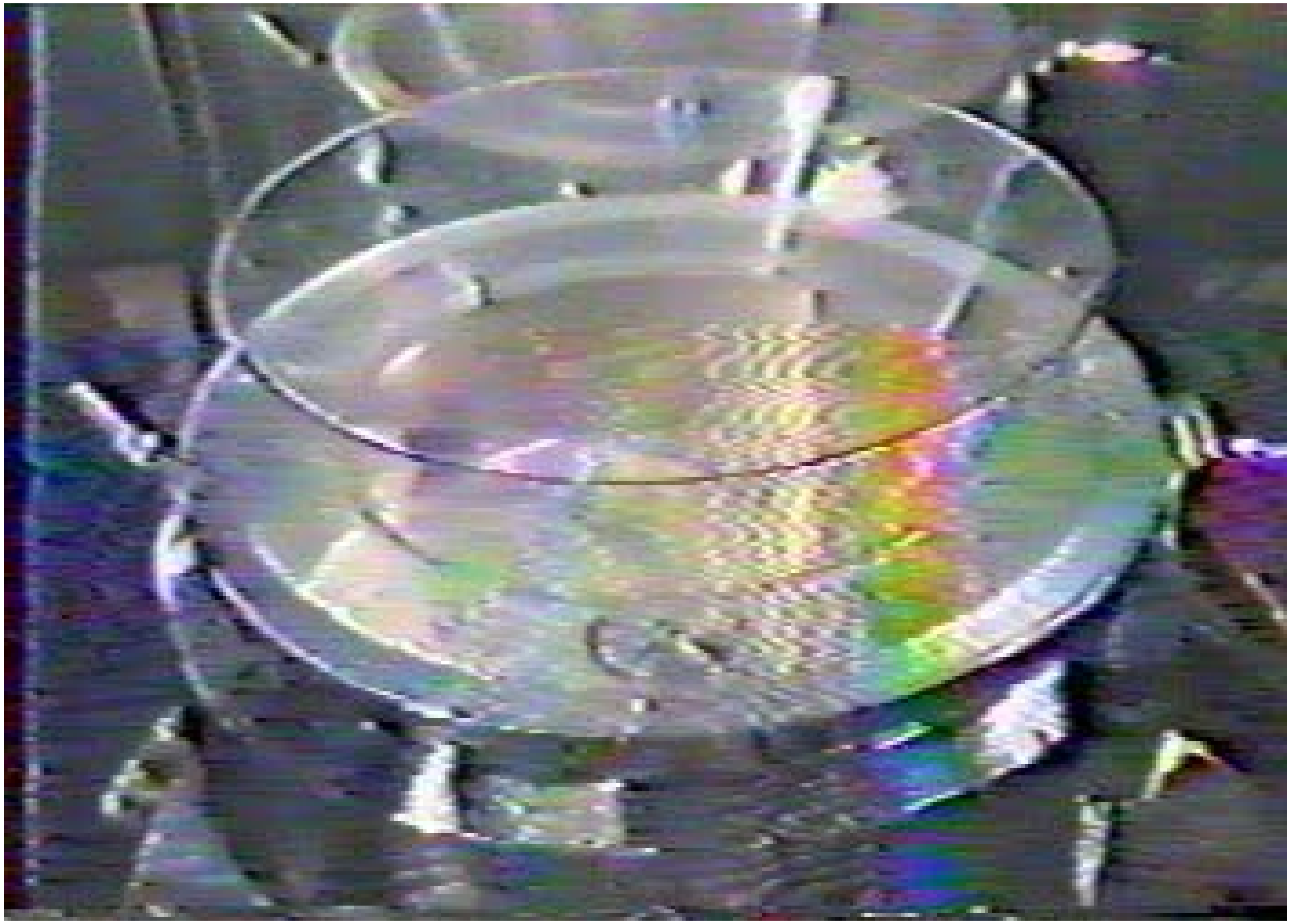
Spheronization
-Equipment Type
-Residence time
-Disk speed
-Charge

Drying
-Equipment
-Temperature
-Time

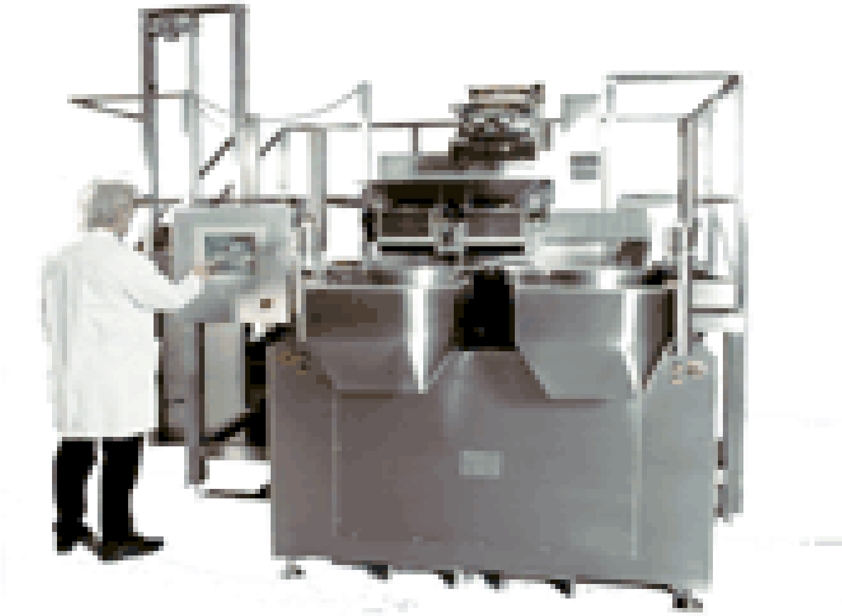
Spheronizer In Action



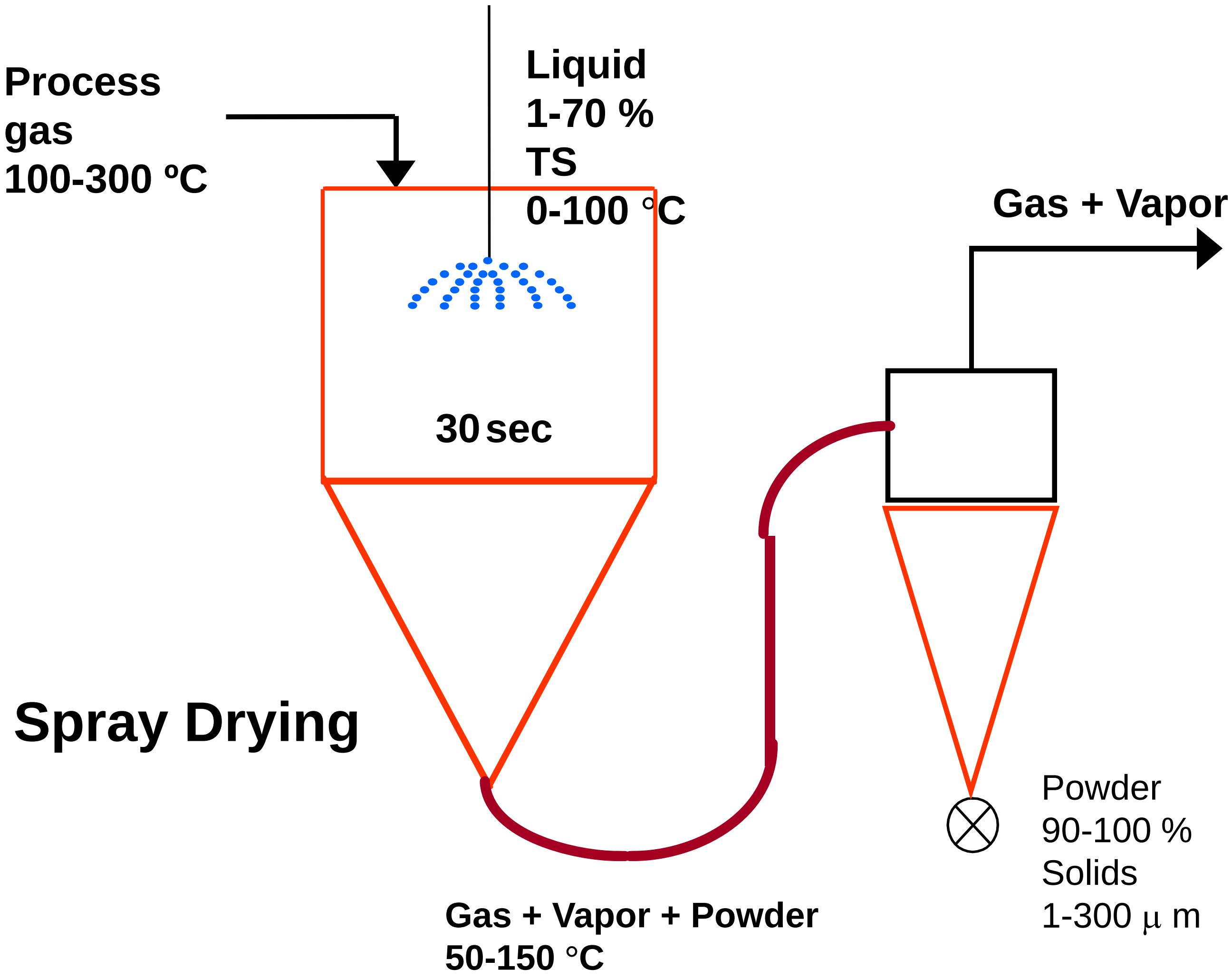
Spheronizer in Action



Production Extruder/Spheronizer



BASIC SPRAY DRYING CONCEPT



Process
gas
100-300 ºC

Liquid
1-70 %
TS
0-100 °C

Gas + Vapor

30 sec

Spray Drying

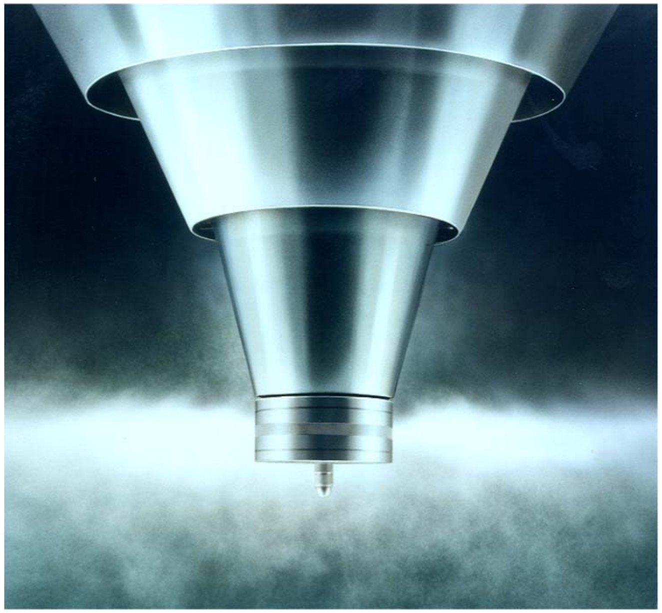
Powder
90-100 %
Solids
1-300 µ m

Gas + Vapor + Powder
50-150 °C

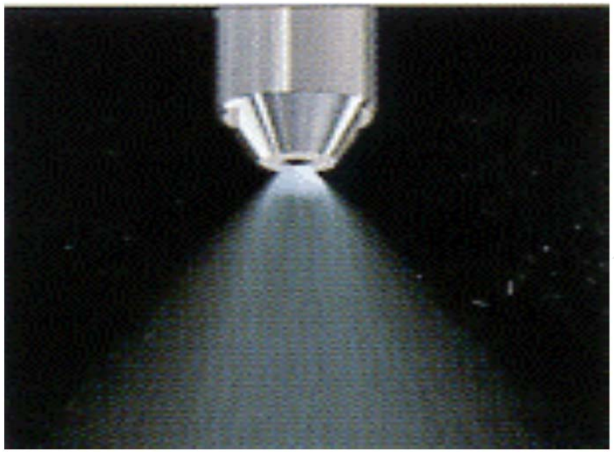
Small Scale Spray Dryer

Courtesy Anhydro

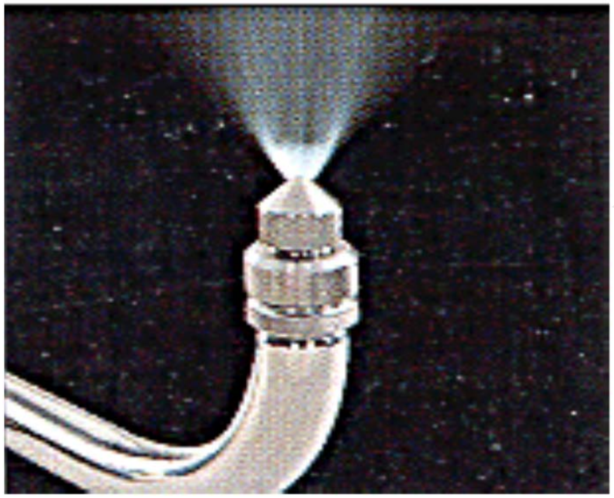
Atomization Options



Rotary Atomizer

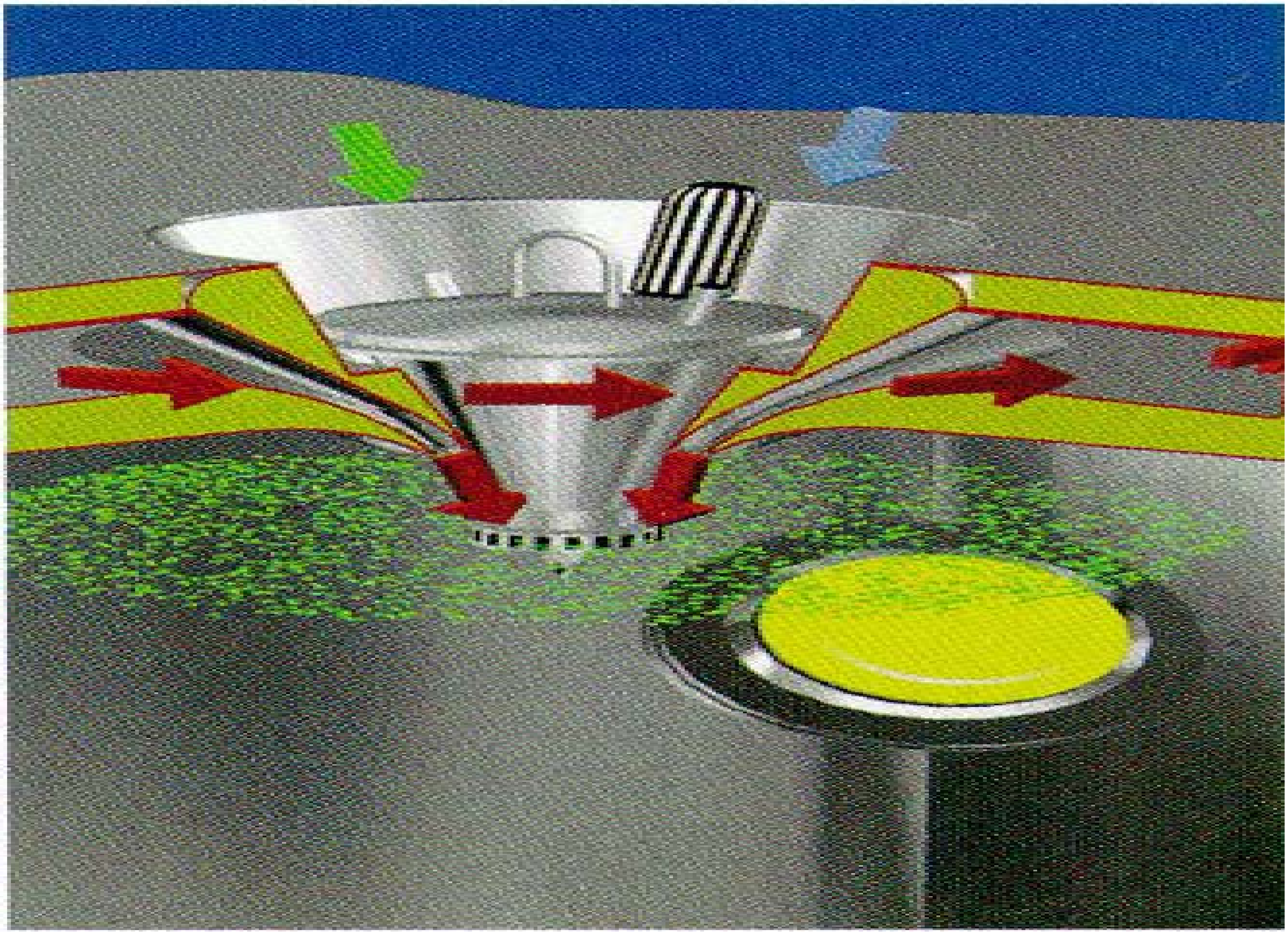


Pressue Nozzle

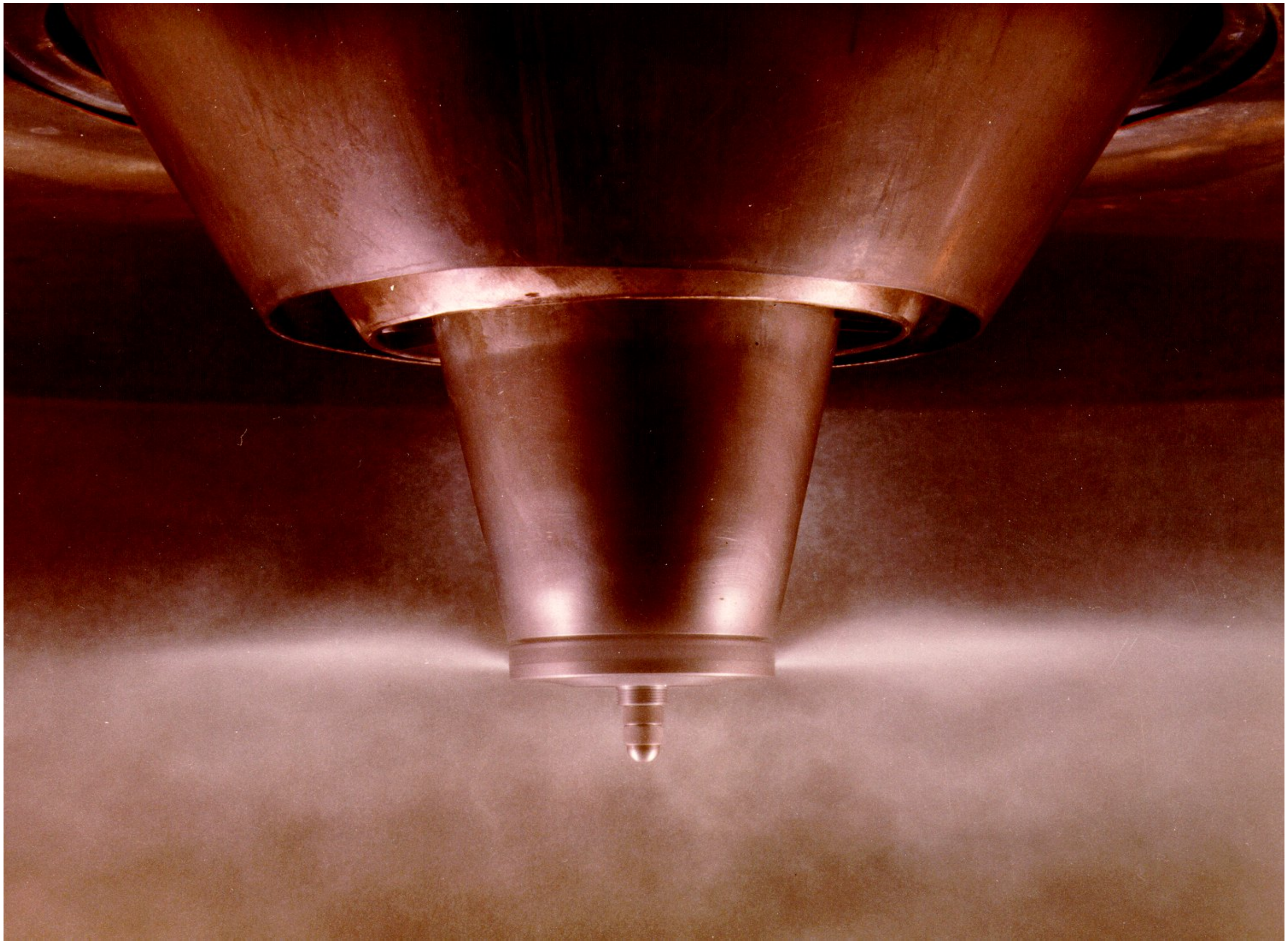


Two Fluid Nozzle

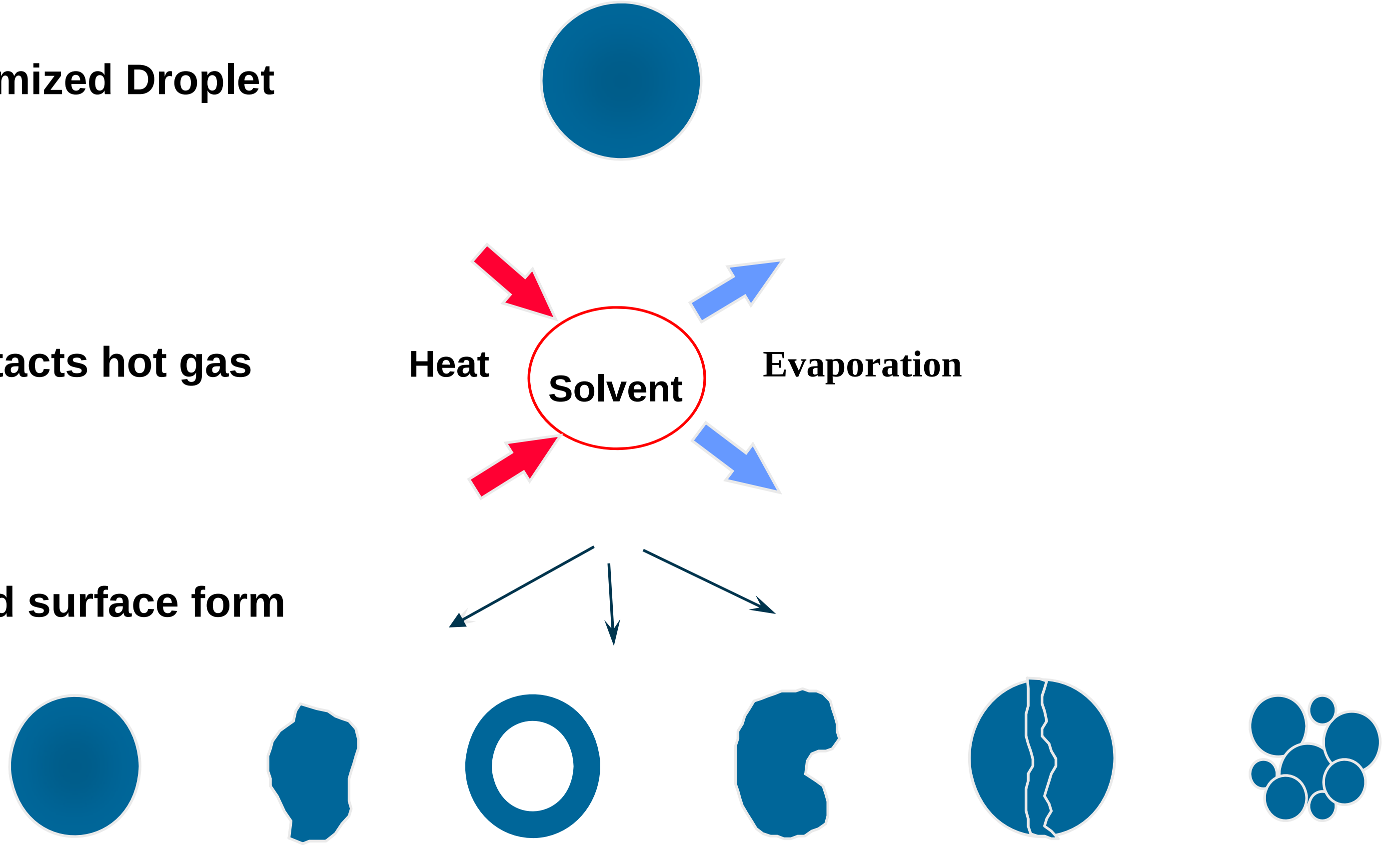
Spray Dryer Atomizer Wheel



Spray Dryer Atomizer Wheel



Particle Formation



Atomized Droplet

Contacts hot gas

Heat

Solvent

Evaporation

Dried surface form

Solid particle

Shrivelled Particle

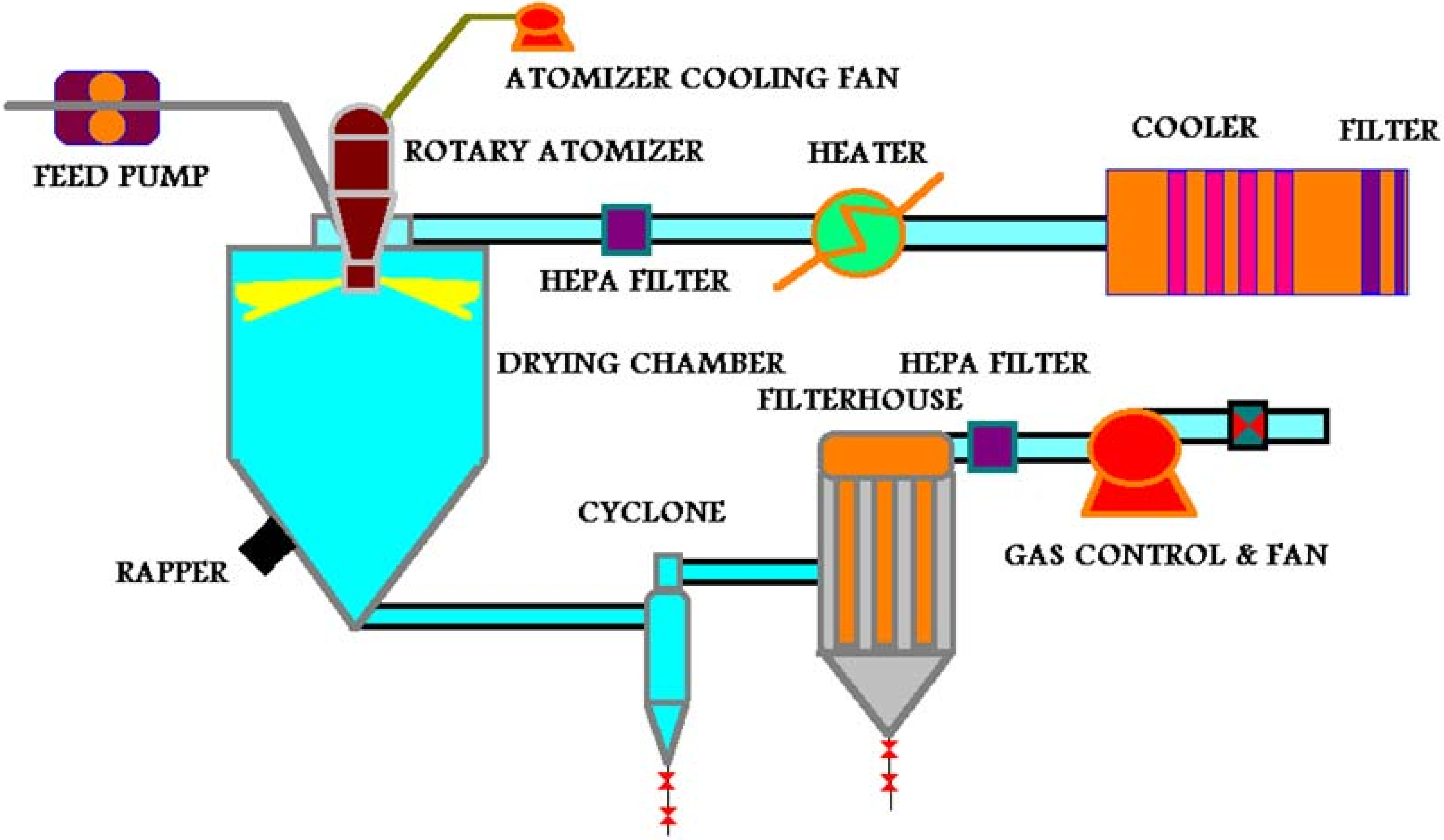
Hollow Particle

Cenosphere

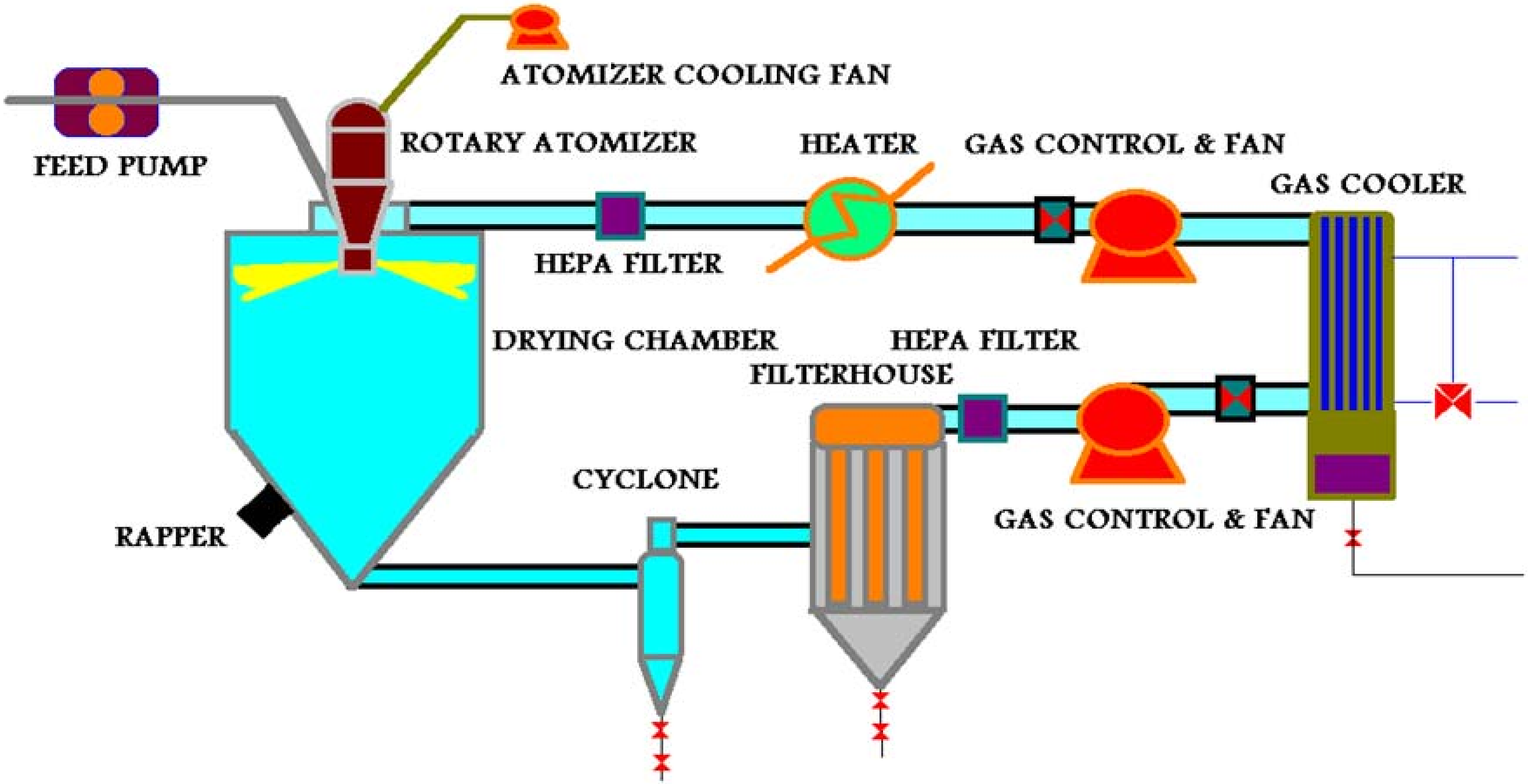
Disintegrated Particle

Agglomerated Particle

OPEN CYCLE SPRAY DRYER (AQUEOUS SOLVENT)



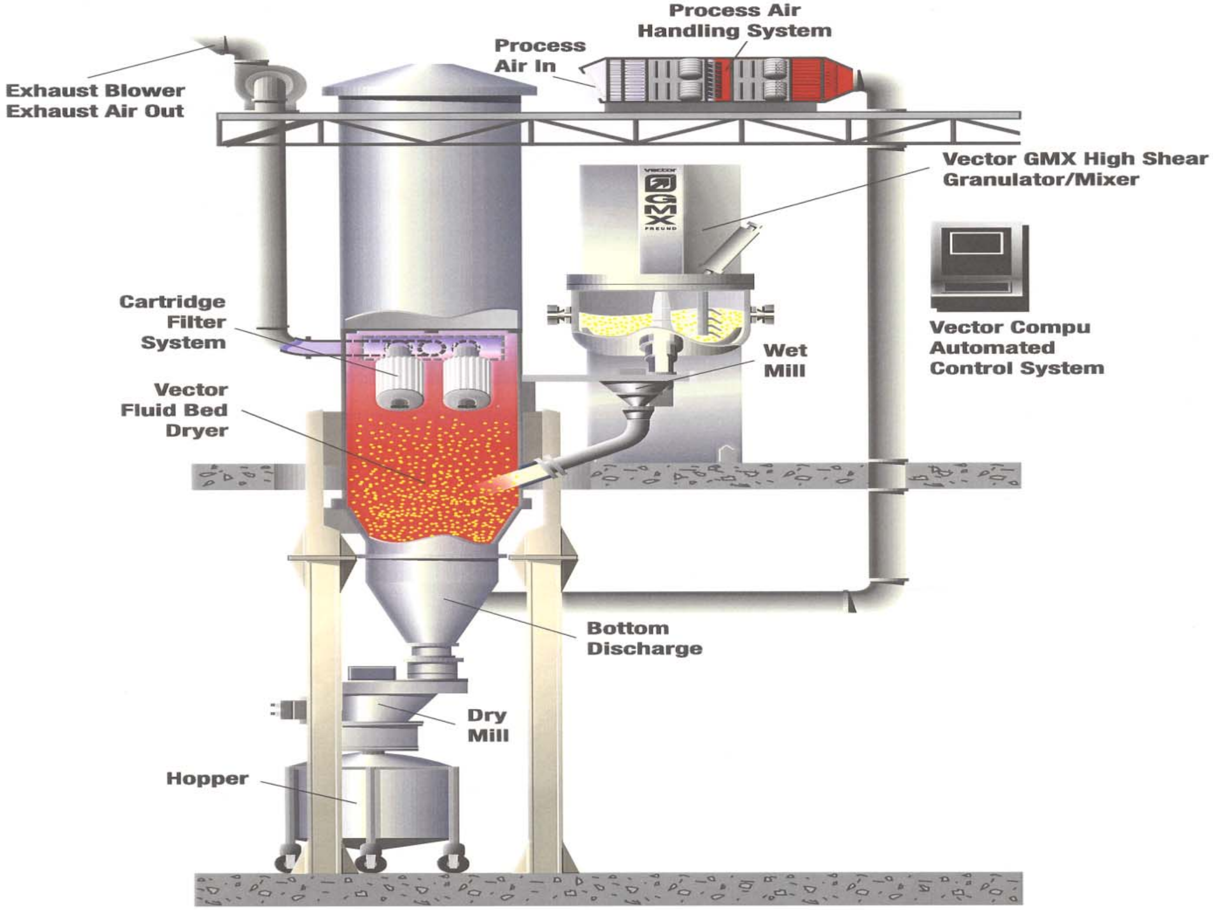
CLOSED CYCLE SPRAY DRYER (ORGANIC SOLVENT)



Integrated Systems

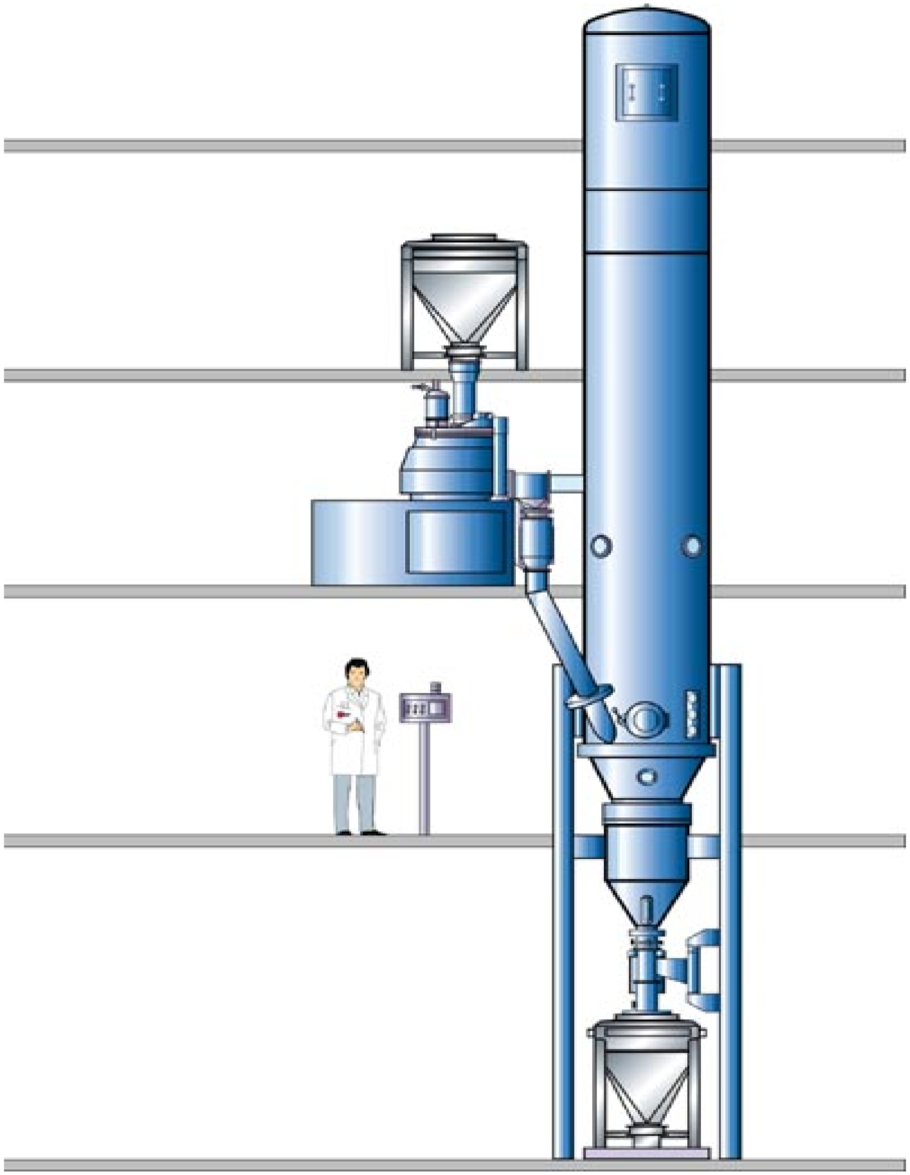
- Integrating High shear and Fluid bed id the most common set used in the industry.
- The rapid granule formation in high shear granulator with desired densification and efficient drying in a fluid bed offers the process efficiency.
- In line milling and process controls offer further advantages and reduces the material handling.

Integrated System for Granulation

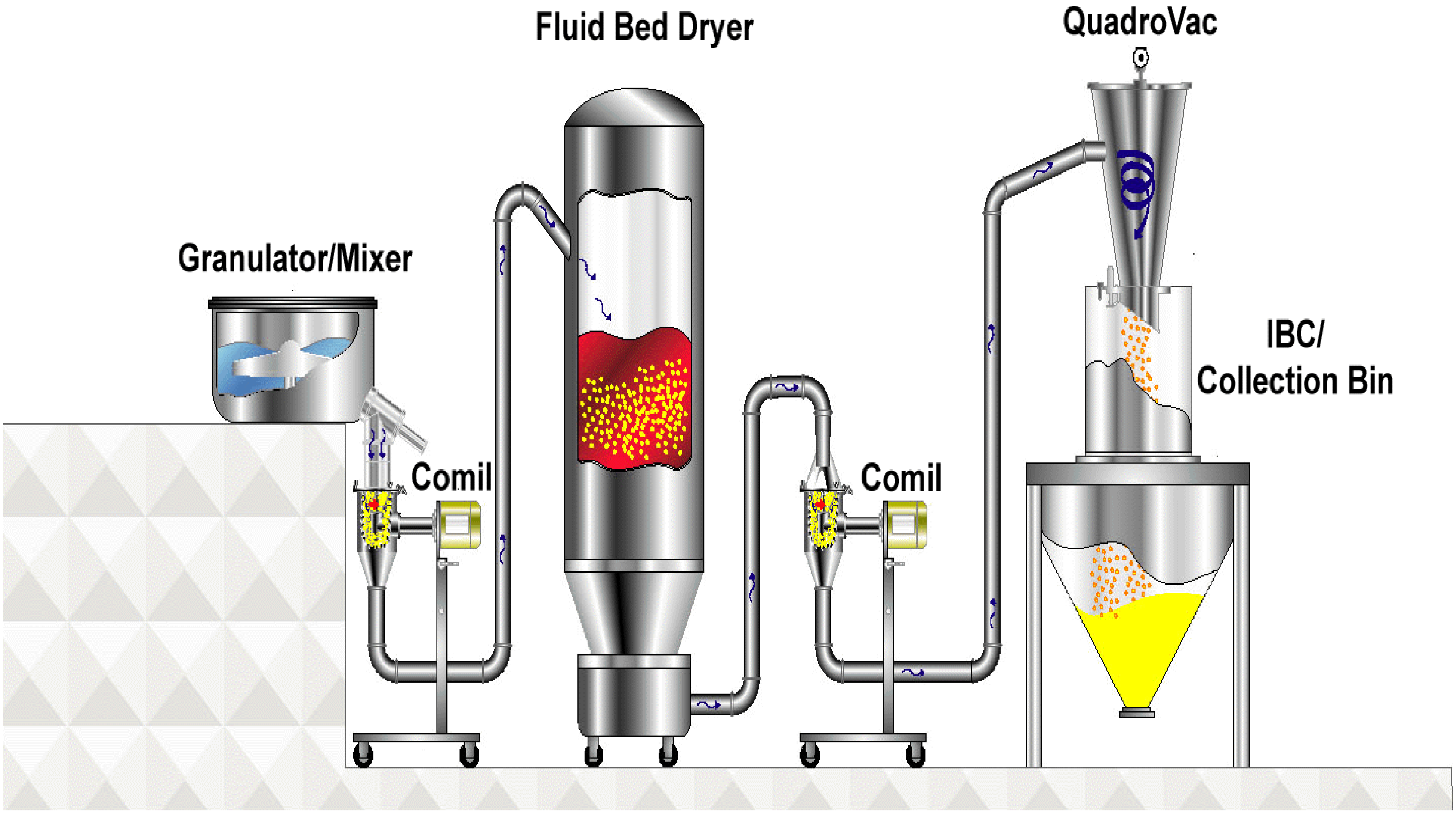


Courtesy Vector corp.

Integrated Systems



Typical Granulation Suite



Courtesy: Quadro Enginnering

Drying Product From High Shear Mixer Unit

Continuous Granulation

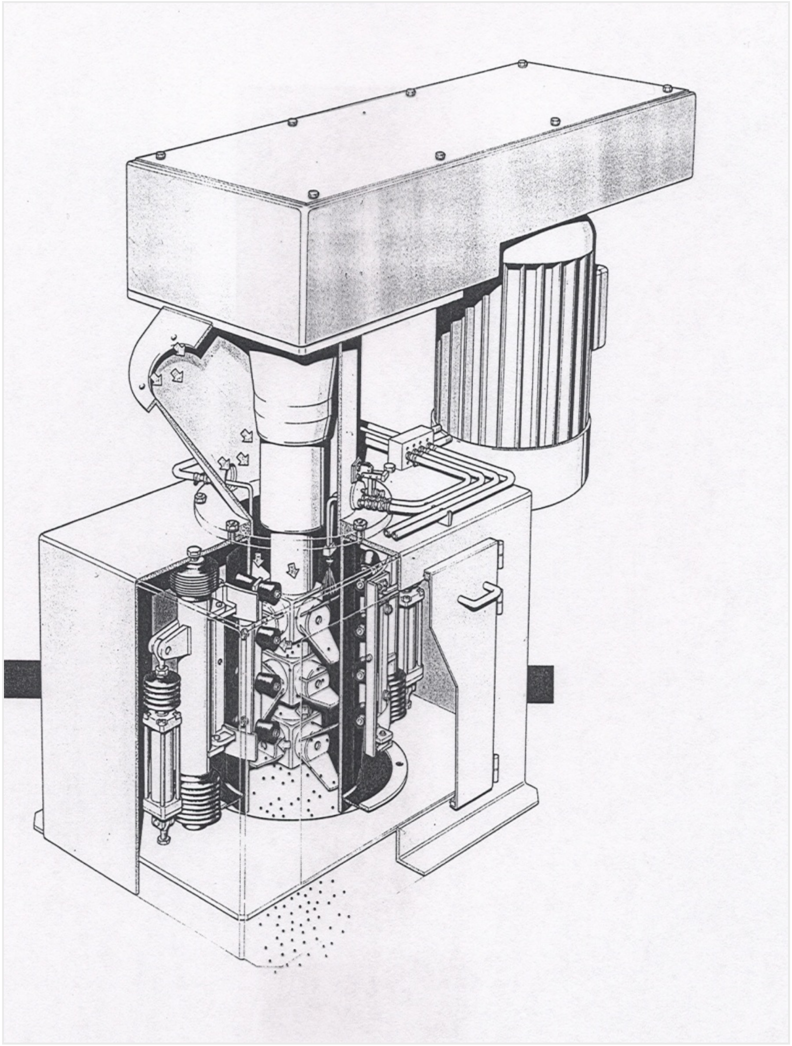
- Pharmaceutical Industry uses mainly batch process
- Some Processes are semi continuous (milling, roller compaction, tableting, etc.)
- Continuous techniques may be suitable for high volume, low cost type product

Continuous/Semi Continuous Granulation System

- Fluid Bed (Glatt, Niro, Heinen, Vector)
- Mechanical Systems for Wet Granulation (Bepex, Loedige, Nica)
- Roller Compactors (Thomas Eng., Alexanderwerks,Vector)
- Continuous/semi-continuous Extrusion Systems (LCI, Nica, Caleva)
- Spray Dryer as a granulator (Anhydro, Niro)

Continuous Granulator

SCHUGI



BEPEX

Conclusion

- Granulation is a critical unit operation in the development and manufacture of the solid dosage forms
- Specific techniques can be selected from the various options based on the physico chemical characteristics of the product to be granulated, scale-up and the end product desired

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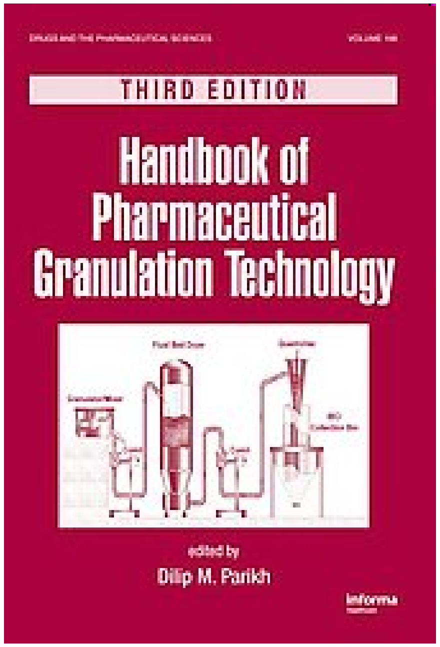
- 13. Dilip M. Parikh. "Granulation" Tablets & Capsules" Volume 5 (1) January 2007, Pages 36-46
- 14. Dilip M. Parikh, "Advances in Spray Drying Technology: New Applications for a proven Process" American Pharmaceutical Review, Volume 11, Issue 4 Jan/Feb. 2008 PP34-41

Recommended Reading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Handbook of Pharmaceutical Granulation Technology

edited by

Dilip M. Parikh

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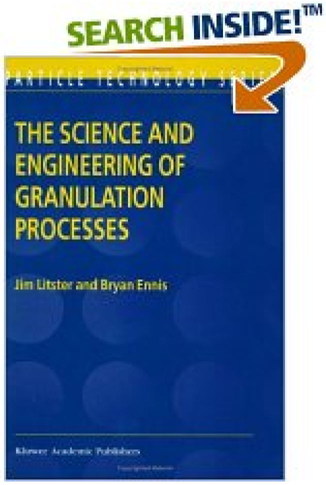
SEARCH INSIDE!™

THE SCIENCE AND ENGINEERING OF GRANULATION PROCESSES

Jim Litster and Bryan Ennis

Kluwer Academic Publishers

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By: Jim Litster and Bryan Ennis

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Publisher: Kluwer Academic Publishers,

Norwell, MA 02061 , 2004

ANY QUESTIONS?

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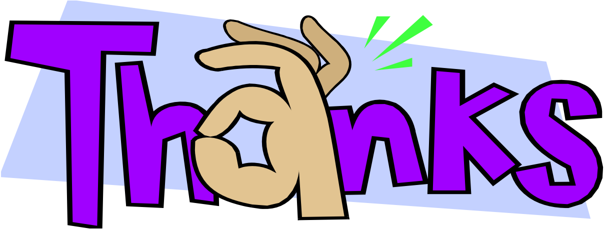
Díky


Thanks


Merci


Vielen
Dank


Grazie


Gracias

FLUIDIZED BED SPRAY GRANULATION:

Equipment and Processing Considerations

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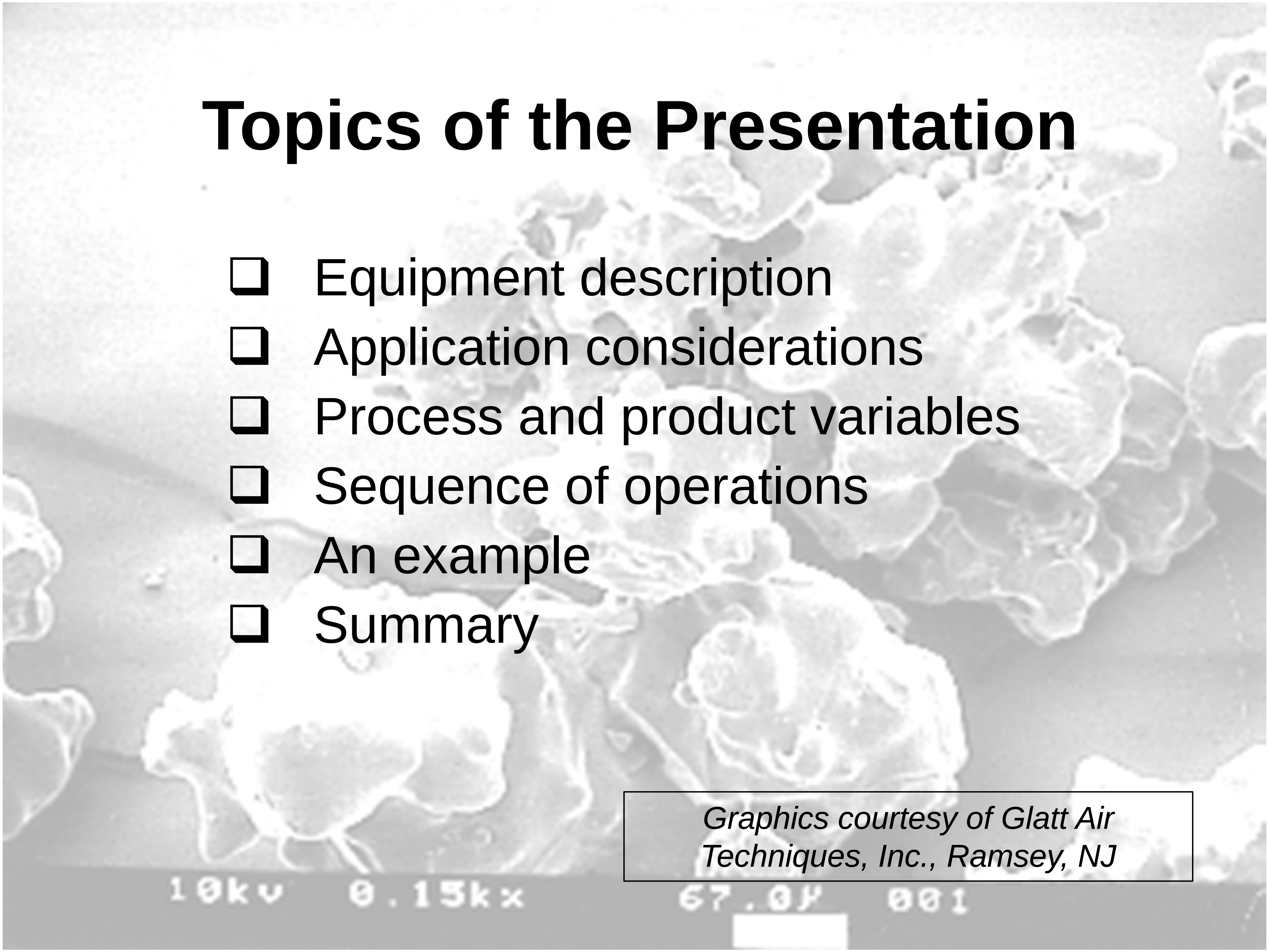
OWI-Consulting Inc
Onsite With Insight

Topics of the Presentation



- ☐ Equipment description
- ☐ Application considerations
- ☐ Process and product variables
- ☐ Sequence of operations
- ☐ An example
- ☐ Summary

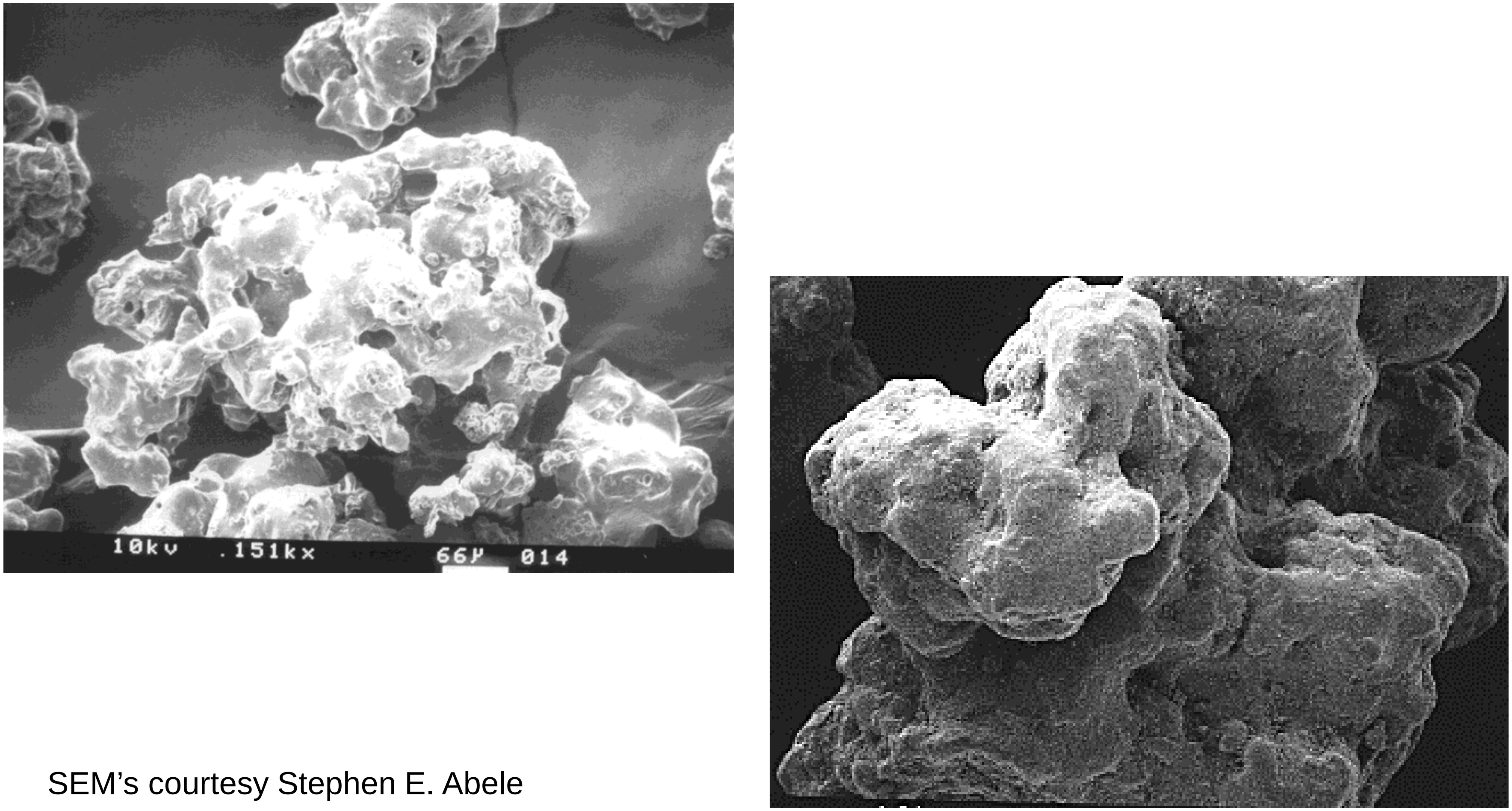
Graphics courtesy of Glatt Air Techniques, Inc., Ramsey, NJ

Why consider fluid bed spray granulation?

Attributes of Fluid Bed Spray Granulation

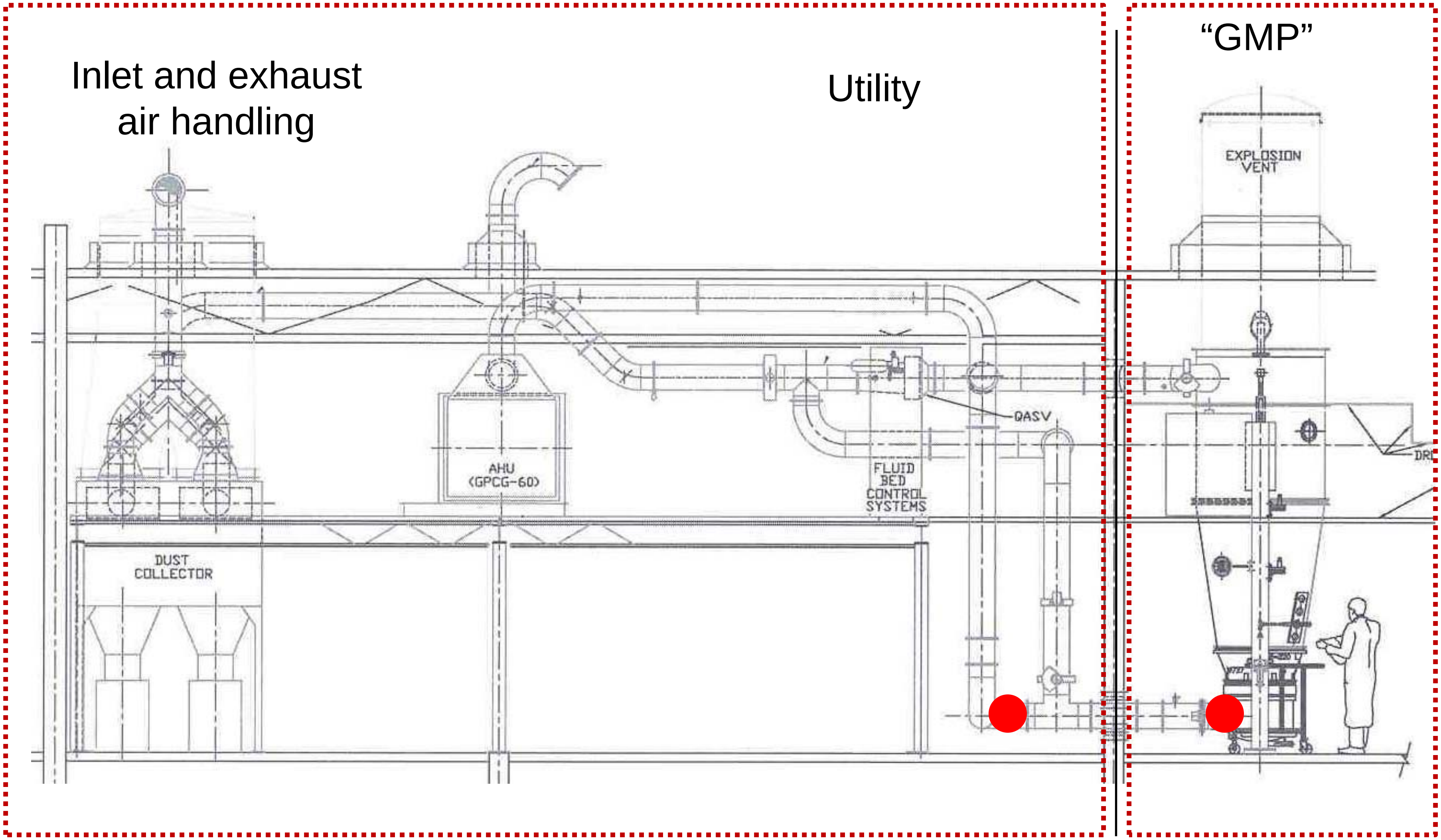
1. High rates of heat and mass transfer
   A. Quantity of liquid is immaterial
   B. Control of in-process moisture content
   C. Water or organic solvents are possible
2. Excellent mixing
   A. As a solid, added to the product container
   B. As a liquid, sprayed onto the substrate
3. Porosity of agglomerates yields high wettable surface area

Fluid bed agglomerates



SEM's courtesy Stephen E. Abele

A Typical Fluid Bed Spray Granulator Installation



Inlet and exhaust air handling

Utility

"GMP"

Inlet Air Handling (AHU) and interconnect ducting

1) Older machines:
   - Filtration, heating
2) More recent machines:
   - Filtration, dehumidification, heating, face and bypass
3) “State of the Art”
   - Filtration, dehumidification, humidification, heating, face and bypass. May also include desiccant for very low dew points

1) Older machines:
   - Direct connection
2) More recent machines:
   - Preconditioning bypass
3) “State of the Art”
   - Active bypass

The Machine Tower Components

Outlet filter housing

Expansion chamber

Spray nozzle wand

Product container

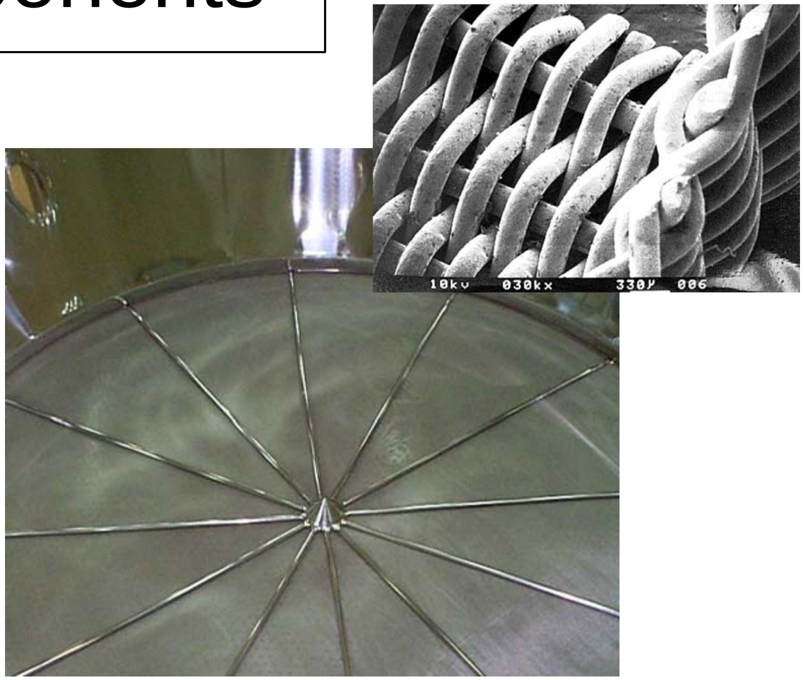
Inlet duct and lower plenum

The Machine Tower Components

Product container

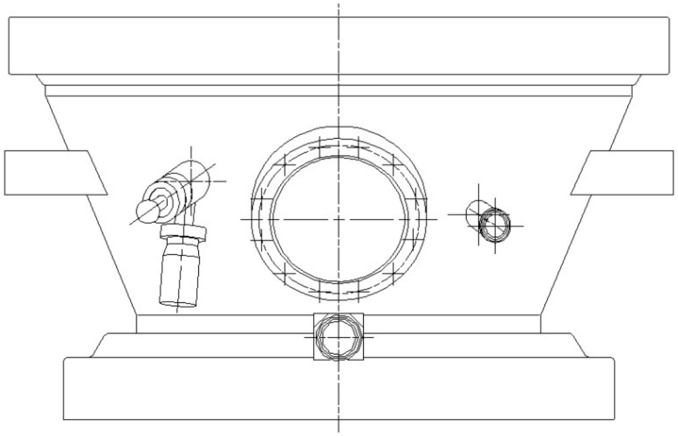
The product container may be comprised of several components

The distributor plate provides resistance to help distribute air flow across the base of the product container. It also supports the retention screen and product.



The screen retains the product, and must be strong. The rods hold the screen in place (against the strong suction of the fan).

Product Container Components



The Machine Tower Components

Expansion chamber

The spray nozzle wand is mounted in the expansion chamber, spraying downward. Make sure that the pump has the capability of pumping the binder solution at the rate at which it is needed.

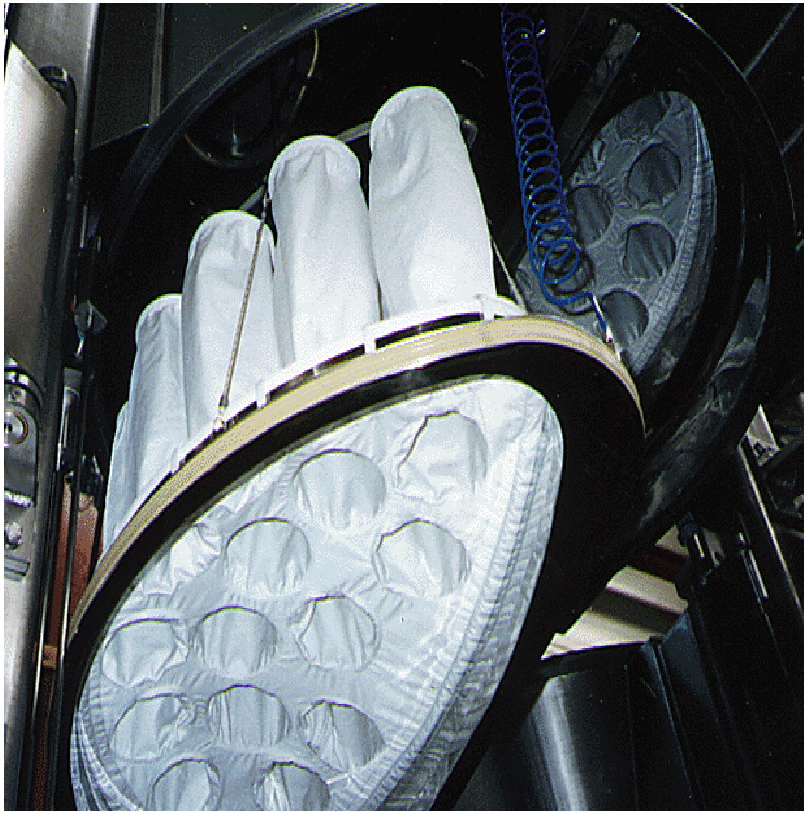
The Machine Tower Components

Outlet filter housing

The Machine Tower Components

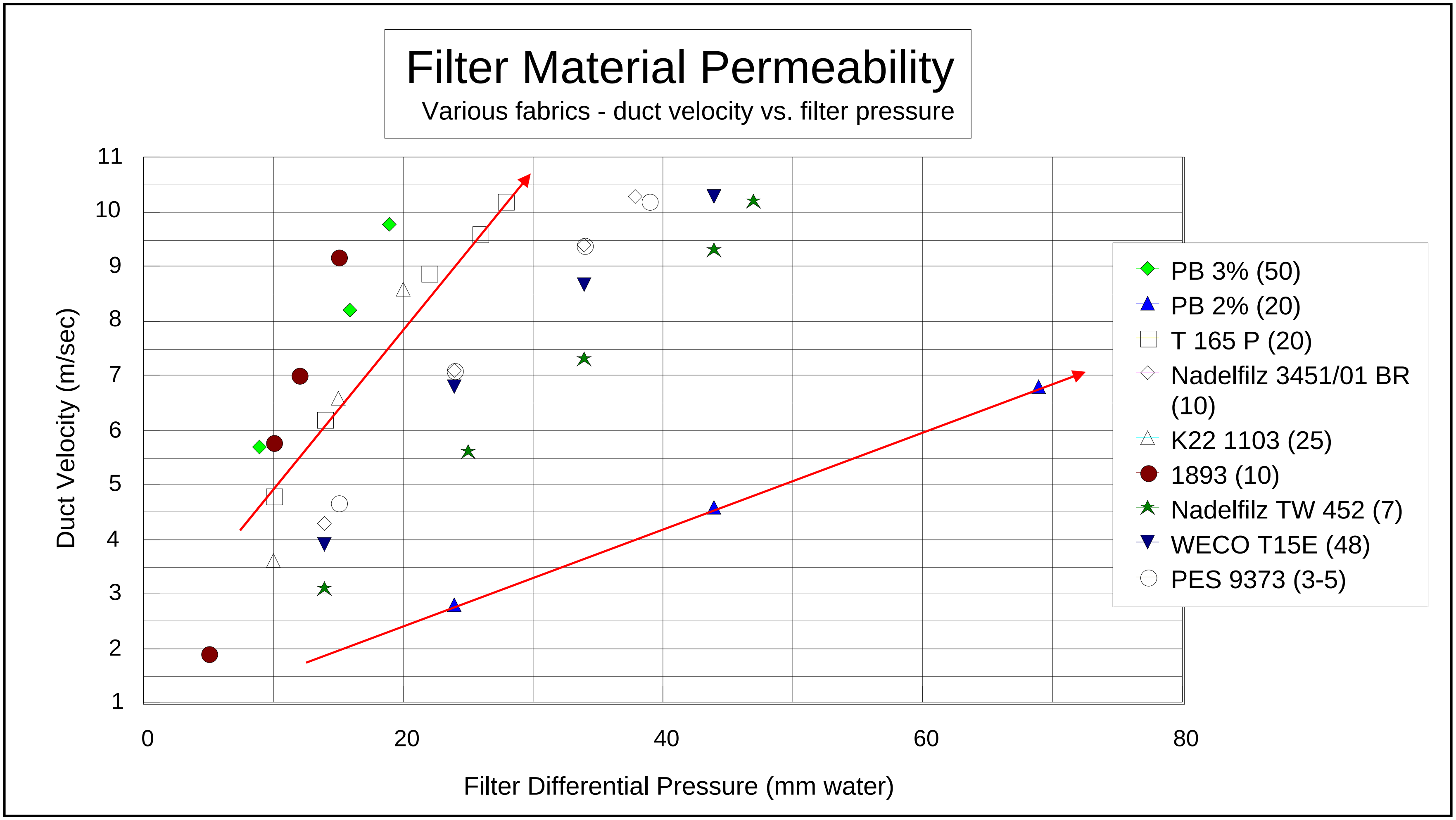
The vast majority of fluid bed systems incorporate the use of fabric filters (as shown). The two dominant considerations are:

A. Porosity (the size of the openings in the fabric)
B. Permeability (the number of openings per unit area



However: there is NO standardized test for determining this behavior, and periodically, fabrics are discontinued.

Filter Fabric - Performance

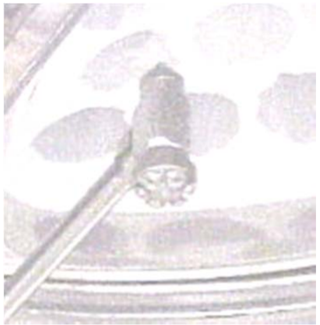


Any questions related to the equipment?

Fluidized Bed Spray Granulation:

The Unit Operations

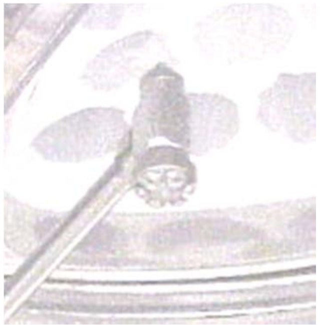
What are the Basic Principles of Operation?



1. Product is loaded into the product container (order of addition is generally not important)
2. Heated/treated air is drawn through the product container and fluidization begins
3. The materials fluidize for 1-2 minutes to begin mixing (it is NOT mixed completely)
4. Spraying commences with simultaneous accumulation of moisture and evaporation of water
5. At the completion of spraying, drying continues
6. When drying is complete, the granulation is discharged

Product – What Goes Where?

1. Product is loaded into the product container (order of addition is generally not important)



Granulation components:

- API (if >1% of the mix)
- Bulking agents
- Disintegrants

(Product container)

Spray components:

- API (if <1% of the mix)
- Binder
- Water

(Liquid vessel)

Blending components:

- Lubricants
- Extra-granular excipients

(Blended externally)

What are the Basic Principles of Operation?

1. Product is loaded into the product container (order of addition is generally not important)
2. Heated/treated air is drawn through the product container and fluidization begins
3. The materials fluidize for 1-2 minutes to begin mixing (it is NOT mixed completely)
4. Spraying commences with simultaneous accumulation of moisture and evaporation of water
5. At the completion of spraying, drying continues
6. When drying is complete, the granulation is discharged

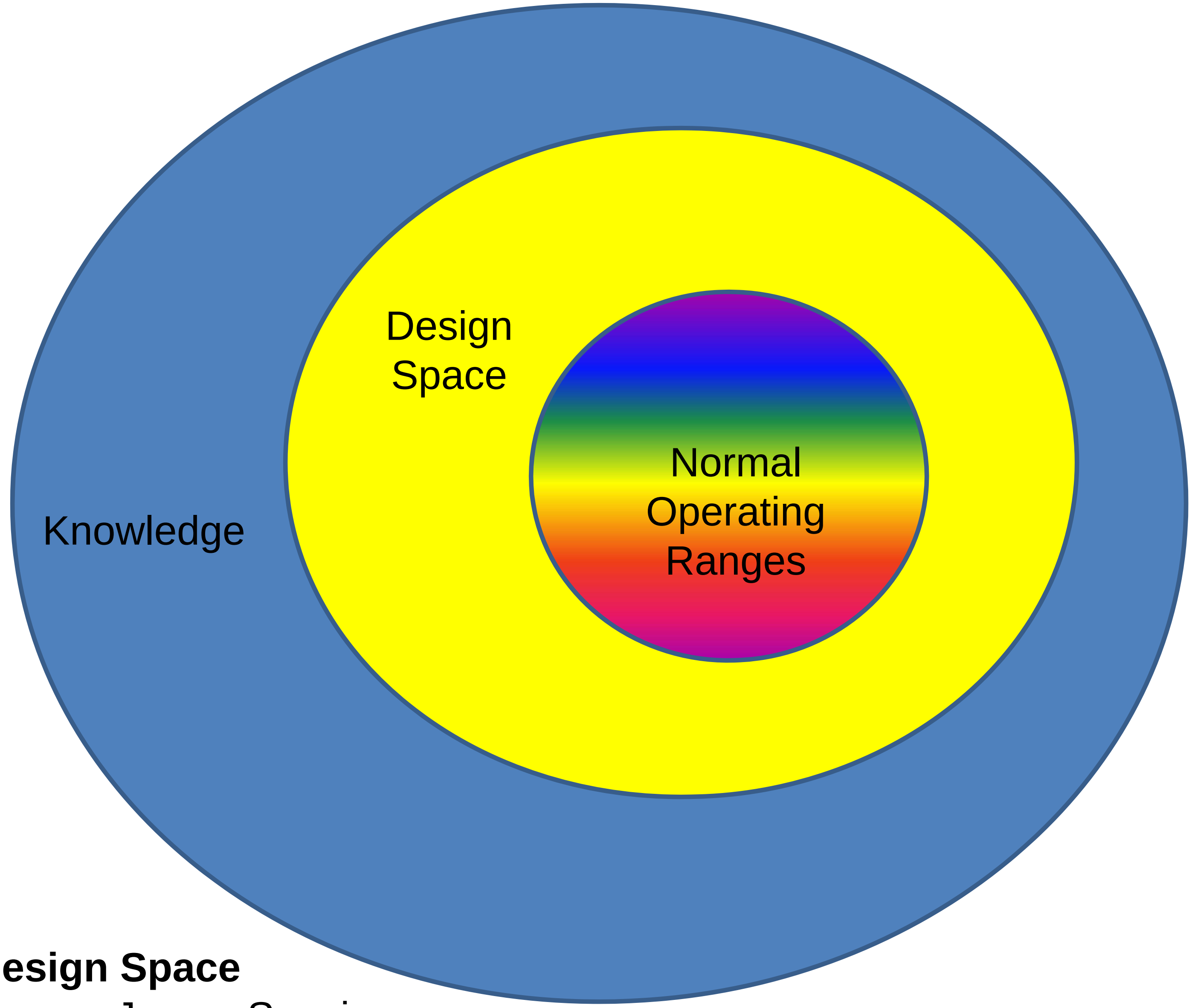
Process Parameters

Process Air	Spraying	Other
Ambient Air Dew Point	Spray rate	Bed Depth
Dehumidifier Dew Point	Atomizing Air Pressure	Batch Size
Pre-heater Temperature	Atomizing Air Volume	Outlet Filter Media
Process Air Dew Point Temperature	Liquid Line Pressure	Bowl Screen Media
Bypass Air Temperature	Liquid Viscosity	Filter Shake Interval
Process or Inlet Air Temperature	Nozzle Port Size	Filter Shake Time
Total Air Volume	Air Cap Position	Atomizing Air Dew Point
Process Air Volume	Nozzle height	dP Product
		dP Outlet Filter

Of This List, Which are the “Critical Process Parameters”?

Definition:

Critical Process Parameters (CPP) have a direct and significant influence on Critical Quality Attributes (CQA) and must therefore operate within a defined or limited operating range.



PQLI Design Space
John Lepore, James Spavins
J. Pharm. Innov. (2008) 3:79-87

Critical Process Parameters

Note: some parameters are defined as CPP only during certain process steps – a process is comprised of heating (machine tower/ substrate), spraying, drying and cooling steps.

With this as background, which of the listed items ARE likely to be CPP? What are the direct impacts on product attributes?

Process Parameters

Process Air	Comments	Steps: H, S, D, C
Ambient Air Dew Point	It depends if the machine has dew point control	If yes: S, D, C
Dehumidifier Dew Point	No – it can vary independently of process air dew point	
Pre-heater Temperature	No – it operates independently of process air temperature	
Process Air Dew Point Temperature	Yes, unless the process air temperature is very high (>90 C)	H,S, D, C
Bypass Air Temperature	No – controlled by process air temperature PID in pre-conditioning	
Process or Inlet Air Temperature	Yes	S, D
Total Air Volume	No – accommodates process air volume	
Process Air Volume	Yes	H, S, D, C

Process Parameters

Spraying	Comments	Steps: H, S, D, C
Spray rate	Always a CPP – impacts granule structure	S
Atomizing Air Pressure	Almost always – impacts granule size via droplet size	S
Atomizing Air Volume	Linked to AAP – the REAL factor in droplet size control (sensor needed)	S
Liquid Line Pressure	No – typically just an indicator of nozzle performance (clogging)	
Liquid Viscosity	Yes – for viscose binders; no for low viscosity binders or water alone	If yes: S
Nozzle Port Size	No – accommodates liquid delivery – generally does not impact droplet size	
Air Cap Position	Machine parameter. Must be specified and documented	
Nozzle height	Machine parameter. Must be specified and documented.	

Product Temperature (CPP)

Condition	Comments	Impact to moisture profile
No dew point control	Seasonal variation in ambient dew point will cause it to rise or fall, impacting drying rate	Up or down
Process air dew point - dehumidifier only	Minimizes seasonal variation. Batches will run dryer in winter (low dew points)	Down
Process air dew point – set point control	Consistent year 'round. Best system.	None
Process air volume	At saturation there is NO impact on product temperature. Below saturation the PT will change depending on adjustment to air flow. Be careful with ramping!	Up or down
Process air temperature	Direct impact on PT. Very high temperatures mitigate seasonal dew point variation; low temperatures are strongly impacted. Beware of ramping – if it is necessary, small increments are recommended to avoid condensation impacts.	Up or down

Although product temperature is a CPP, DIRECT control is NOT recommended!

Operating Ranges

- Sensor reading range
- Calibrated range
- OQ range from installation (empty machine)
- Operating range derived experimentally

An example: Process Air Temperature

- 0 – 100°C
- 5, 50, 95°C
- 35 - 90°C
- Operating range derived experimentally

Operating Ranges

Process Air	Operating Range	Comments
Ambient Air Dew Point		
Dehumidifier Dew Point	± 2°C	Final dew point control depends to an extent on narrow upstream control.
Pre-heater Temperature	±3°C	
Process Air Dew Point Temperature	± 1°C	Water in air is exponential. If it is a CPP, it must operate in a narrow range.
Bypass Air Temperature	±2°C	Process air temperature is a CPP for all products and should be controlled in a narrow range.
Process or Inlet Air Temperature	±2°C	
Total Air Volume	± 5% of full scale	Tuning for these parameters is critical. Avoid 'competing controllers' and over-correcting. Fluidization impacts behavior.
Process Air Volume		

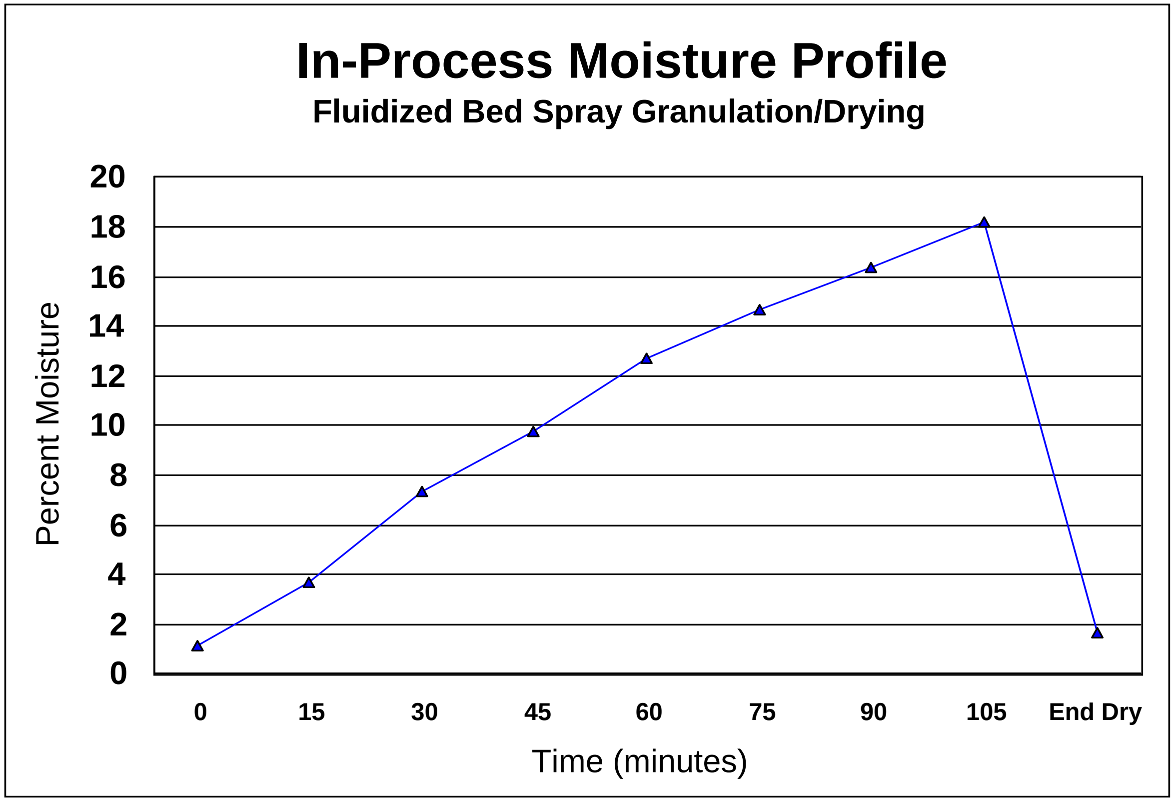
Operating Ranges

Spraying	Operating Range	Comments
Spray rate	± 20 g/min	Always a CPP, erratic variability can indicate poor nozzle performance.
Atomizing Air Pressure	± 0.1 bar	Must operate in a stable, narrow range.
Atomizing Air Volume	± 5 cfm/ nozzle	Reflects reproducibility of nozzle set-up.
Liquid Line Pressure		
Liquid Viscosity		
Nozzle Port Size		Machine parameter
Air Cap Position		Machine parameter
Nozzle height		Machine parameter

How do the parameters work together?

1. Droplet size
    a. Atomizing air pressure
    b. Spray rate
    c. Viscosity
2. Evaporation rate
    a. Process air volume
    b. Process air temperature
    c. Process air dew point temperature

A Useful Dependent Variable…

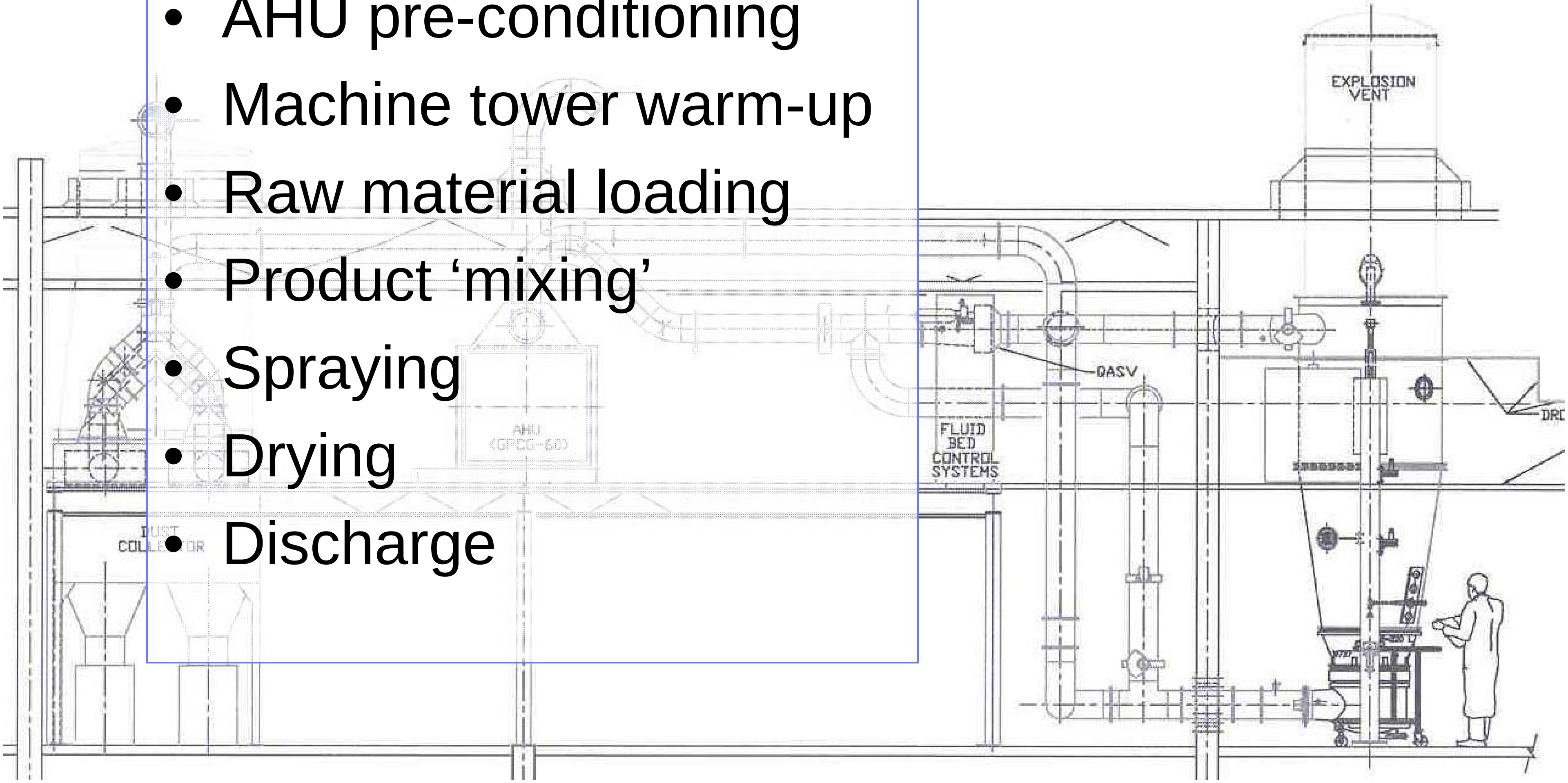


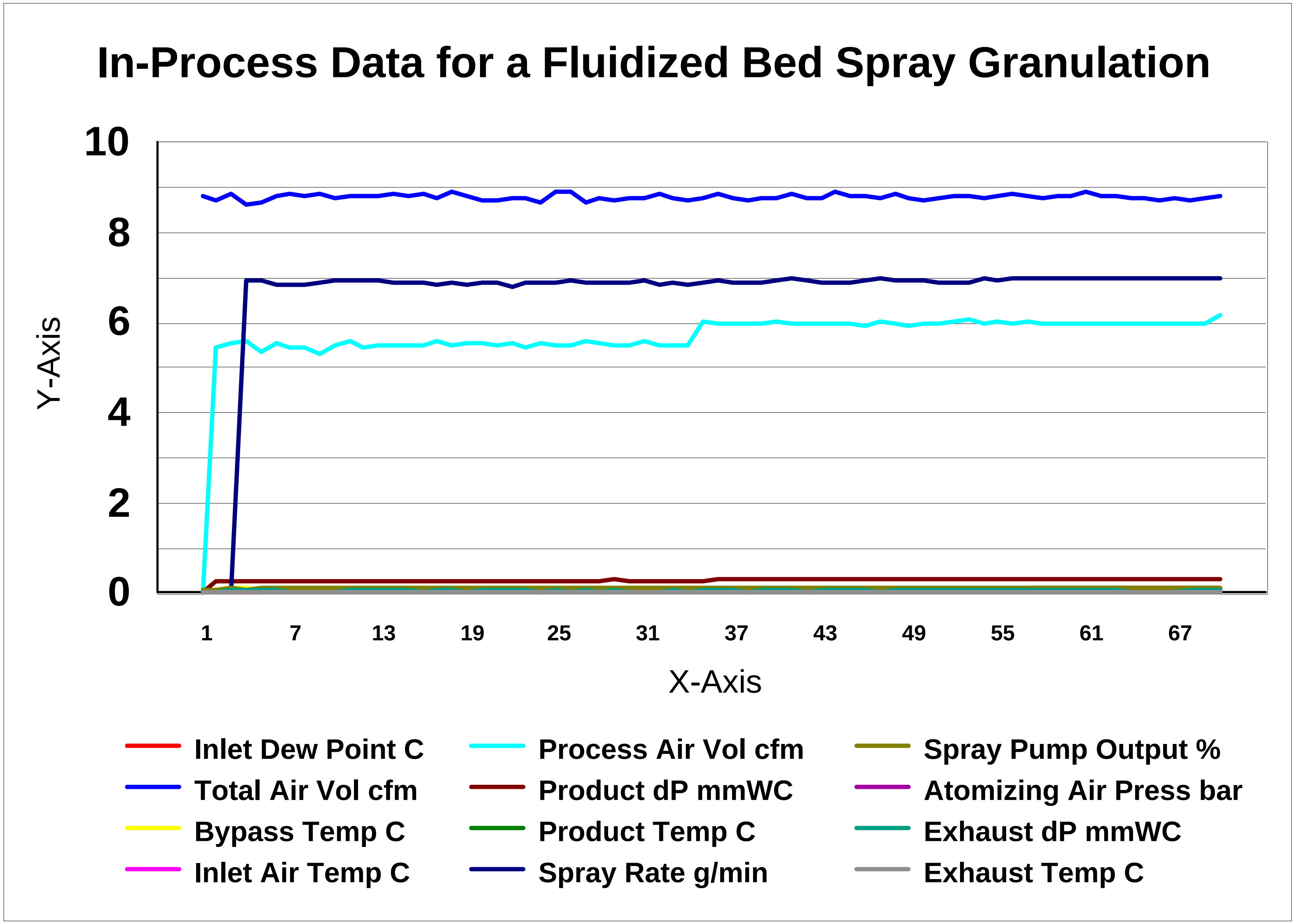
An in-process moisture profile may be followed and confirms the accuracy of several of the process variables

Process Variables as Observed During Manufacturing

Process Steps – a Recipe

- AHU pre-conditioning
- Machine tower warm-up
- Raw material loading
- Product ‘mixing’
- Spraying
- Drying
- Discharge





Data overview for the process variables. “Grouping” by type is more revealing…

OWI-Consulting inc
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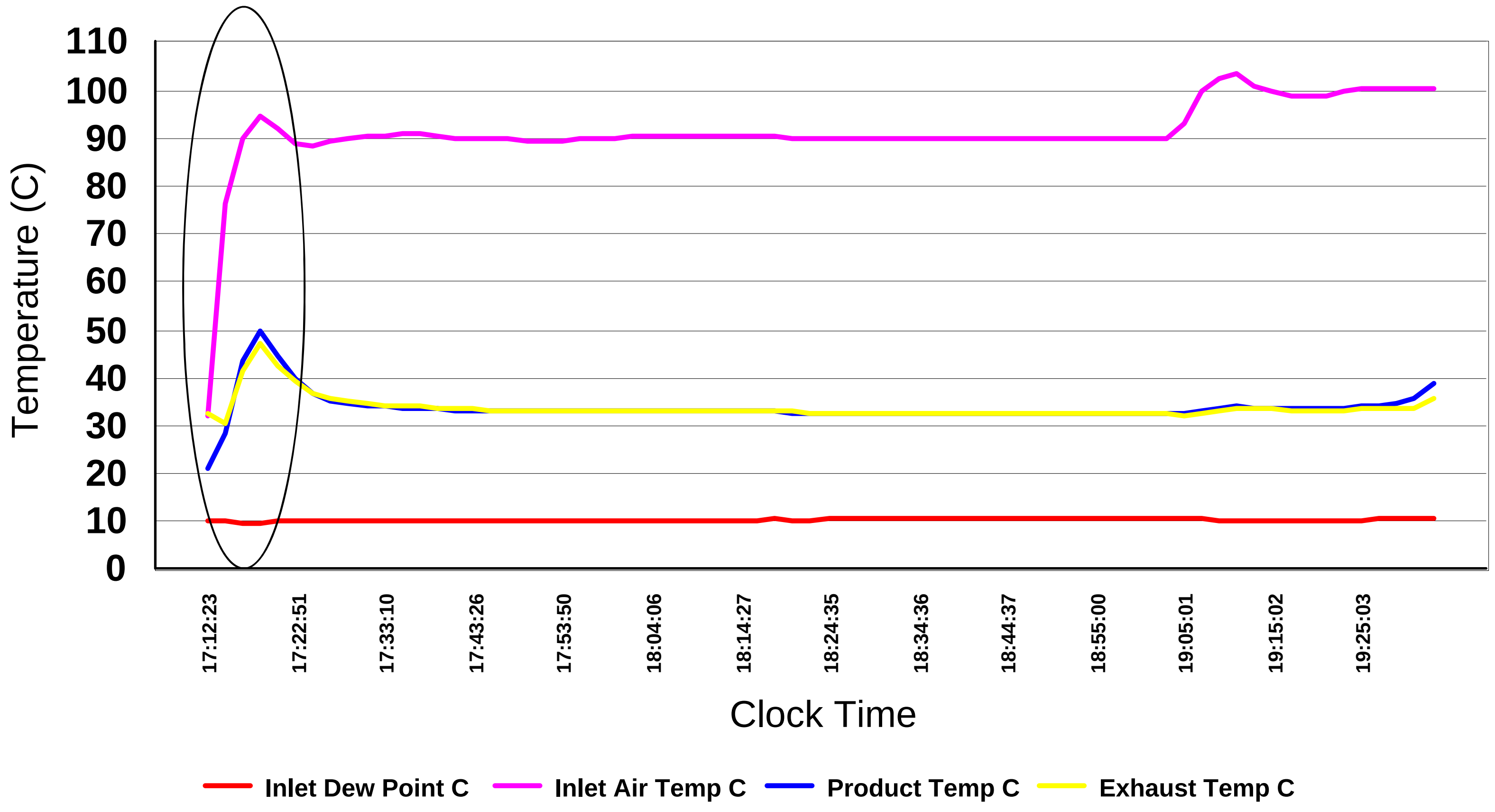
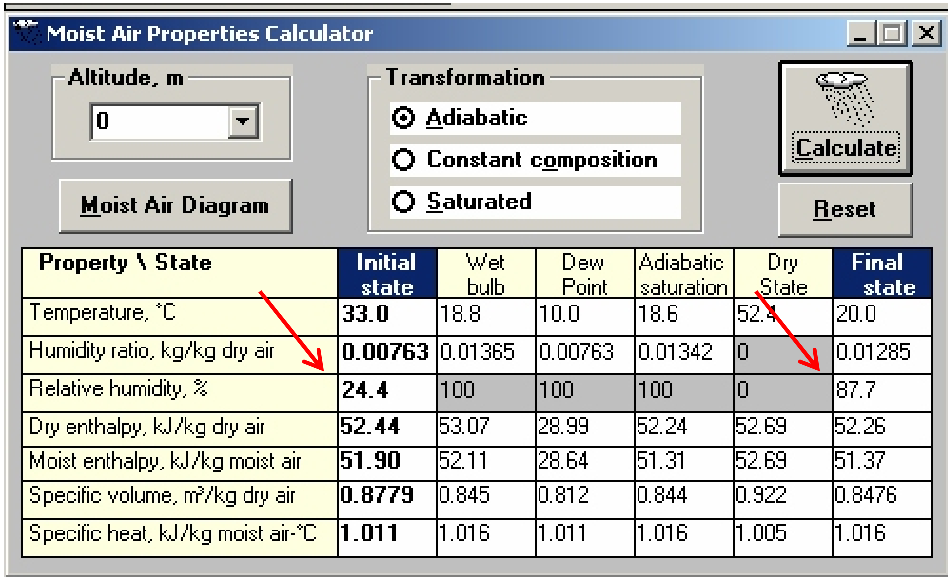
Fluidized Bed Spray Granulation

Process data - temperatures



Pre-mix: The inlet temperature approaches its set point, product and exhaust temperatures rise. Is it really mixing, or is there something else to think about?

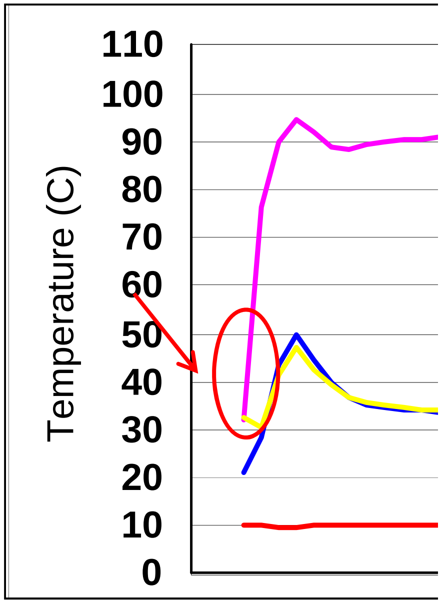


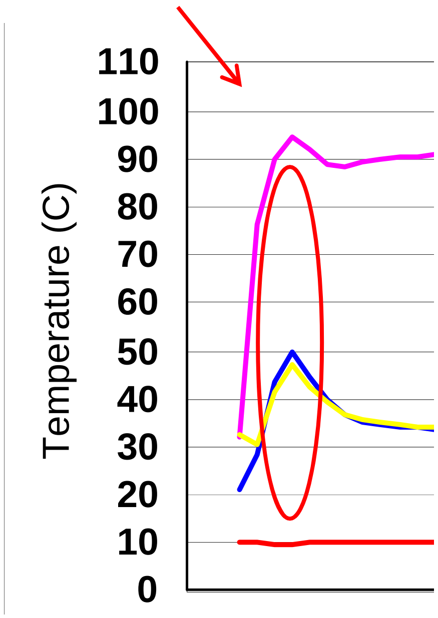
Altitude, m: 0

Transformation
● Adiabatic
○ Constant composition
○ Saturated

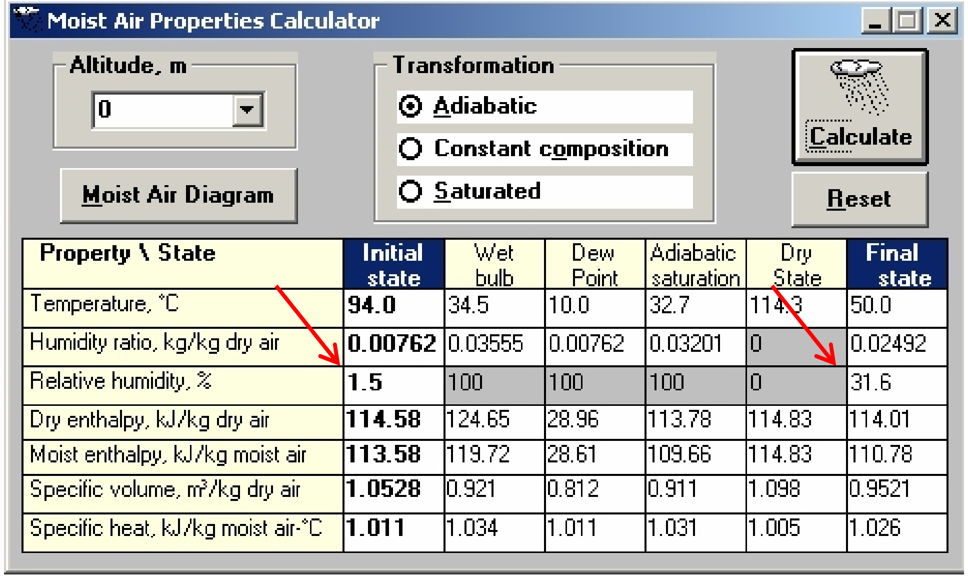
Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**33.0**	18.8	10.0	18.6	52.4	20.0
Humidity ratio, kg/kg dry air	**0.00763**	0.01365	0.00763	0.01342	0	0.01285
Relative humidity, %	**24.4**	100	100	100	0	87.7
Dry enthalpy, kJ/kg dry air	**52.44**	53.07	28.99	52.24	52.69	52.26
Moist enthalpy, kJ/kg moist air	**51.90**	52.11	28.64	51.31	52.69	51.37
Specific volume, m³/kg dry air	**0.8779**	0.845	0.812	0.844	0.922	0.8476
Specific heat, kJ/kg moist air·°C	**1.011**	1.016	1.011	1.016	1.005	1.016

The beginning of mixing…





Only 5 minutes later, at the start of spraying…



Altitude, m: 0

Transformation
● Adiabatic
○ Constant composition
○ Saturated

Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**94.0**	34.5	10.0	32.7	114.3	50.0
Humidity ratio, kg/kg dry air	**0.00762**	0.03555	0.00762	0.03201	0	0.02492
Relative humidity, %	**1.5**	100	100	100	0	31.6
Dry enthalpy, kJ/kg dry air	**114.58**	124.65	28.96	113.78	114.83	114.01
Moist enthalpy, kJ/kg moist air	**113.58**	119.72	28.61	109.66	114.83	110.78
Specific volume, m³/kg dry air	**1.0528**	0.921	0.812	0.911	1.098	0.9521
Specific heat, kJ/kg moist air·°C	**1.011**	1.034	1.011	1.031	1.005	1.026

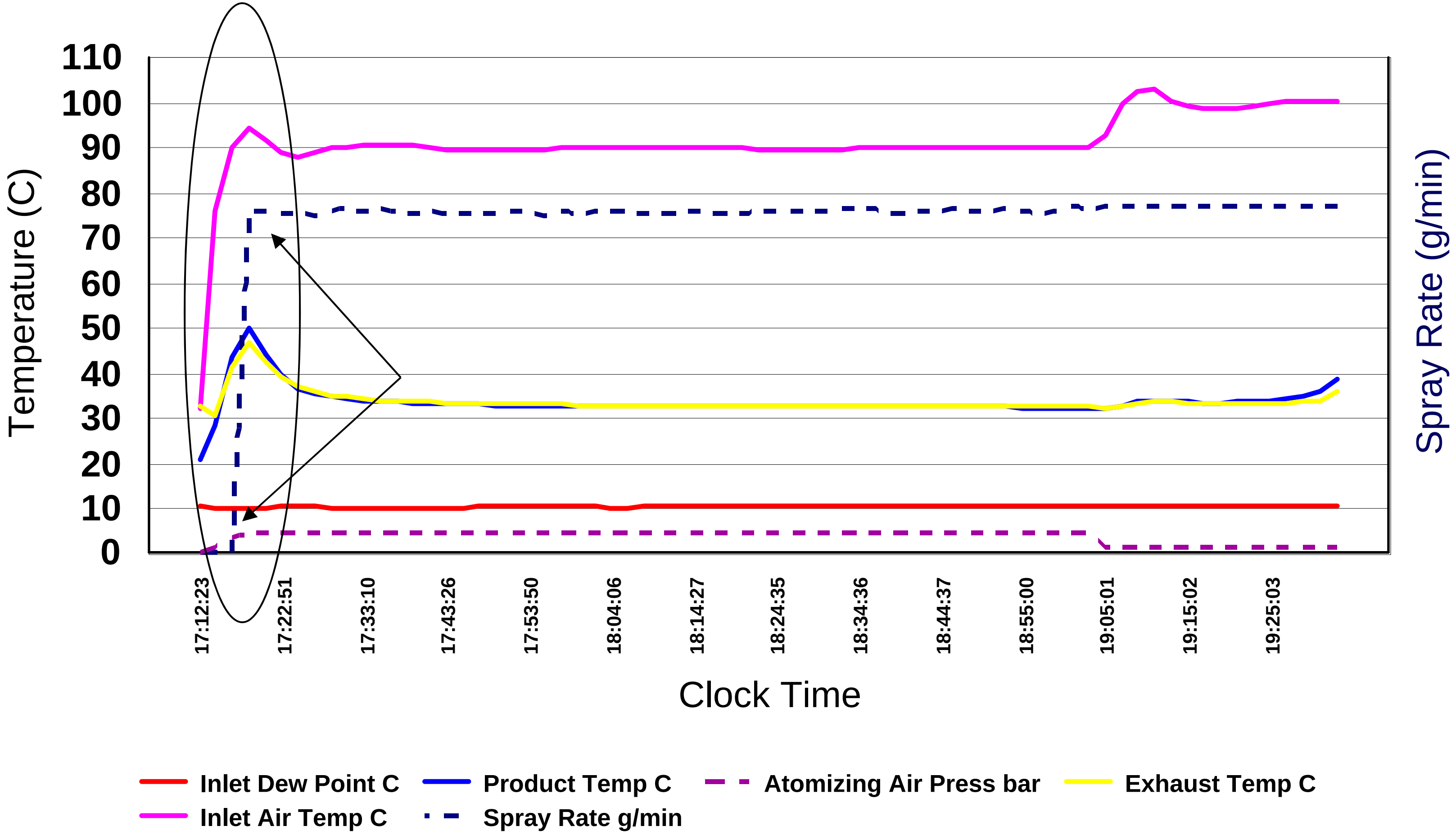
After the brief pre-mix…

Spraying is initiated at a controlled rate

- Moisture builds slowly in the bed
- Treated process air is used to evaporate some of the moisture as it is being applied
- Evaporation raises the relative humidity in the processor, helping to dispel electrostatic charge
- Droplets help to produce and build granules
- Granules are held together primarily by liquid bridges

Fluidized Bed Spray Granulation

Process data - temperatures, spray rate, atomizing air



Spraying - The pump is enabled and atomizing air increases from purge pressure to the spraying set point.

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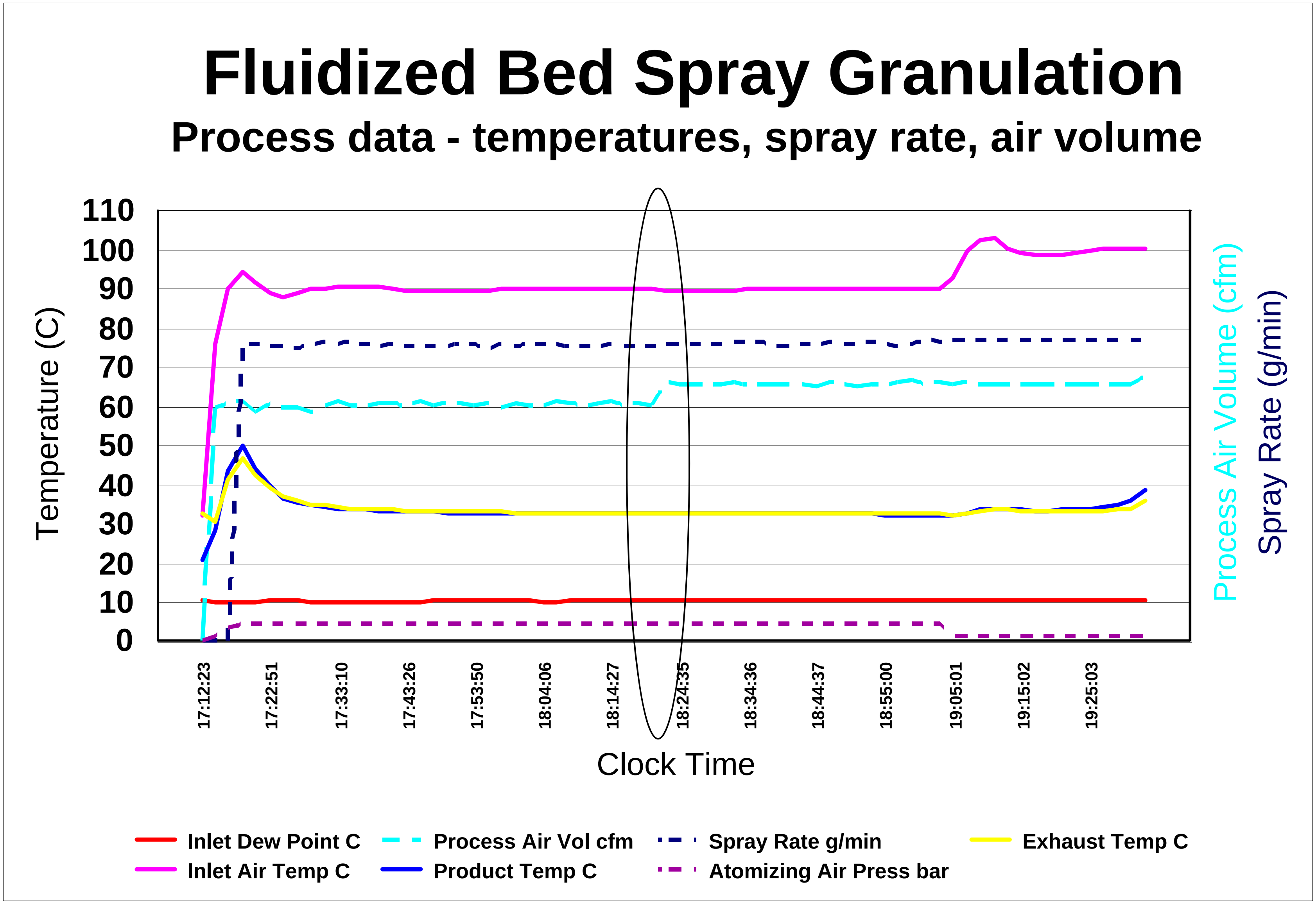
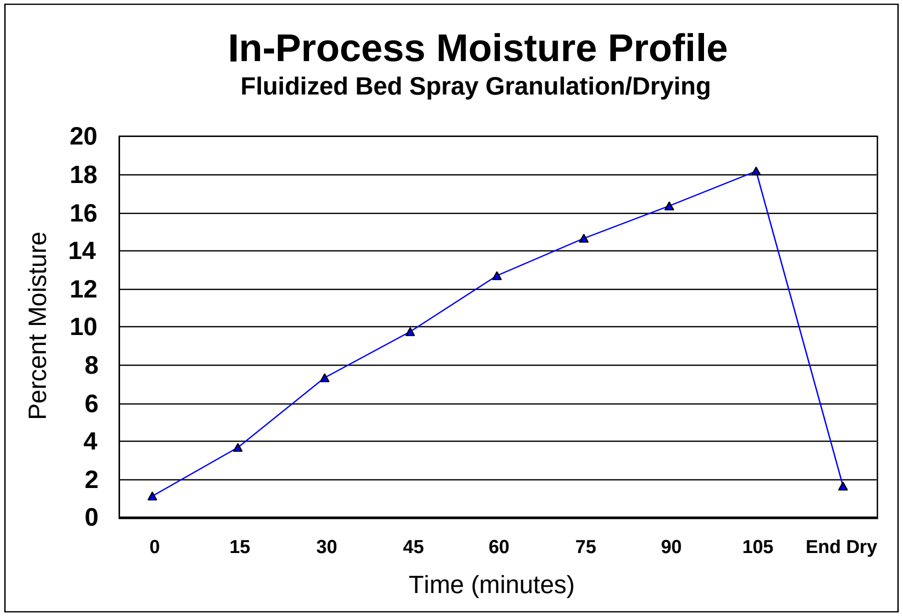
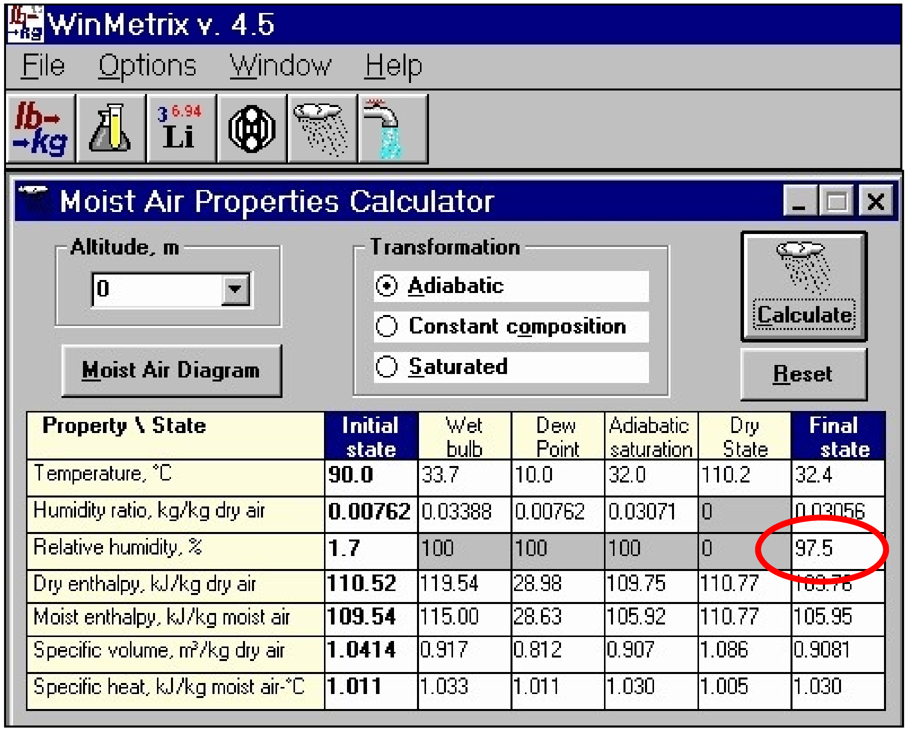


Later, air volume is increased to accommodate the increasing batch weight (to maintain a reasonable degree of fluidization).



Moisture builds in the bed as the water addition rate exceeds the drying rate. Properties of the granulation may rely heavily on the moisture profile, and it should be reproduced.

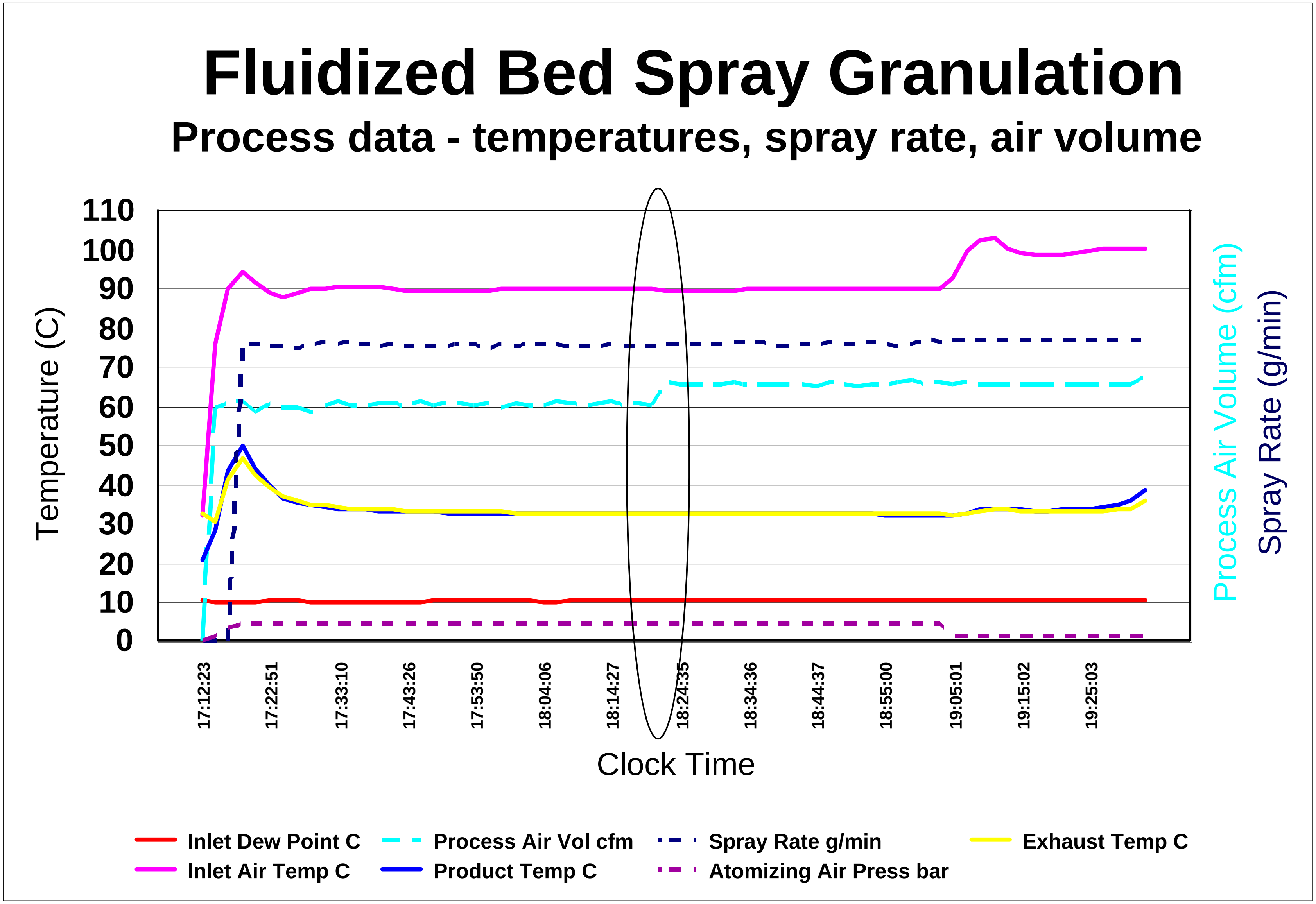
At steady state, the air leaving the machine tower is at or near saturation.



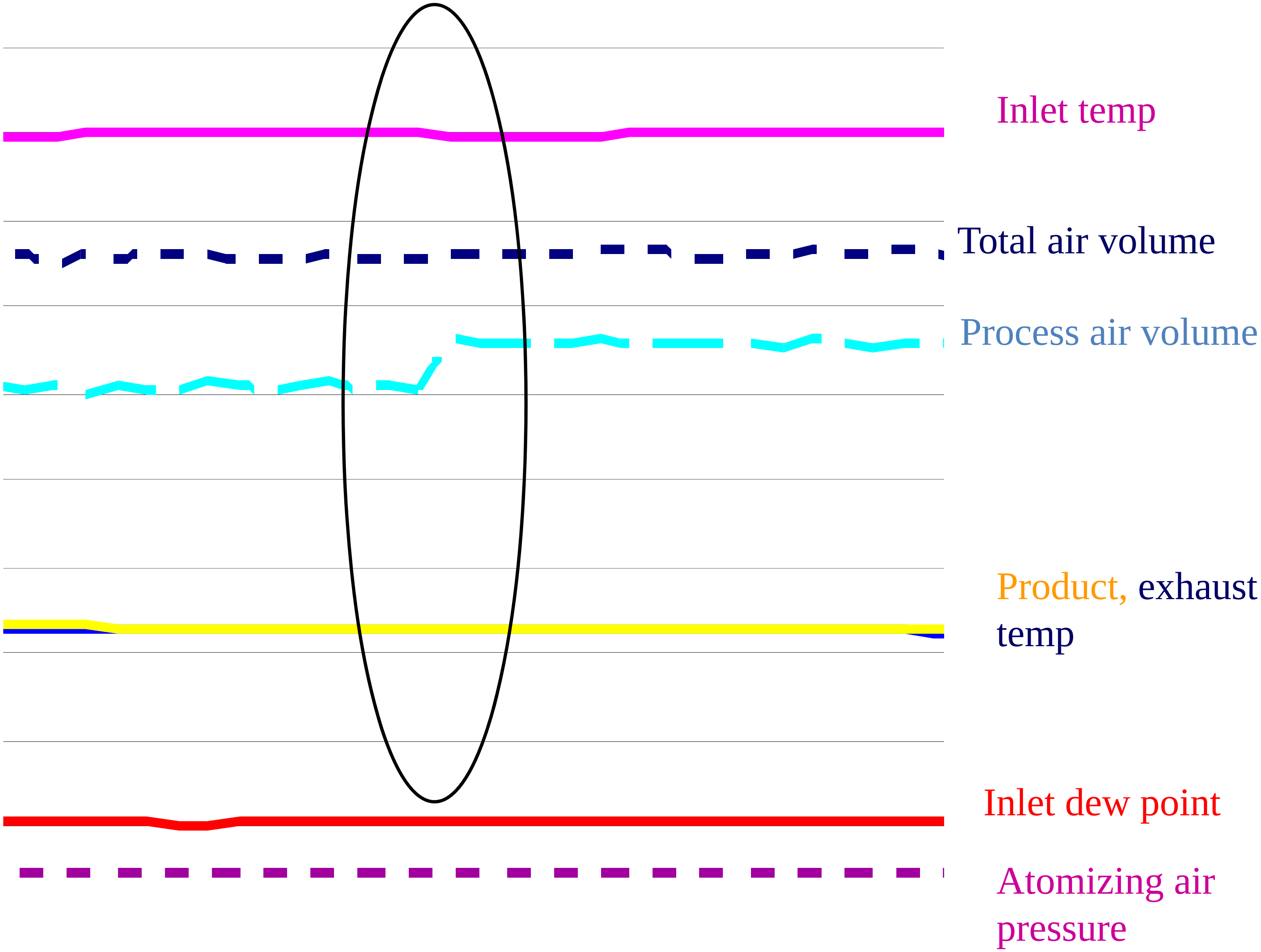
Altitude, m: 0

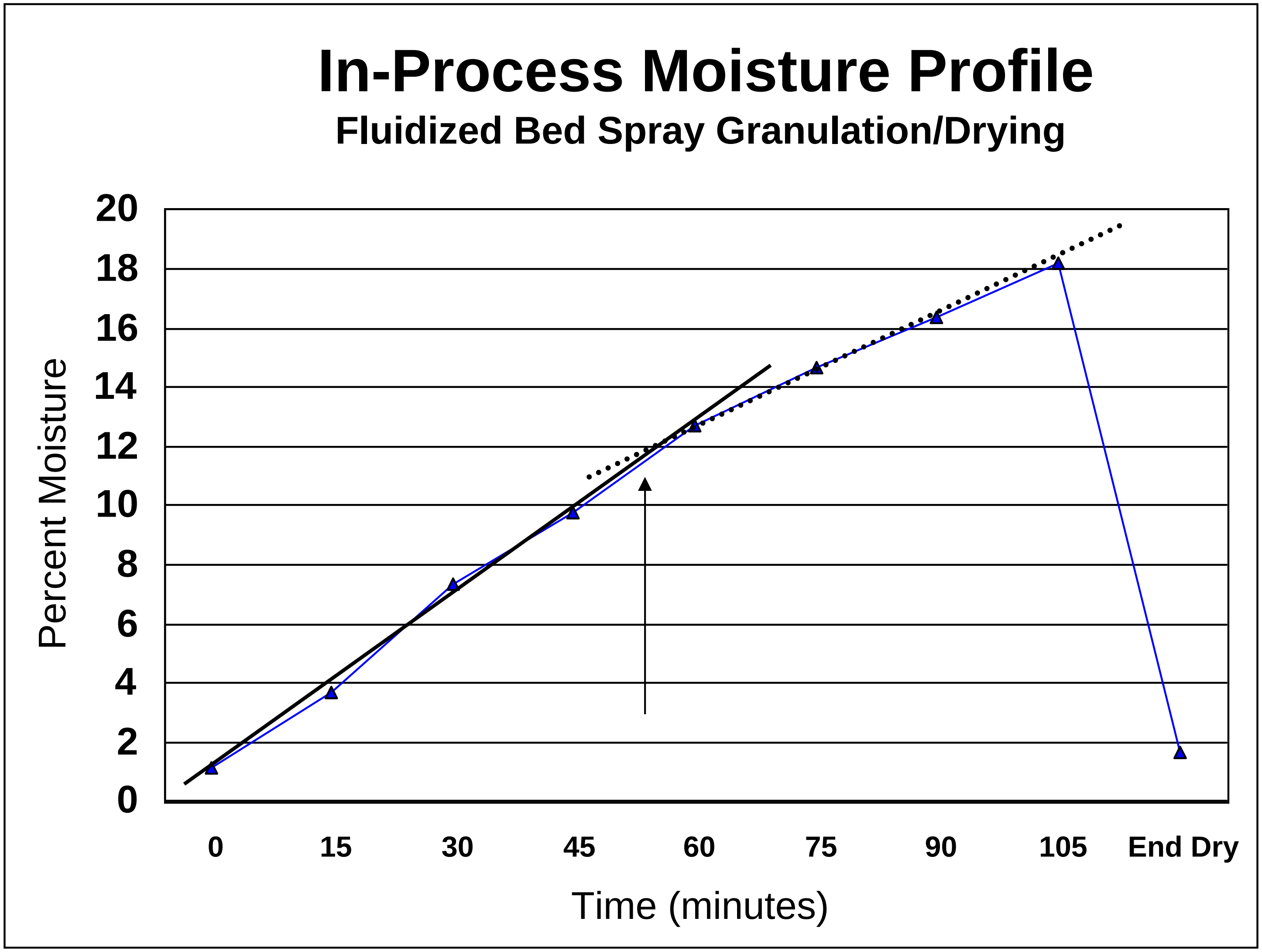
Transformation:
● Adiabatic
○ Constant composition
○ Saturated

Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**90.0**	33.7	10.0	32.0	110.2	32.4
Humidity ratio, kg/kg dry air	**0.00762**	0.03388	0.00762	0.03071	0	0.03056
Relative humidity, %	**1.7**	100	100	100	0	97.5
Dry enthalpy, kJ/kg dry air	**110.52**	119.54	28.98	109.75	110.77	109.76
Moist enthalpy, kJ/kg moist air	**109.54**	115.00	28.63	105.92	110.77	105.95
Specific volume, m³/kg dry air	**1.0414**	0.917	0.812	0.907	1.086	0.9081
Specific heat, kJ/kg moist air-°C	**1.011**	1.033	1.011	1.030	1.005	1.030



What impact does the higher air volume have on the product/exhaust temperatures? Is there any impact at all?


Inlet temp
Total air volume
Process air volume
Product, exhaust temp
Inlet dew point
Atomizing air pressure



In-Process Moisture Profile

Fluidized Bed Spray Granulation/Drying

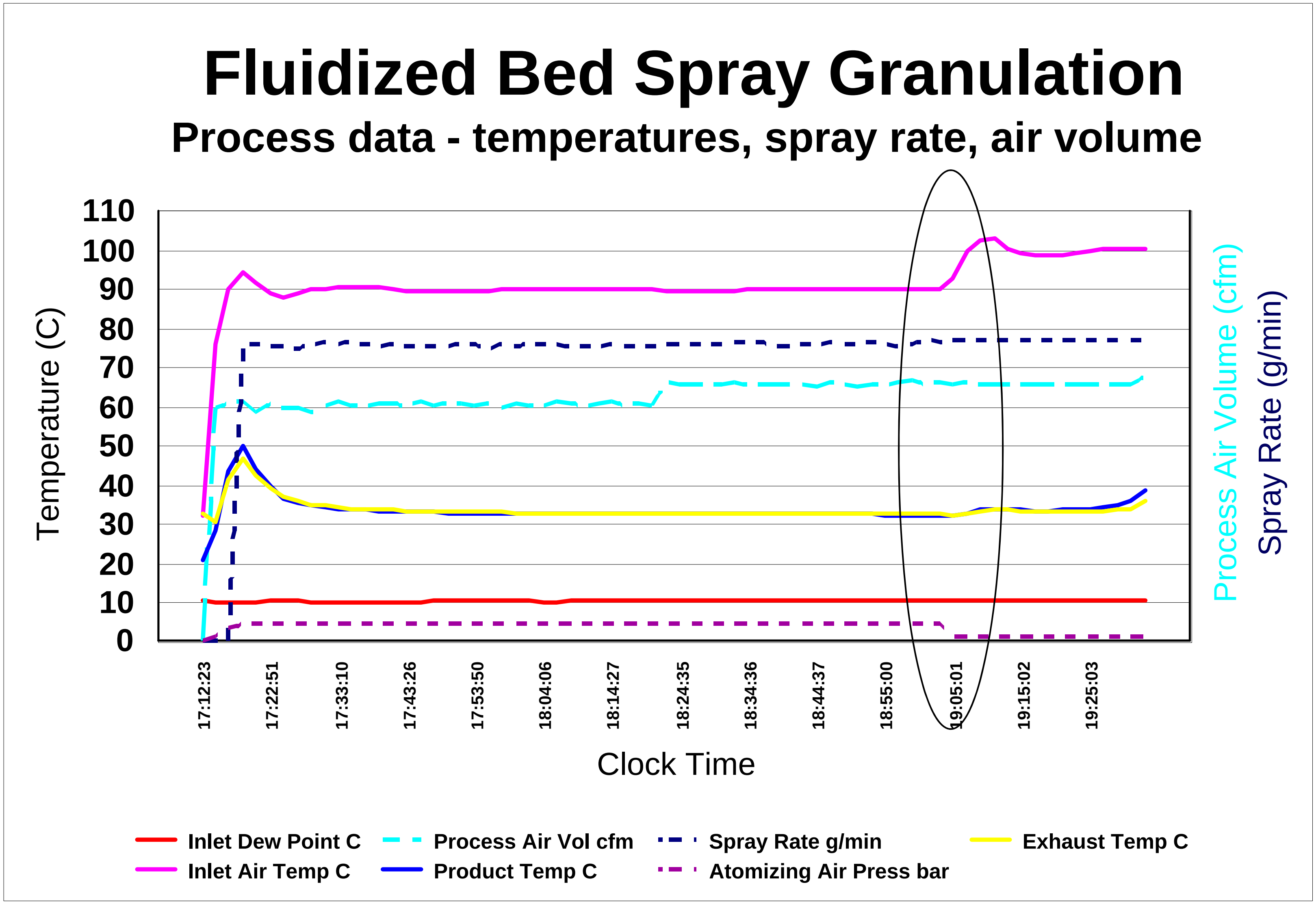
The moisture accumulation rate changes …

How Does the Process Work?

When the liquid is gone, drying continues

- Excess liquid in the batch is evaporated
- Temperature and air volume deliver the energy needed to dry the product (the inlet temperature may change)
- Drying time depends on how much moisture needs to be removed and the characteristics of the product
- As product temperature rises, the end is near

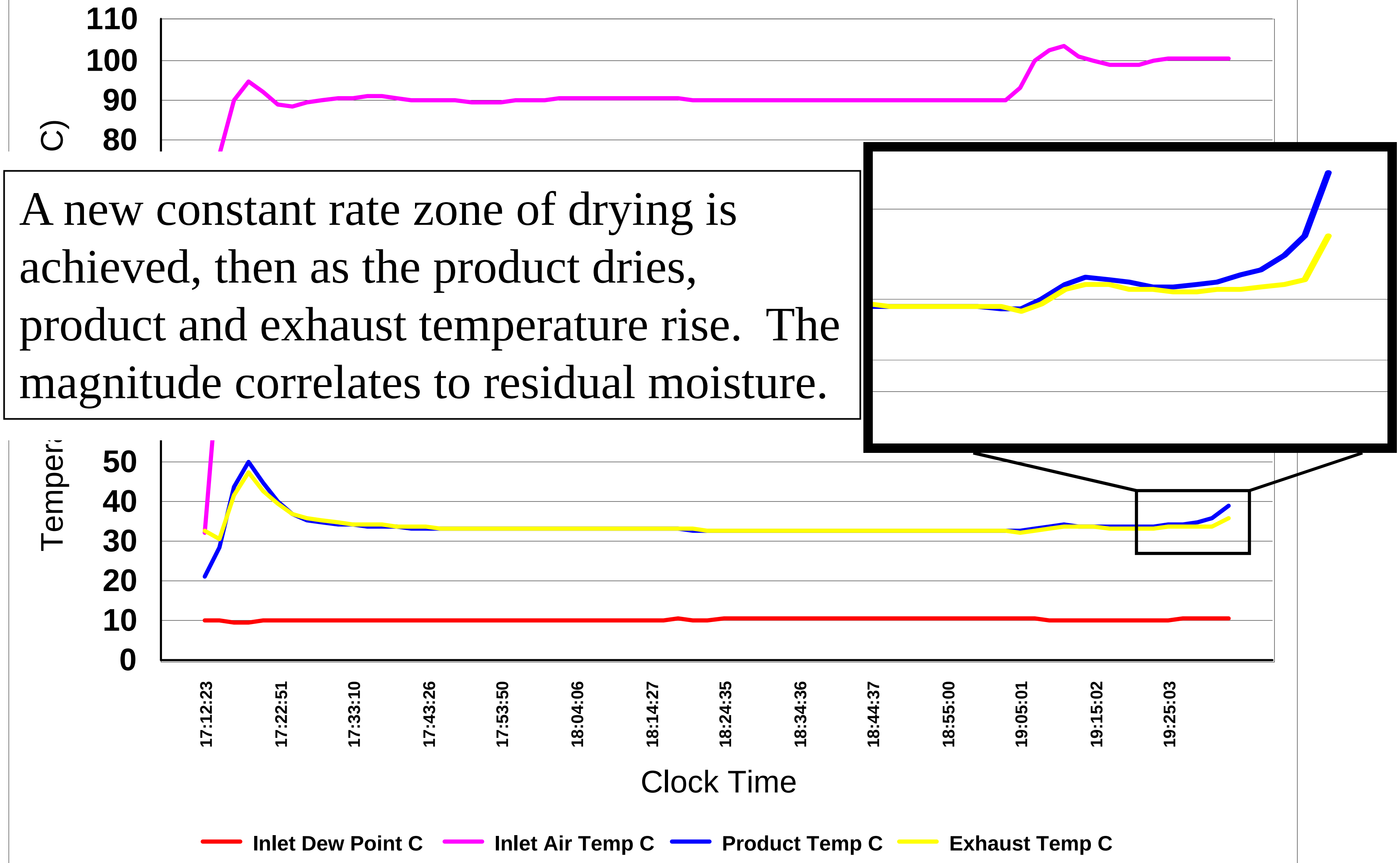
Sample for moisture, stop the process



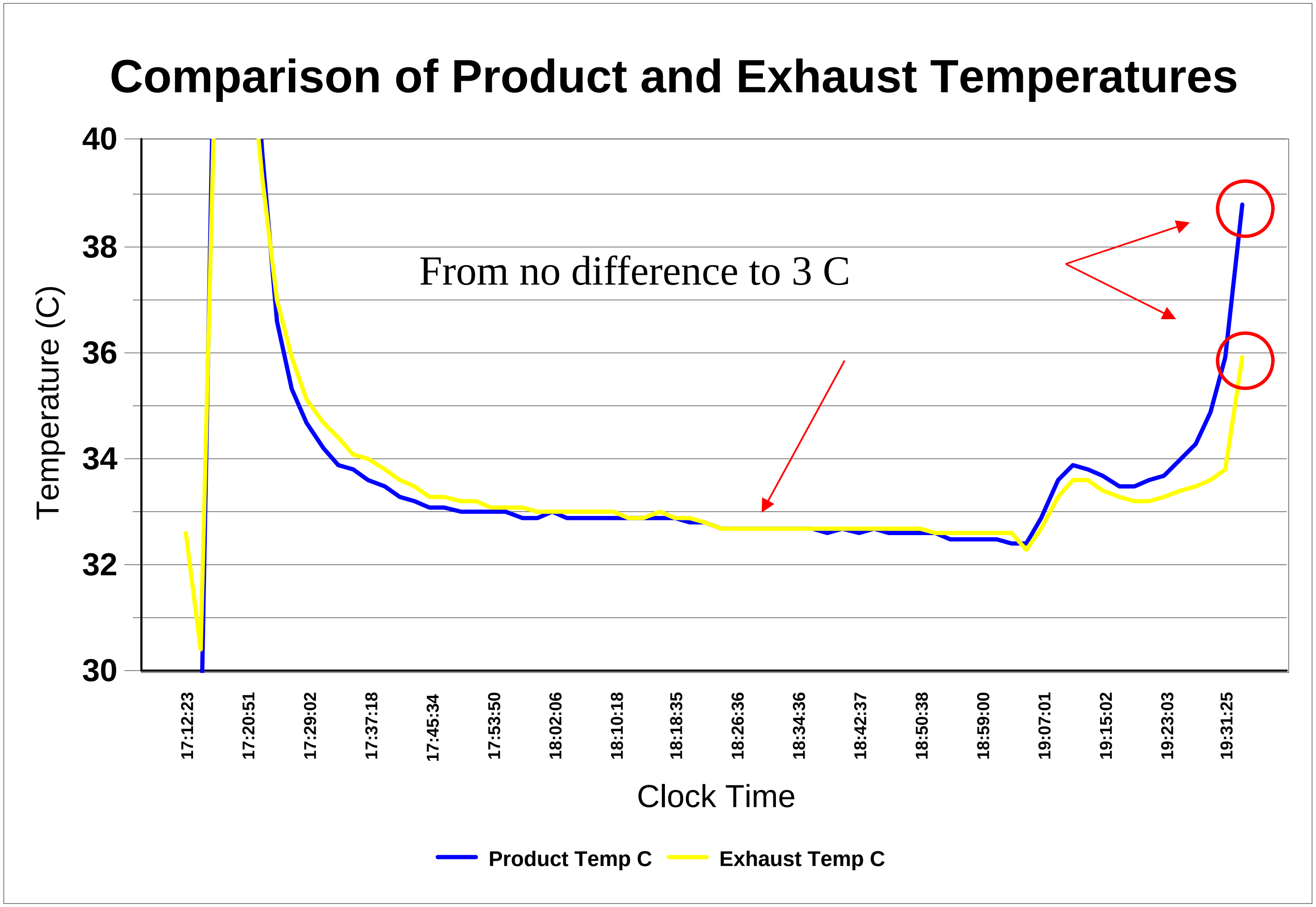
The spray liquid quantity trip point has been reached, the pump goes into recirculation, atomizing air drops to purge pressure, the inlet air temperature is raised to accelerate drying.

Fluidized Bed Spray Granulation

Process data - temperatures

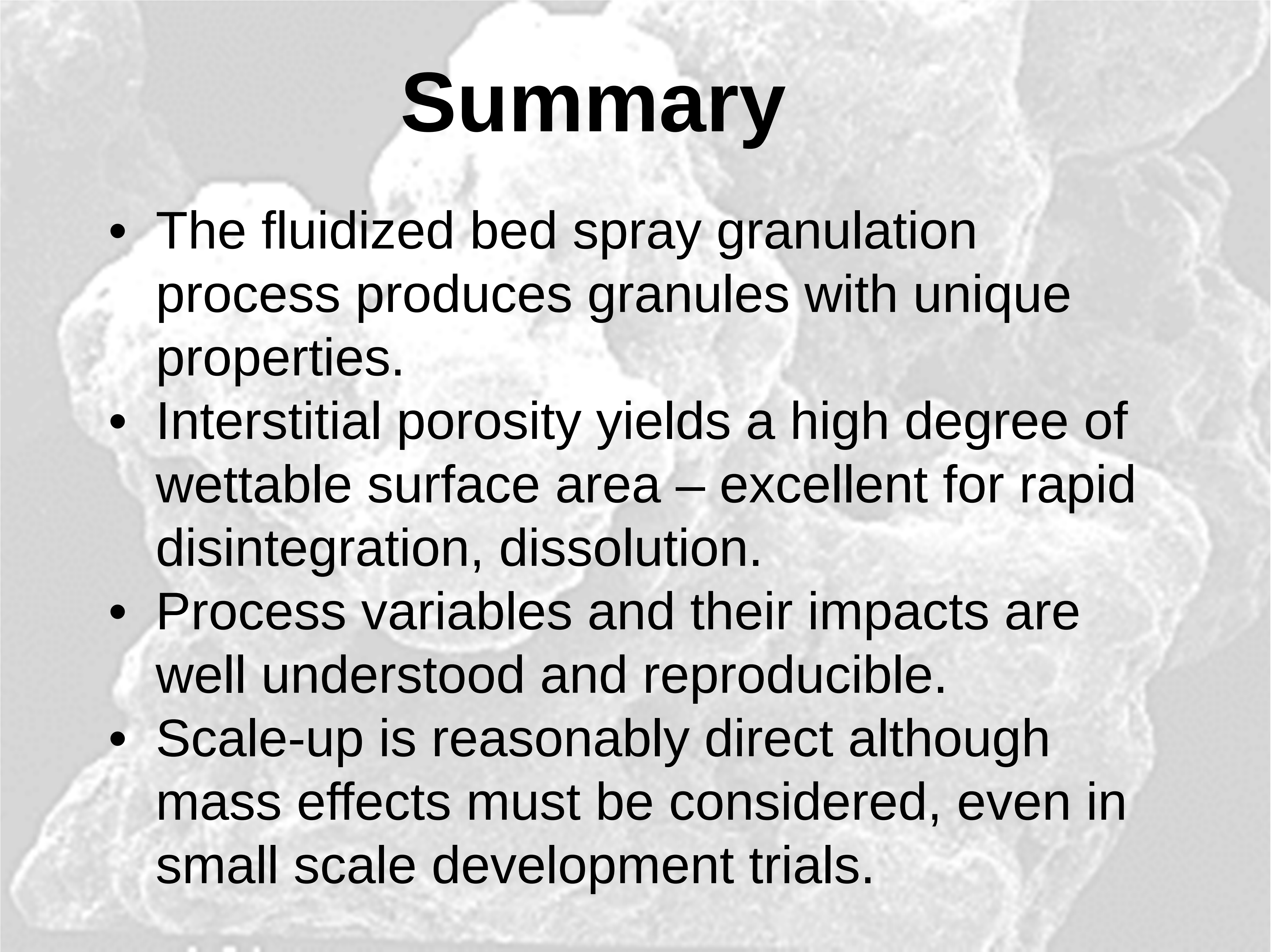


A new constant rate zone of drying is achieved, then as the product dries, product and exhaust temperature rise. The magnitude correlates to residual moisture.



From no difference to 3 C

Why the difference in product and exhaust temperatures? Can either one be used to indicate drying endpoint? Which is better?



Summary

- The fluidized bed spray granulation process produces granules with unique properties.
- Interstitial porosity yields a high degree of wettable surface area – excellent for rapid disintegration, dissolution.
- Process variables and their impacts are well understood and reproducible.
- Scale-up is reasonably direct although mass effects must be considered, even in small scale development trials.

Any Questions?

FLUIDIZED BED SPRAY GRANULATION:

Scale-up Considerations

David M. Jones
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Major Scale-Up Issues to Consider

- Drying capacity

  Spray rates are related to the increase in drying capacity, not the increase in batch size
- Droplet size

  Nozzle type/size, atomizing air pressure/volume, spray rate
- Mass effects

  Agglomerate/granule porosity may be impacted by the increased batch weight

Less Obvious Considerations

- Atomizing air kinetic energy (potential for attrition)
- Proximity to saturation (exit air humidity)
- Variations in ambient process humidity
- A few batches at the commercial scale may not be representative of long term success
- Productivity matters!

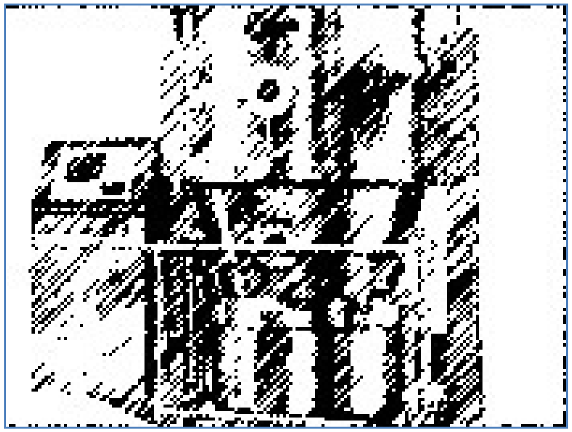
Common Issues in Scale-Up

- The lab trials do not effectively bracket what will be seen in scale-up
- The process used for the formulation was developed in a conservative manner
- The formulators do not have a feel for how production equipment works

Factors to Consider…

- Batch size determination
- Spray rate
- Droplet size
- Process air volume
- Temperatures (process, product)
- Mass effects (bed depth, batch size)

Batch Size Determination



$S_{min} = V \times 0.4 \times BD$

$S_{max} = V \times 0.8 \times BD$

Where:

V = Maximum Working Capacity of the Product Container

S = Batch Size (kg)

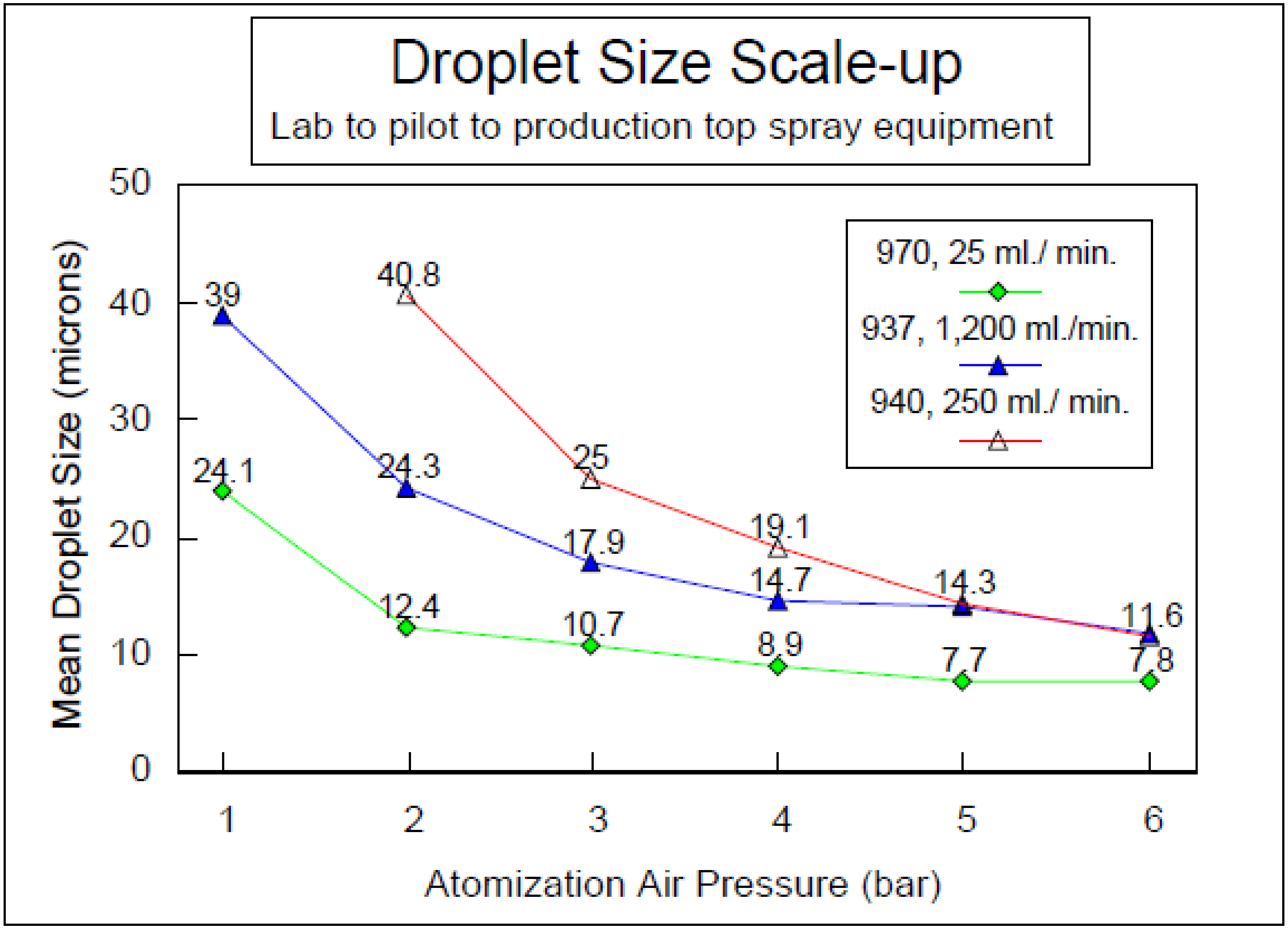
BD = Finished Product Bulk Density (kg/liter)

Droplet Size in Scale-up: From the lab to Pilot and Production

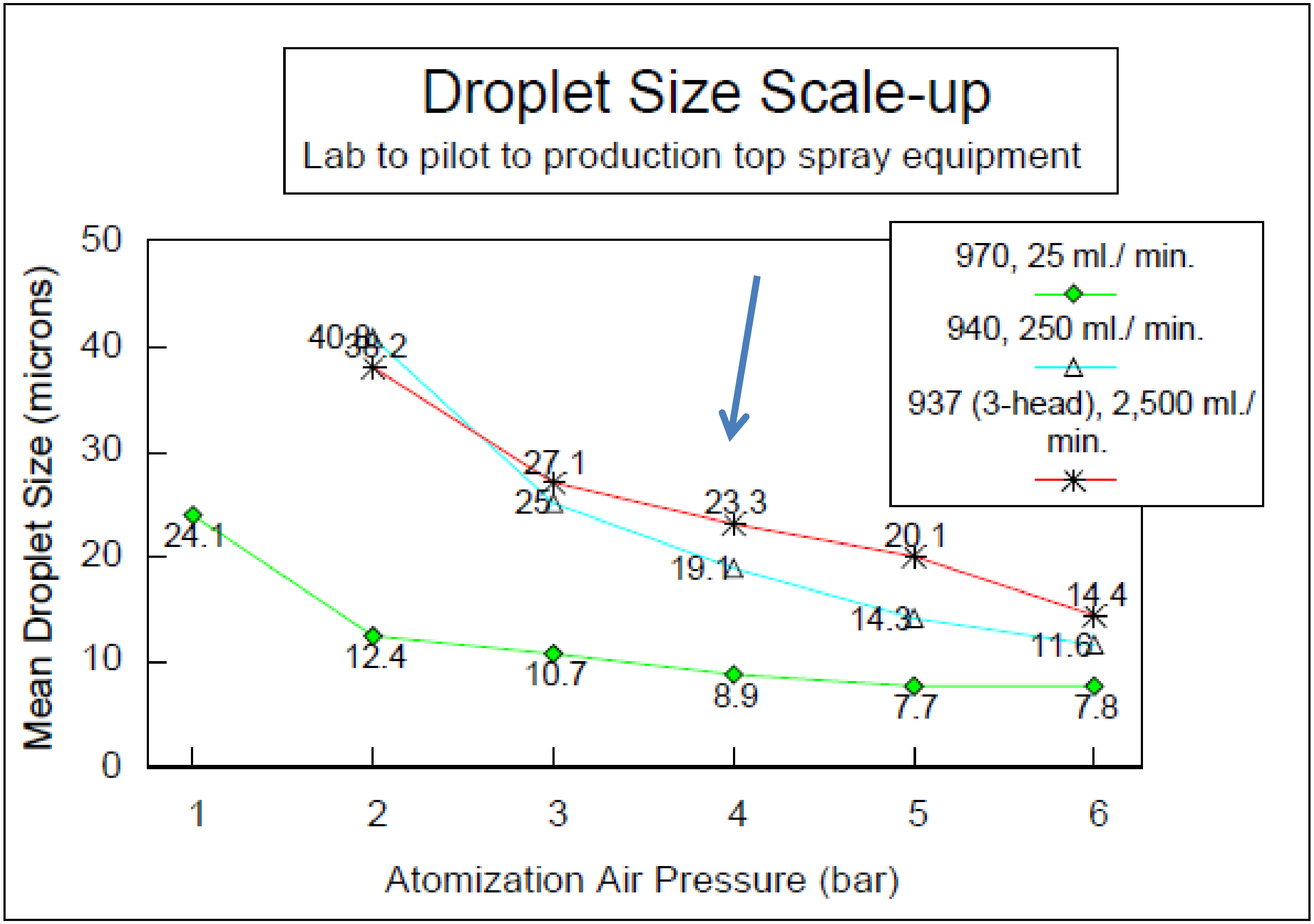
You must maintain the droplet size!

- Project the spray rate based on the expected increase in drying capacity (air volume) for the machine to be used.
- Make sure that the projected spray rate is within the air to liquid mass ratio capacity of the spray nozzle.
- Consider additional or multi-headed nozzles to reduce the spray rate per nozzle port.

For example:



Droplet Size Scale-up
Lab to pilot to production top spray equipment
Mean Droplet Size (microns)
0
10
20
30
40
50
1
2
3
4
5
6
Atomization Air Pressure (bar)
970, 25 ml./ min.
937, 1,200 ml./min.
940, 250 ml./ min.
39
24.3
17.9
14.7
14.3
11.6
24.1
12.4
10.7
8.9
7.7
7.8
40.8
25
19.1



Doubling the spray rate dramatically shifts the droplet size profile upwards

What Schlick nozzle are used in each size of top spray granulator?

- 970 series – up to 100 g/min
- 940 series – up to 500 g/min
- 937 series – up to 2,500 g/min (with 3 ports)
- 937 – up to 5,000 g/min (with 6 ports)
- Multiple 937 nozzles and wands can be used for spray rates exceeding 5,000 g/min

Process Air Volume

If the face velocity is kept constant at the bowl screen, the increase in air volume will be related to the increase in the bottom screen area. For example:

Machine	Bowl size	Screen cross-sectional area	Scale-up factor
GPCG-5	22 liters	0.0415 m	1
GPCG-60	220 liters	0.415 m	10
GPCG-300	1,060 liters	1.0382 m	25

If the ***measured*** air flow in the 22 liter GPCG-5 was 150 cfm, the starting point for the GPCG-60 would be 1,500 cfm and about 3,750 cfm for the production scale GPCG-300.

What About the Spray Rate?

Scale-up in spray rate is based on the increase in drying capacity, not batch size. For example:

Machine	Bowl volume (liters)	Batch size (kg)	Spray rate (g/min)
GPCG-5	22	8	100
GPCG-60	220	80	1,000
GPCG-300	1,060	400	2,500

Although the batch size in the GPCG-300 is 50 times larger than that in the GPCG-5, the drying capacity, at the same inlet temperature is only 25 times greater. Spraying at 50x will quickly over-wet the batch.

Process Air Temperature Considerations

Things to Think About

- In general, deeper beds in larger machines yield denser granules (mass effects – some of the interstitial porosity is compacted).
- Higher process air temperatures yield lower density granules, at least partially countering the mass effect.
- In some circumstances, the goal is to keep the process air and product temperature the same in scale-up (assuming the process air dew point is the same).

HOWEVER…

Process air temperature can be increased to:

- Increase the spray rate (within the performance envelope of the nozzle).
- Shorten the process time.
- Reduce the bulk density of the product (countering the consequences of the mass effect).

…as long as the consequences of the higher process air temperature are known and understood!

Case Studies

1. Spray nozzle maintenance and testing program
2. Effectiveness of DOE in lab/pilot scale
3. ‘Nuisance’ alarms (electronic controls)
4. Identifying ranges for dependent variables
5. “After calibration, everything is the same but now we are having batch failures”

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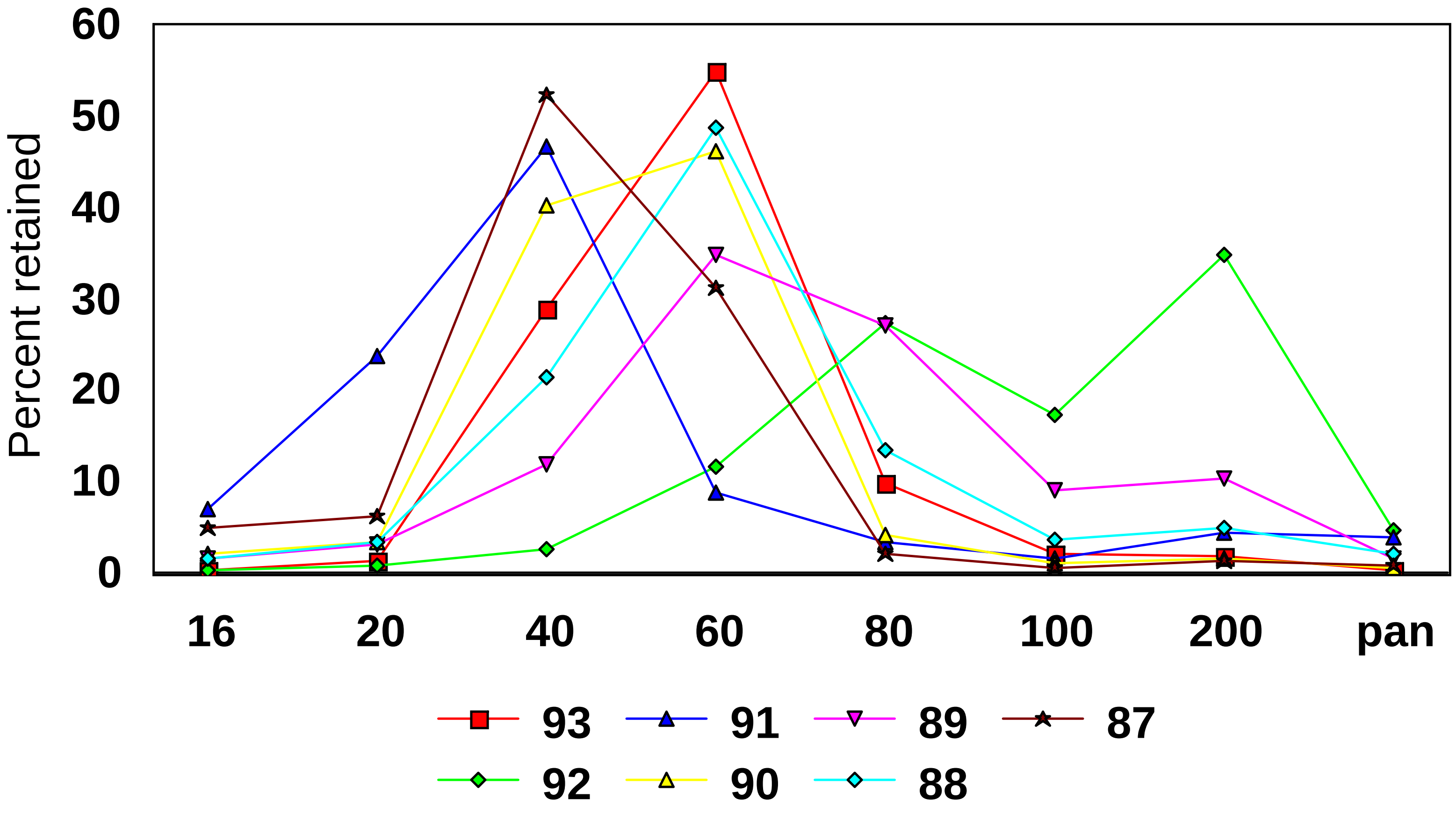
Application of DOE to pilot scale product development

A case study: Top spray fluidized bed spray granulation

A preliminary ‘range’ study to identify the domain for a 3 factor, 2 level DOE.

The factors are inlet air temperature (evaporation rate), liquid spray rate (primarily in-process moisture content) and atomizing air pressure/volume (droplet size)

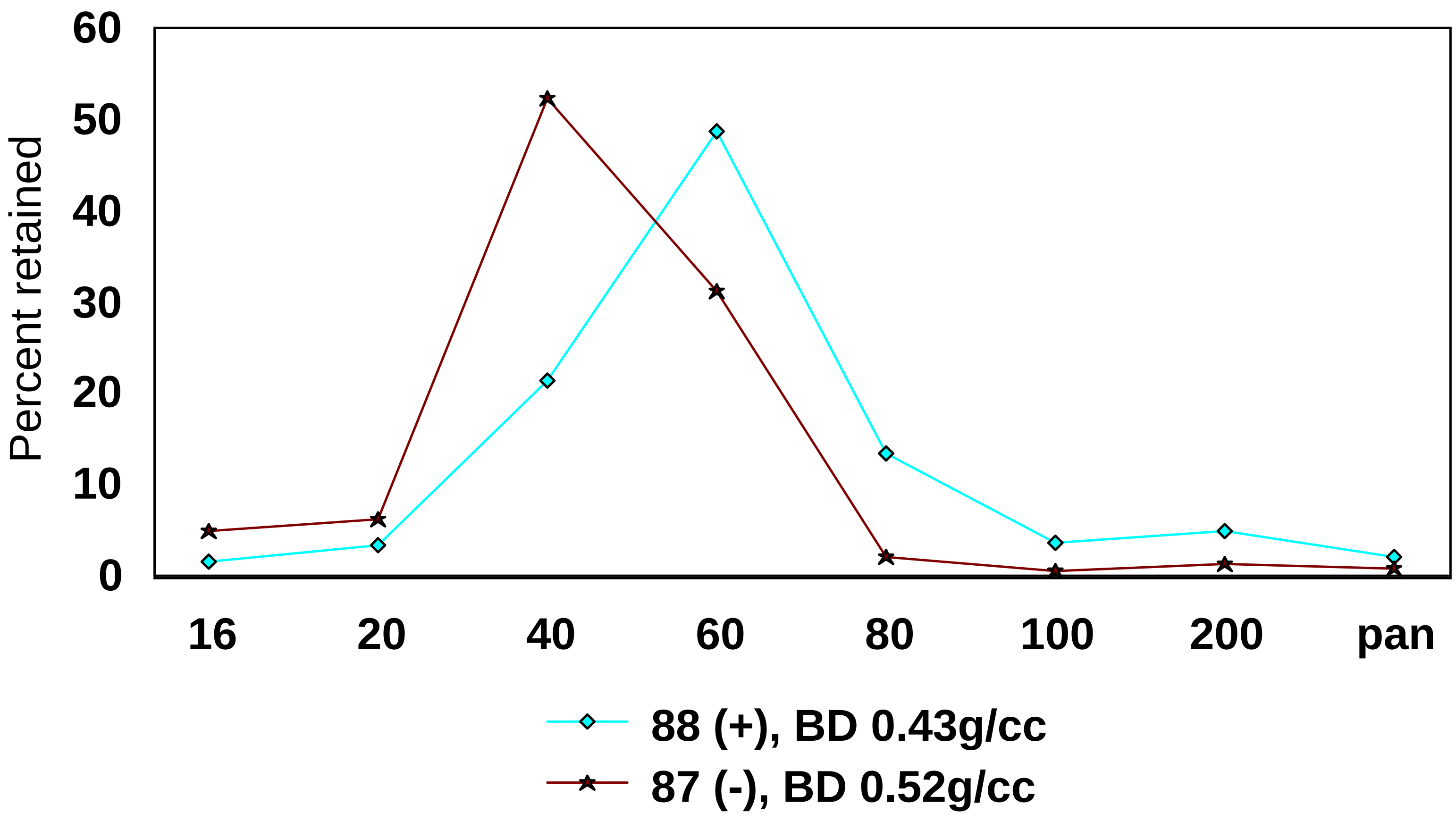
batches 87-93
a series of batches to define DOE domain



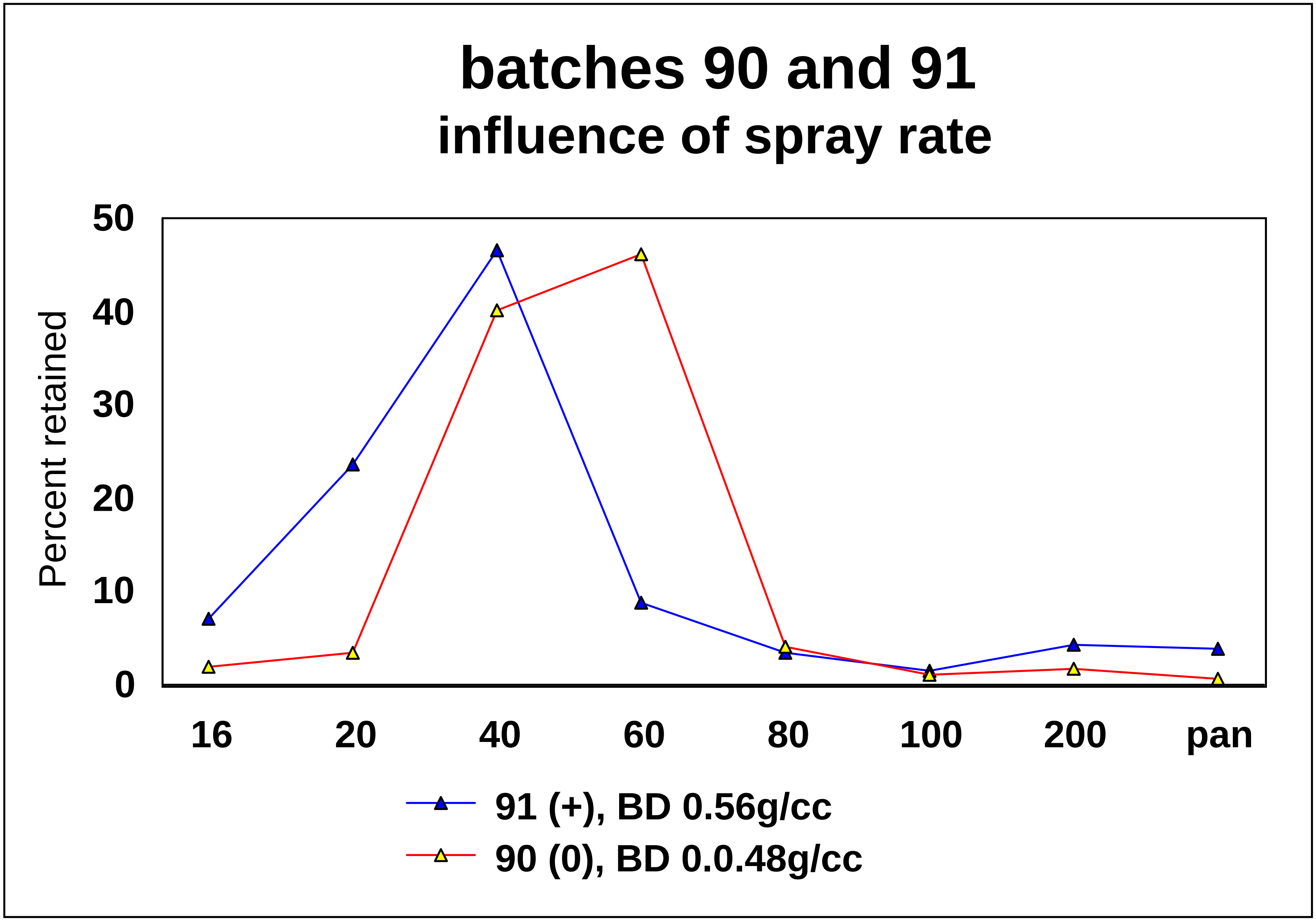
Particle size and distribution respond strongly to the range of process variables selected for study.

batches 87and 88

influence of inlet air temperature



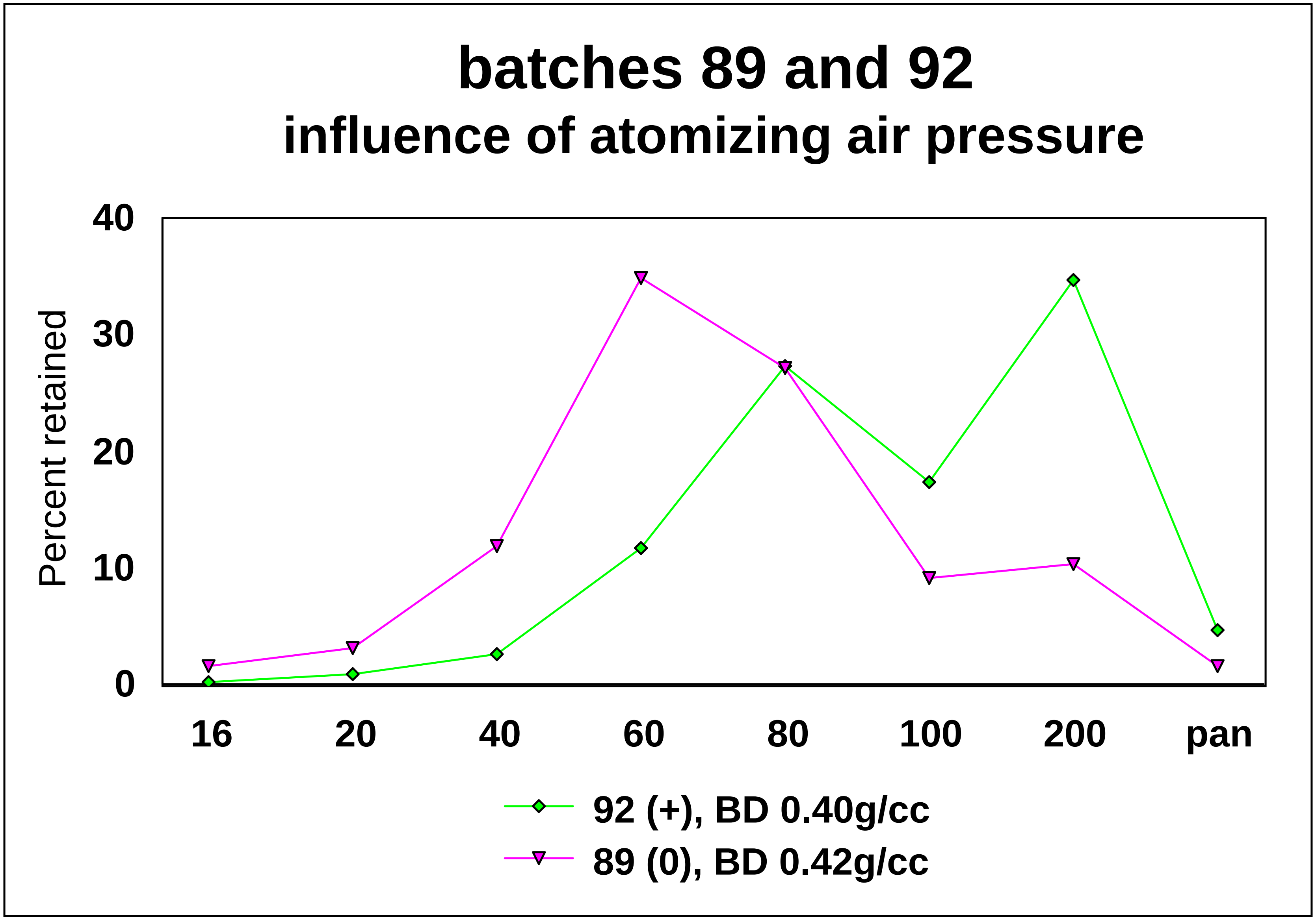
The lower inlet air temperature results in a coarser particle size and higher bulk density (principally due to higher in-process moisture content).



batches 90 and 91

influence of spray rate

The increased spray rate increases particle size and bulk density. Note: this batch was the ‘worst case’ and required a revision to the domain.

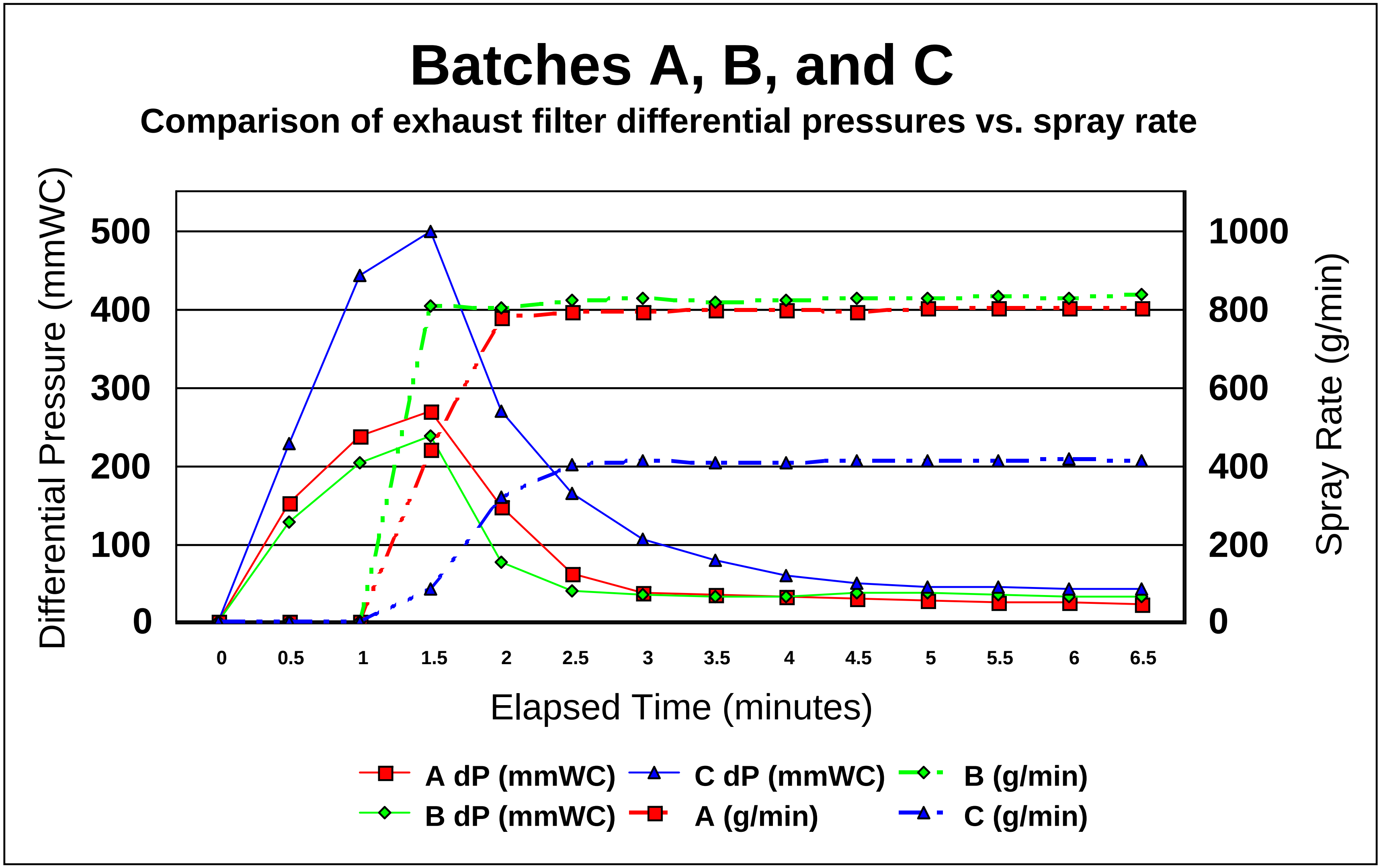


Atomizing air pressure/volume strongly affects droplet size, and ultimately particle size and distribution

Results:

- All batches tabletted successfully. Distribution uniformity, hardness, friability and disintegration time all passed the specification. A robust process? There was an interesting impact on a machine component…

Initial behavior is interesting:



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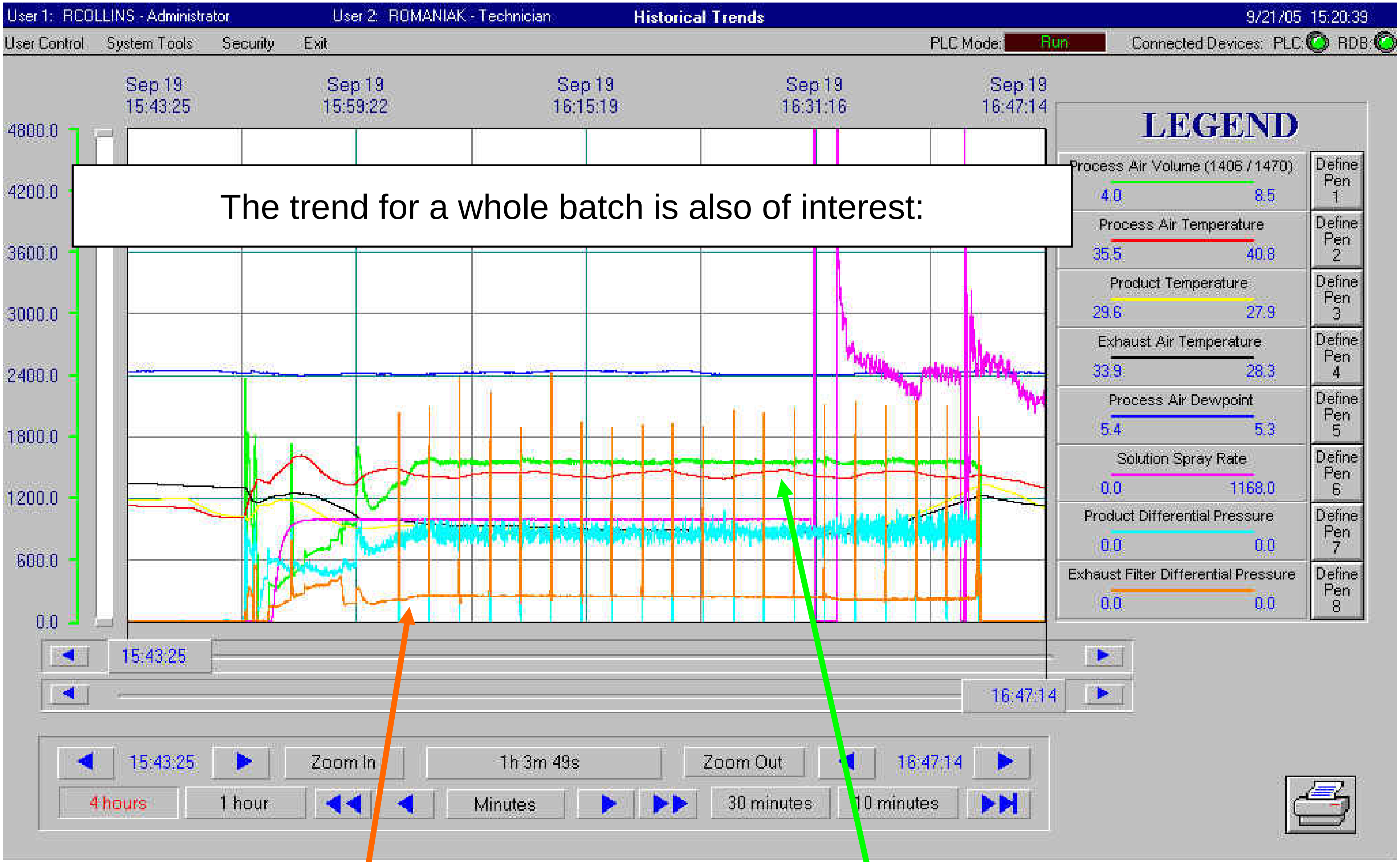
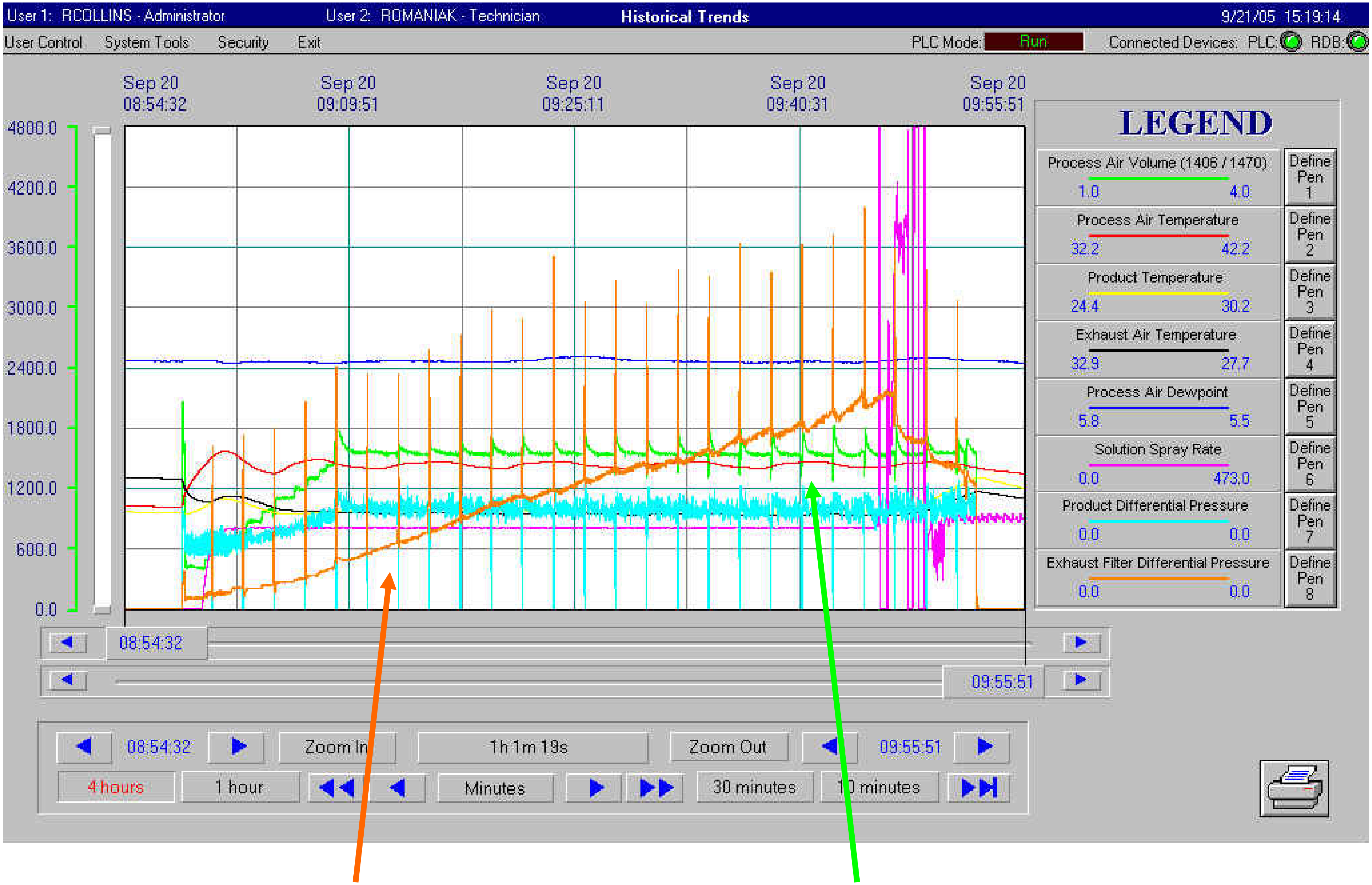
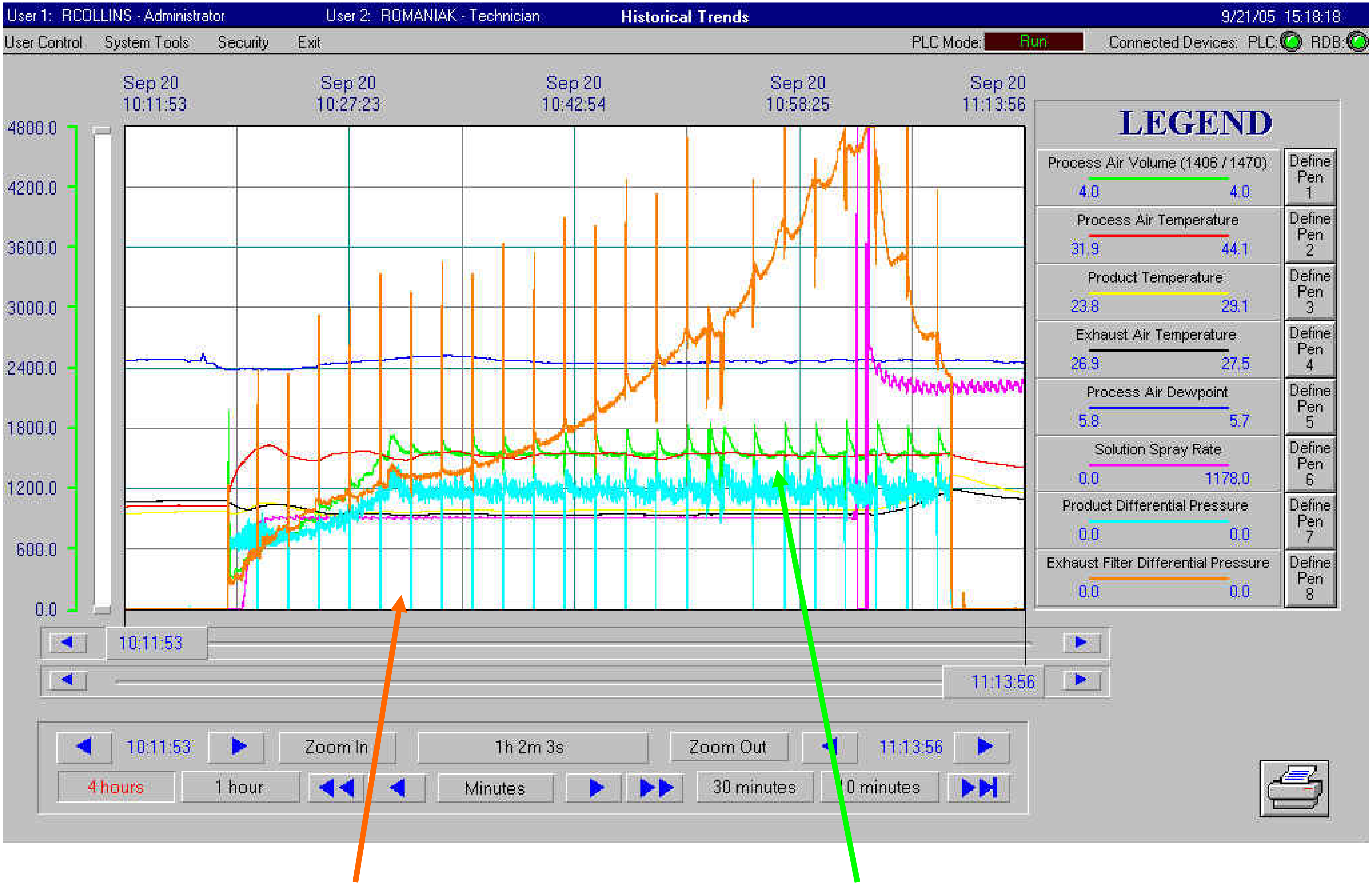


The trend for a whole batch is also of interest:

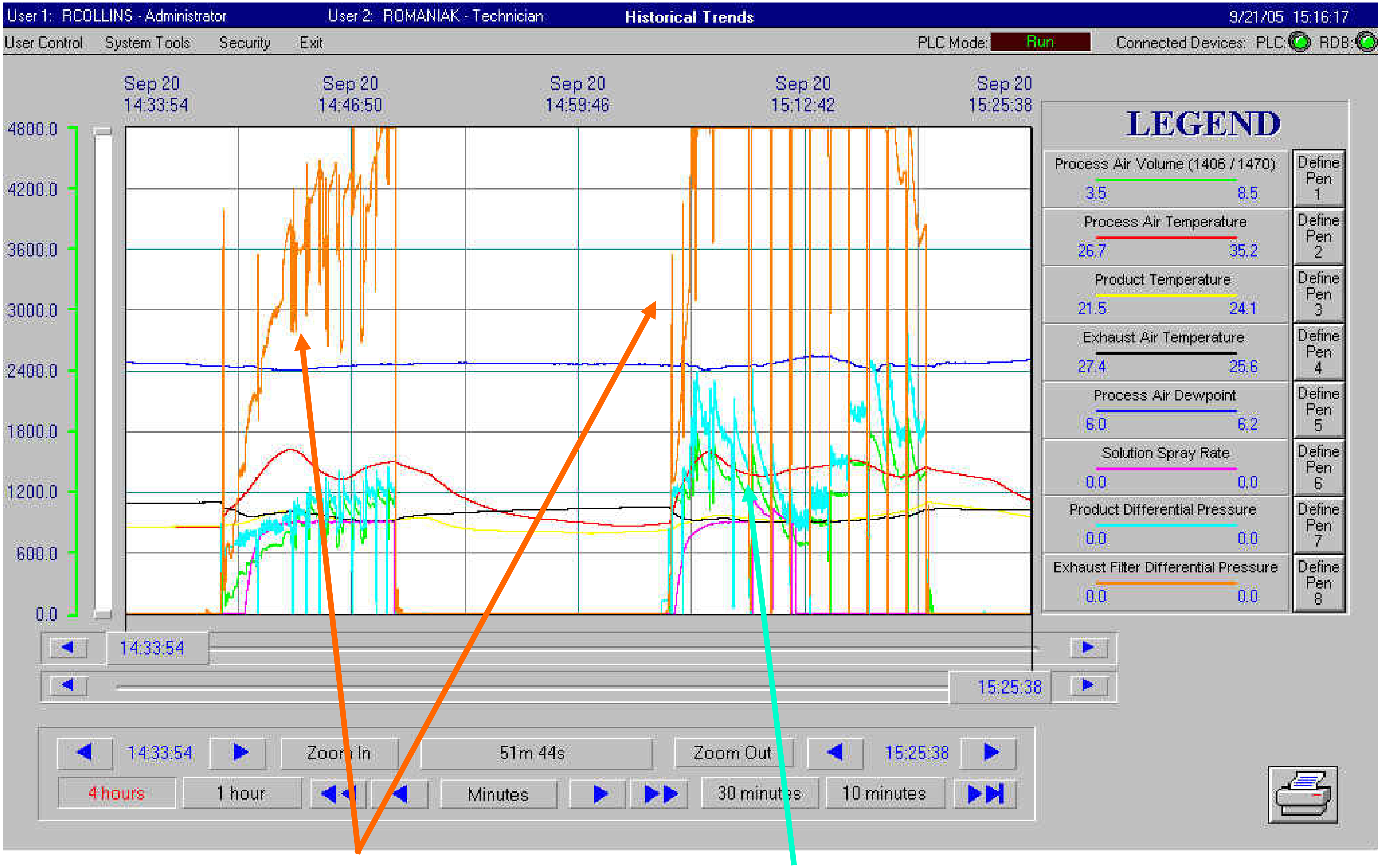
Here, the filter pressure remains low for the entire batch, and there is no appreciable variability in process air volume.



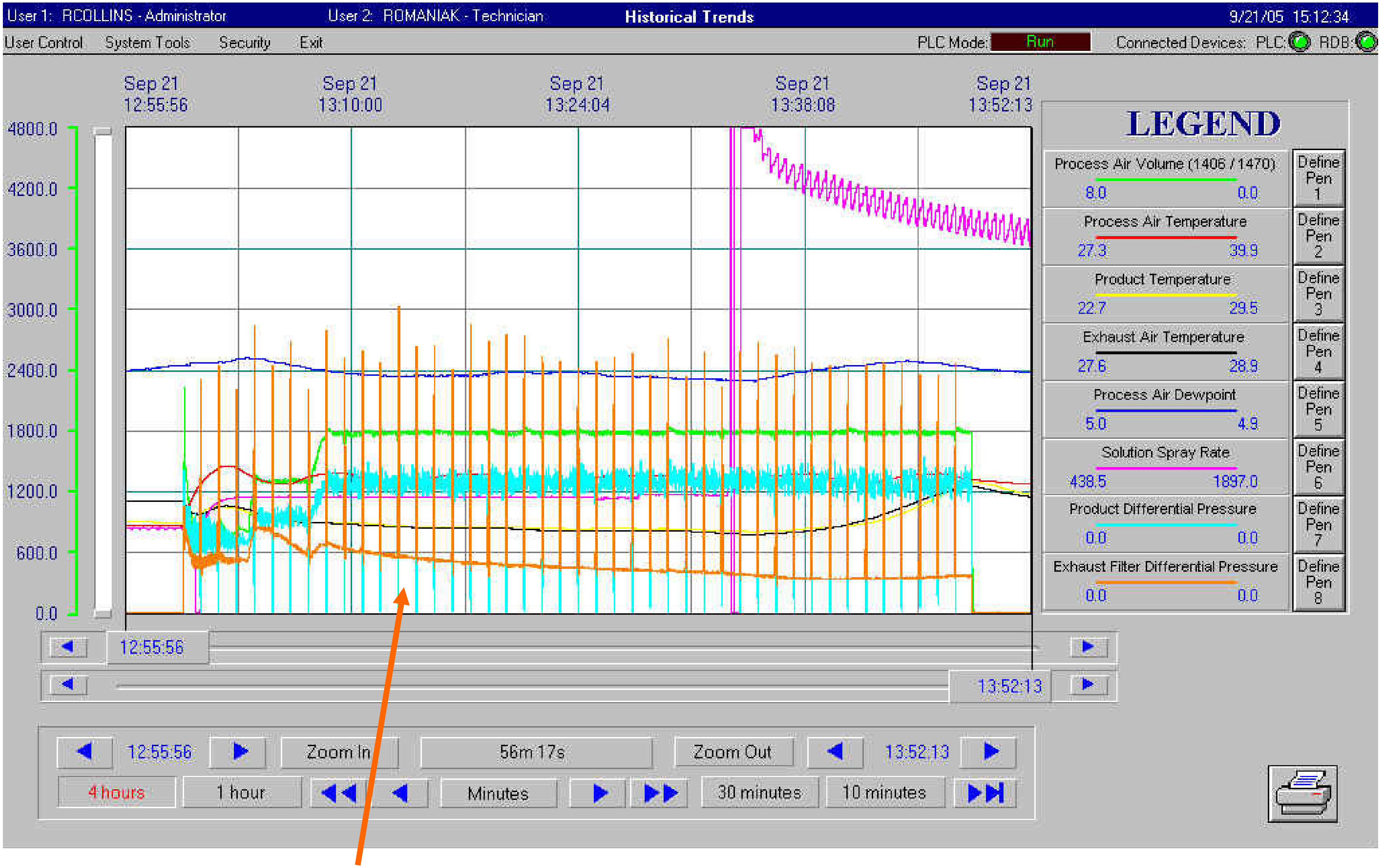
Here, the filter pressure is trending upward, but not to an alarming level. Variability in process air volume is nominal.



Here, the filter pressure reaches the display limit, and variability in process air volume is increasing.



Here, the filter pressure is extreme – the batch was interrupted in an attempt to manually clean the filter. After restart, it was evident that this failed (air flow control not possible). The batch was aborted.



LEGEND

Process Air Volume (1406 / 1470)
8.0 0.0

Process Air Temperature
27.3 39.9

Product Temperature
22.7 29.5

Exhaust Air Temperature
27.6 28.9

Process Air Dewpoint
5.0 4.9

Solution Spray Rate
438.5 1897.0

Product Differential Pressure
0.0 0.0

Exhaust Filter Differential Pressure
0.0 0.0

It was found that the filter pressure was related to in-process moisture content. Wetter batches did not tend to foul the filter. A later batch, at high spray rate, actually seemed to ‘clean’ the same filter.

Case Studies

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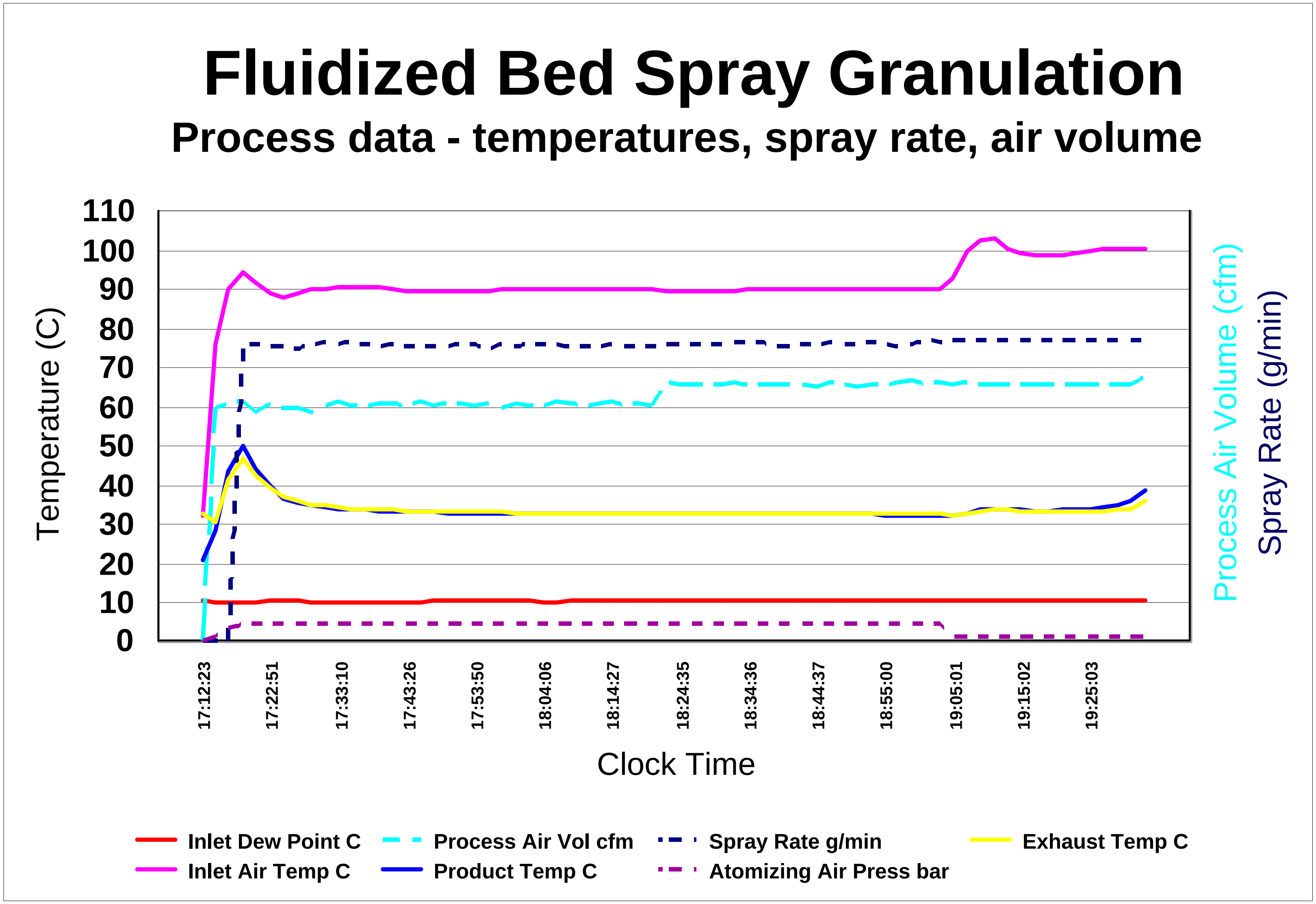
4. Identifying ranges for dependent variables
5. “After calibration, everything is the same but now we are having batch failures”

Nuisance Alarms



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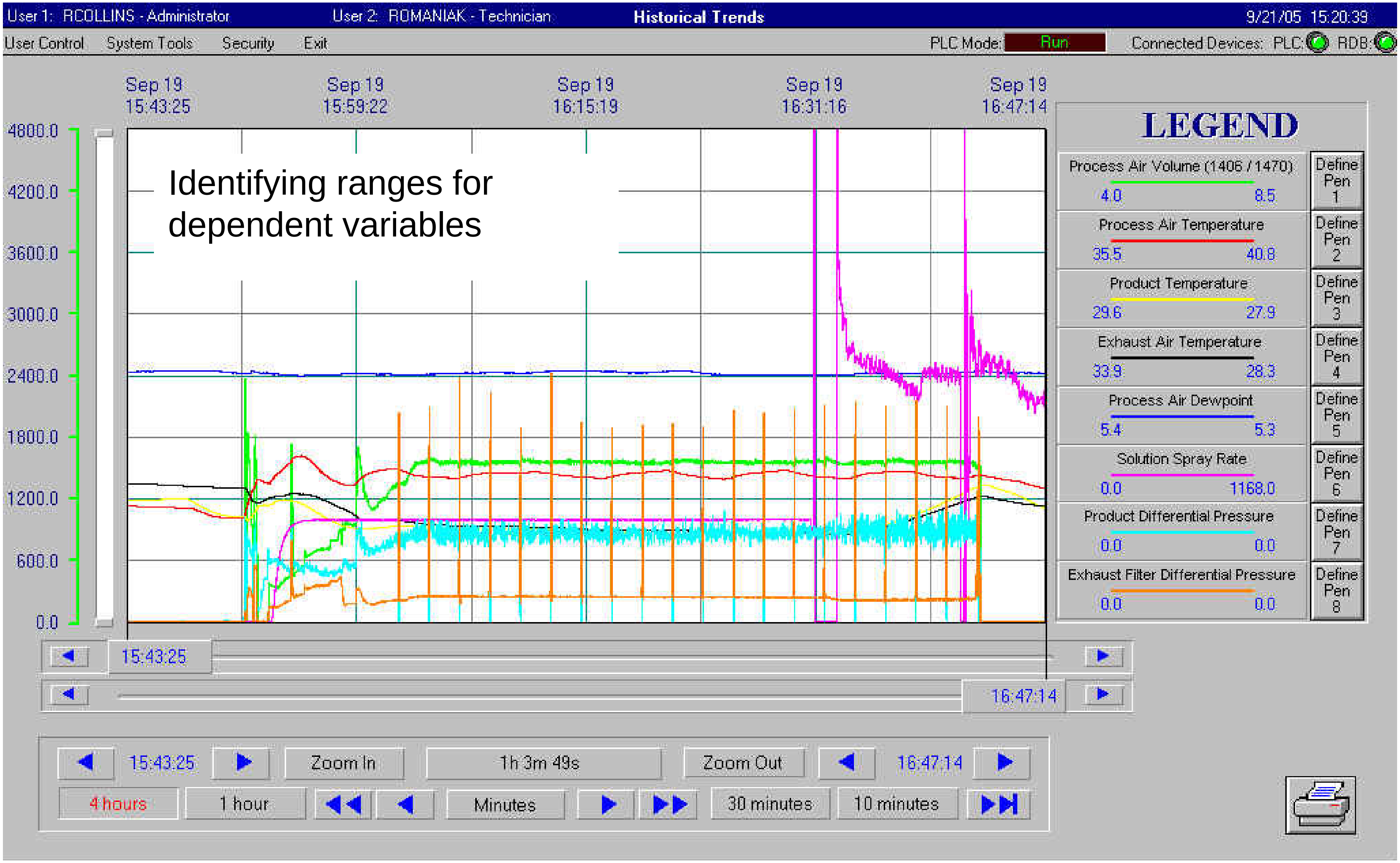

Identifying ranges for dependent variables

In the first example, filter pressure is very low for the duration of the batch. Process air volume is not impacted during shaking.

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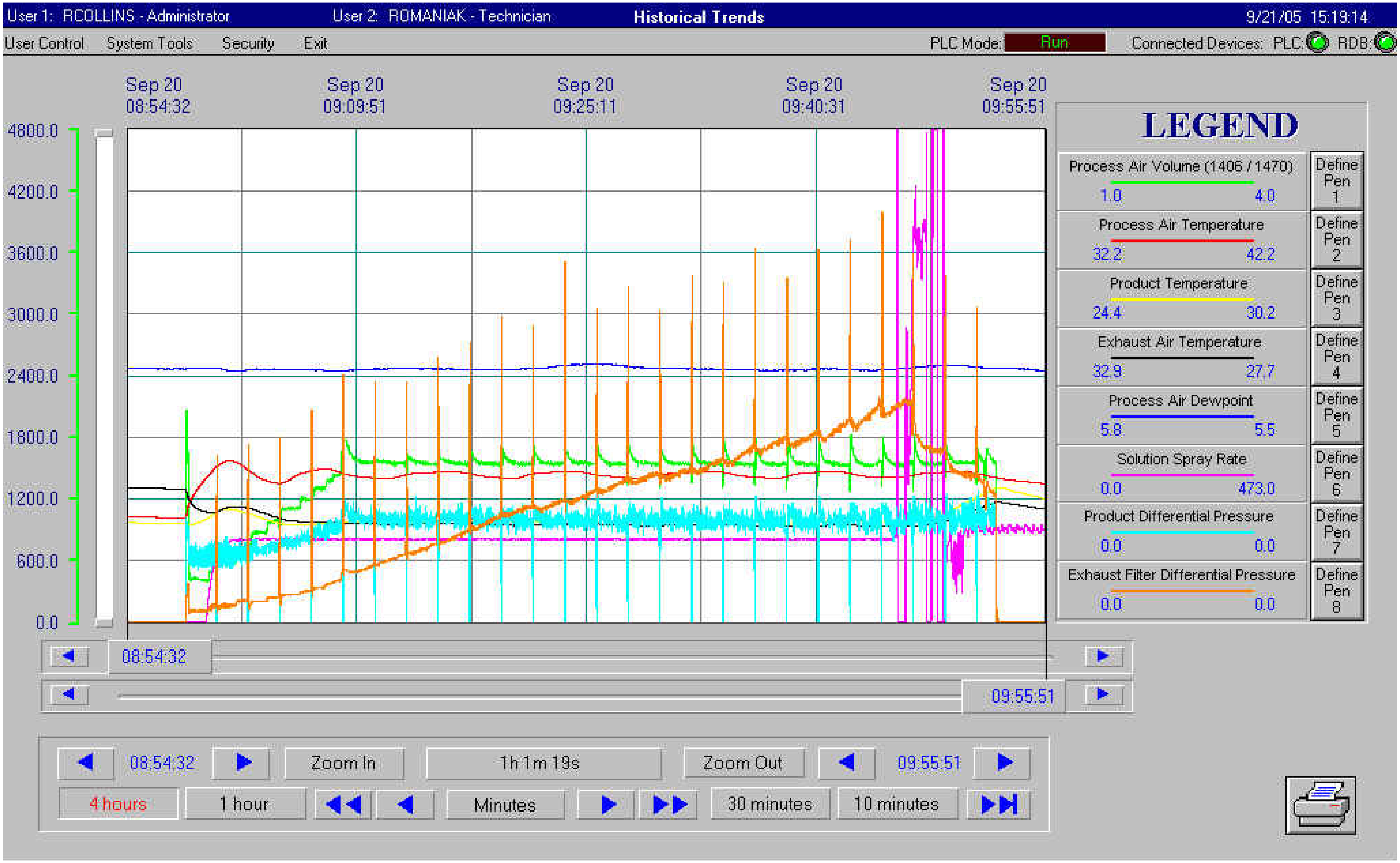
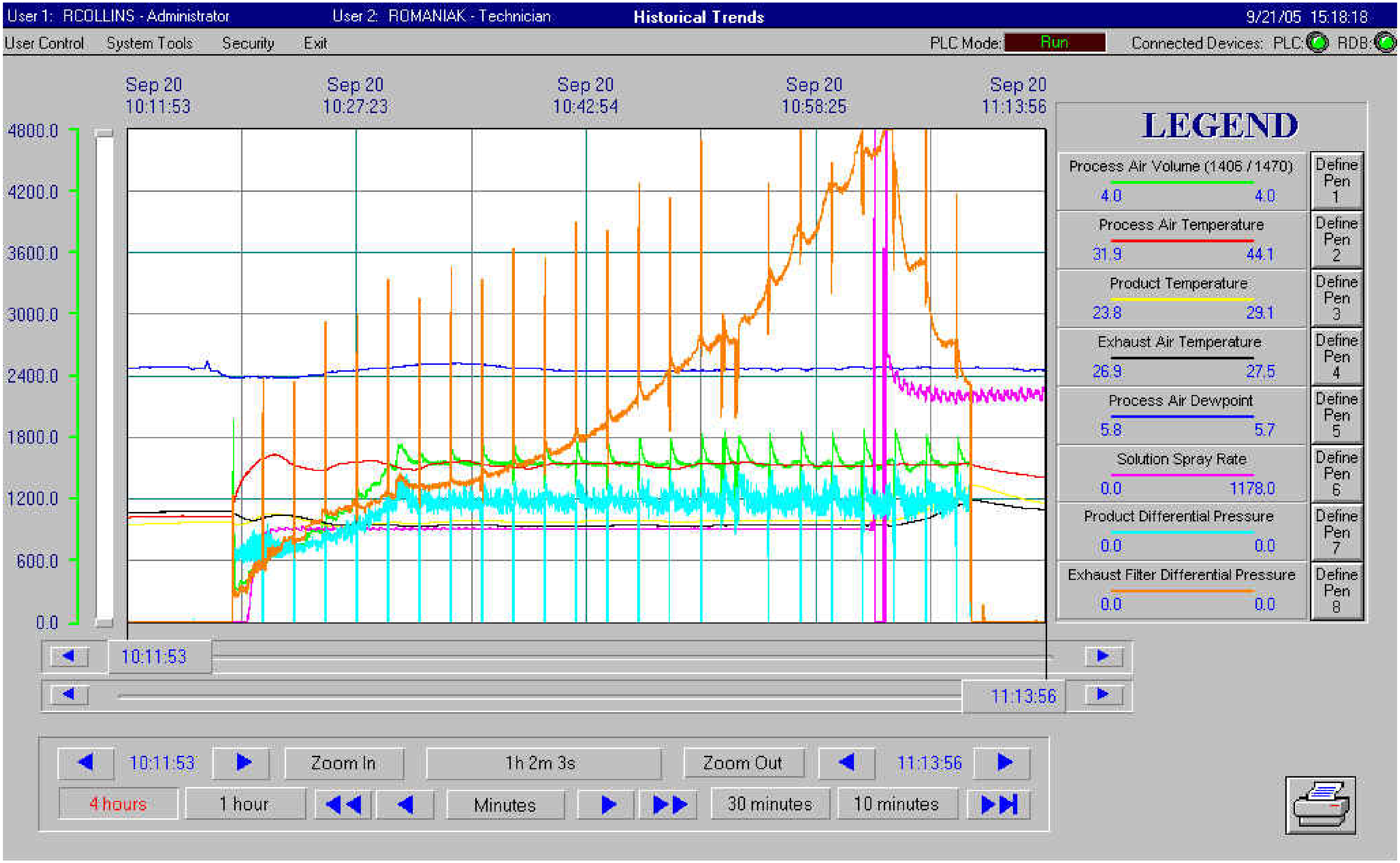


In the second example, filter pressure trends upwards during the batch. Process air volume fluctuates during shaking, but not to a great extent.



Legend	Min	Max	
Process Air Volume (1406 / 1470)	4.0	4.0	Define Pen 1
Process Air Temperature	31.9	44.1	Define Pen 2
Product Temperature	23.8	29.1	Define Pen 3
Exhaust Air Temperature	26.9	27.5	Define Pen 4
Process Air Dewpoint	5.8	5.7	Define Pen 5
Solution Spray Rate	0.0	1178.0	Define Pen 6
Product Differential Pressure	0.0	0.0	Define Pen 7
Exhaust Filter Differential Pressure	0.0	0.0	Define Pen 8

In the final example, filter pressure trends upwards to the maximum display value. Process air volume responds during shaking but the m/c is able to maintain the desired set point between filter shakes.

Case Studies

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2. Effectiveness of DOE in lab/pilot scale
3. ‘Nuisance’ alarms (electronic controls)
4. Identifying ranges for dependent variables
5. “After calibration, everything is the same but now we are having batch failures”

Failure Analysis

1. Batch data was examined for ‘good’ and ‘bad’ batches
2. Calibration data was examined
3. Moisture content at the end of spray was compared
4. Drying time was examined
5. Wetter batches seized, causing batch failures
6. Process air volume accuracy became the focus of attention
7. The air volume sensor was re-calibrated

Summary

- The fluidized bed spray granulation process yields unique product attributes which are attractive for many products.
- Although most commonly conducted using conventional top spray equipment, the process may be performed using the Wurster and rotor techniques.
- Raw material attributes contribute to finished product properties – release specifications must be robust and well defined.
- Process variables are well understood and may be controlled repeatedly.

Any Questions?

Tableting and Compaction training

Colleen E. Ruegger
Novartis Pharmaceuticals

August 29, 2012

Overview

- Definitions and Main Deformation Mechanisms
- Common Equations and Analysis Techniques
- Particle properties
- Troubleshooting
- Bilayer Compaction
- Compaction Simulation
- Case studies

Definitions

&

Main Deformation Mechanisms

What do we need to know about compaction?

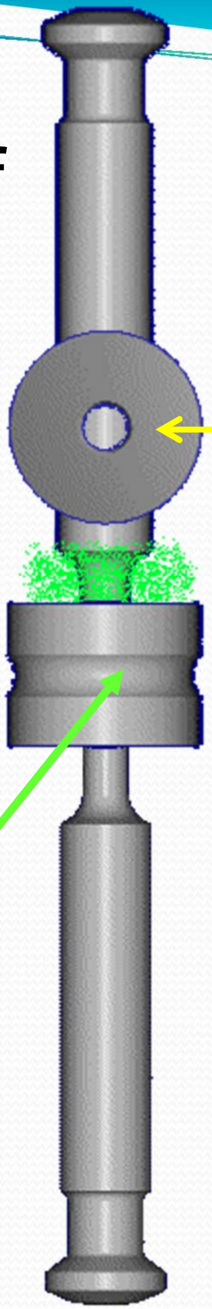
- COMPRESSION is a reduction in bulk volume of the material, as a result of displacement of the gaseous phase.
- CONSOLIDATION is an increase in the mechanical strength of the material, as a result of particle/particle interaction.
- COMPACTION is the compression and consolidation of a two phase (particulate solid/ gas) system due to an applied mechanical force.
- TABLETTING is the compaction of a powdered or granular mixture in a die, between two punches, by application of a significant mechanical force.

Compression & Consolidation

- COMPRESSION may involve:
  - particle re-arrangement
  - elastic deformation,
  - plastic defiormation
  - visco-elastic deformation
  - brittle deformation
- CONSOLIDATION may involve:
  - Intra-molecular interactions
  - Inter-molecular interactions
  - Re-solidification of liquid films
  - Mechanical interlocking


dissolution rate
mechanical strength
porosity
compression
consolidation
compaction

One Station of Tooling



Upper Punch

Die Cavity

Powder

Die

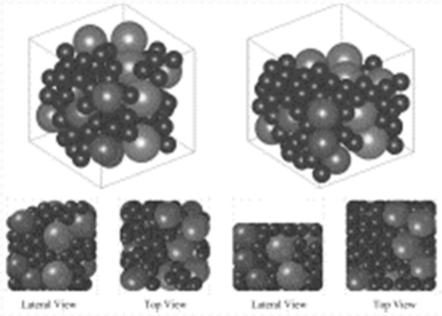
What is occurring inside the die ?

Lower Punch

Stages of Compaction

- Particle rearrangement/interparticle slippage
- Deformation of particulates
- Bonding/Cold welding
- Deformation of the solid body
- Elastic recovery/expansion of the mass as a whole

Stages of Compaction

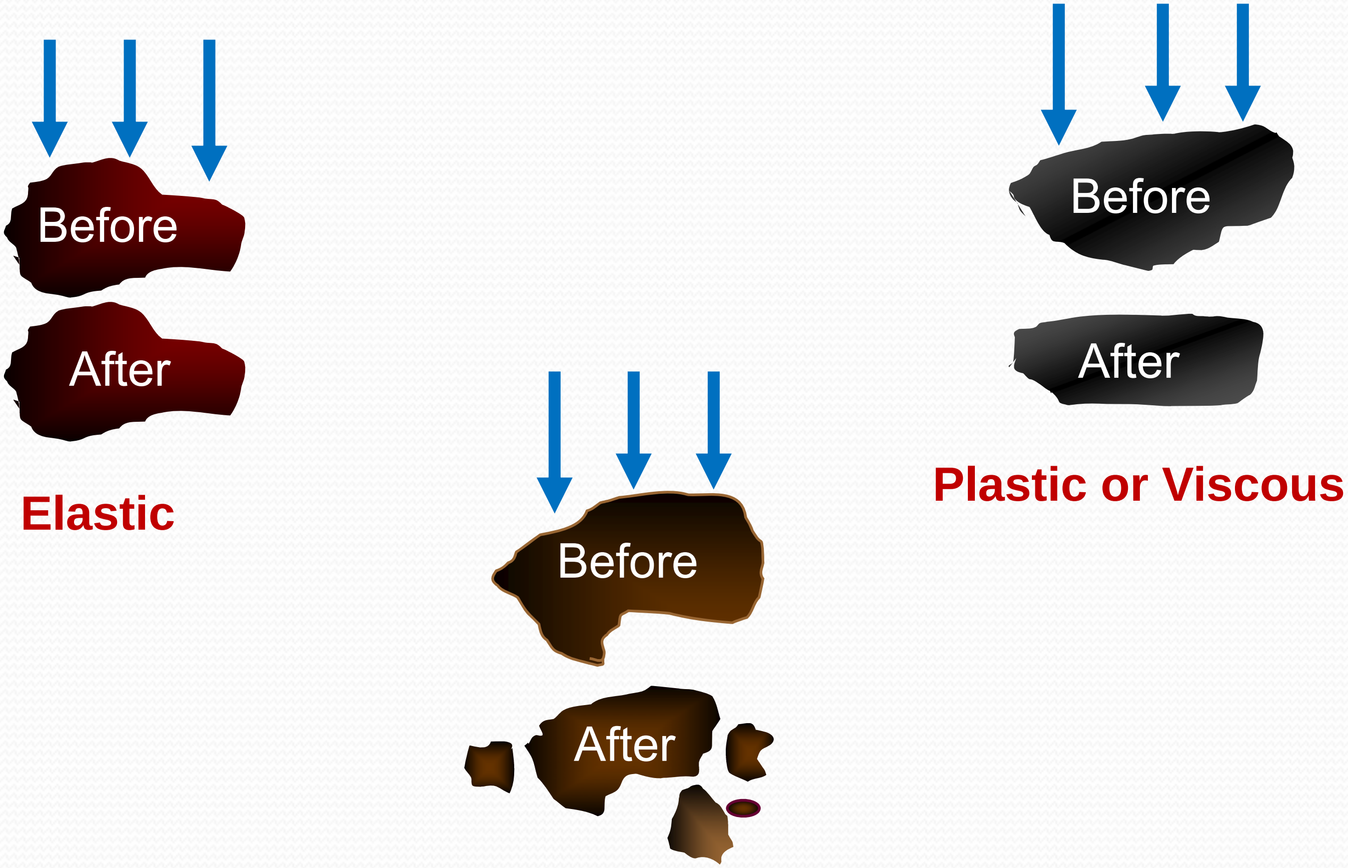


- Particle rearrangement
  - occurs at low pressures
  - reduction in the relative volume of powder bed
  - small particles flow into voids between larger particles leading to a closer packing arrangement

As pressure increases, relative particle movement becomes impossible, inducing deformation

Stages of Compaction

Deformation Mechanisms of Materials

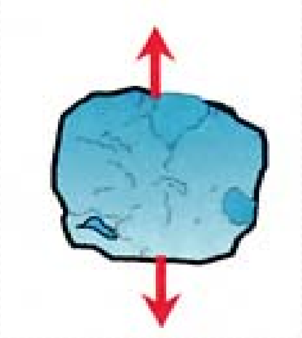


Elastic

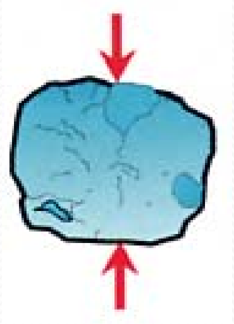
Brittle Fracture

Plastic or Viscous

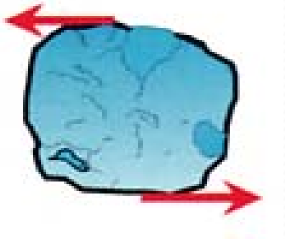
Stress – Strain Relationship



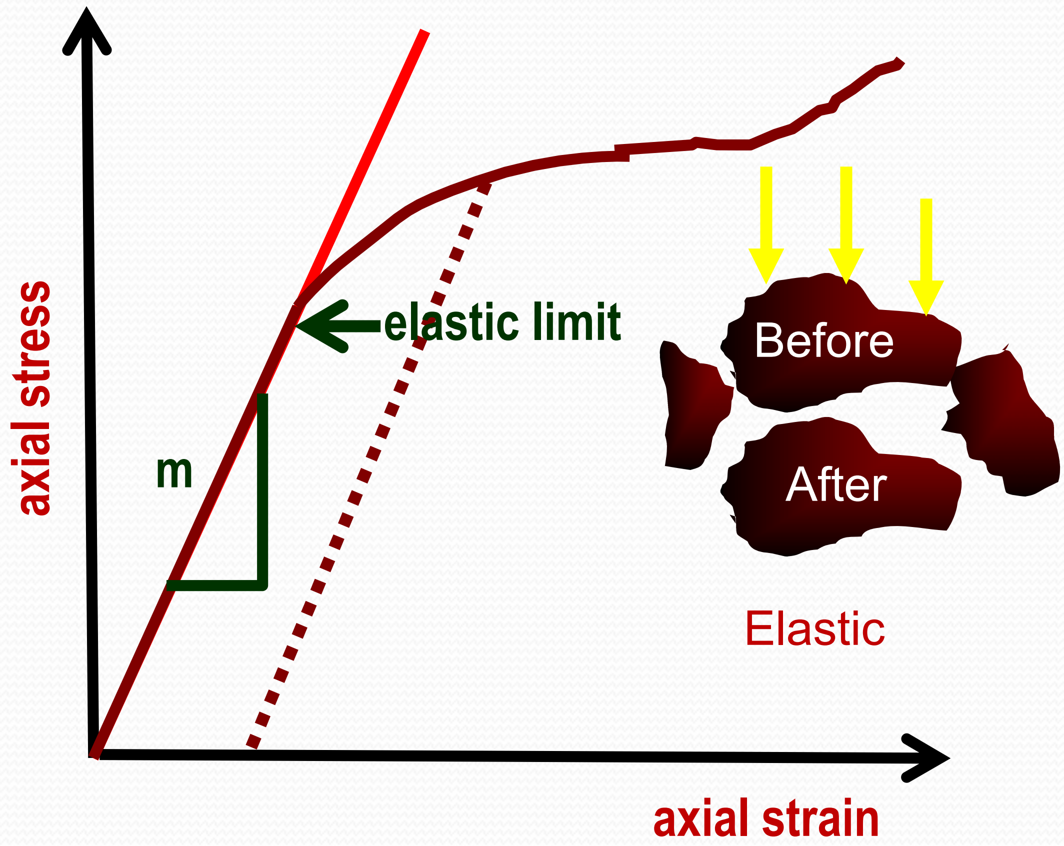
tensile stress



compressive stress

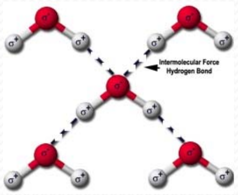


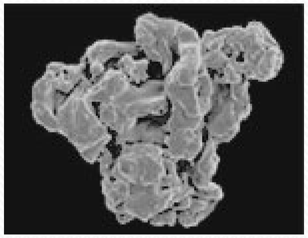
shear stress



Stages of Compaction

- Bonding
  - Solid Bridges
    - form directly across particles in the absence of any binding elements or additives
  - Intermolecular/Electrostatic Forces
    - forces projecting beyond the particle surface as small discrete fields with very short range order
  - Mechanical Interlocking
    - shape dependent





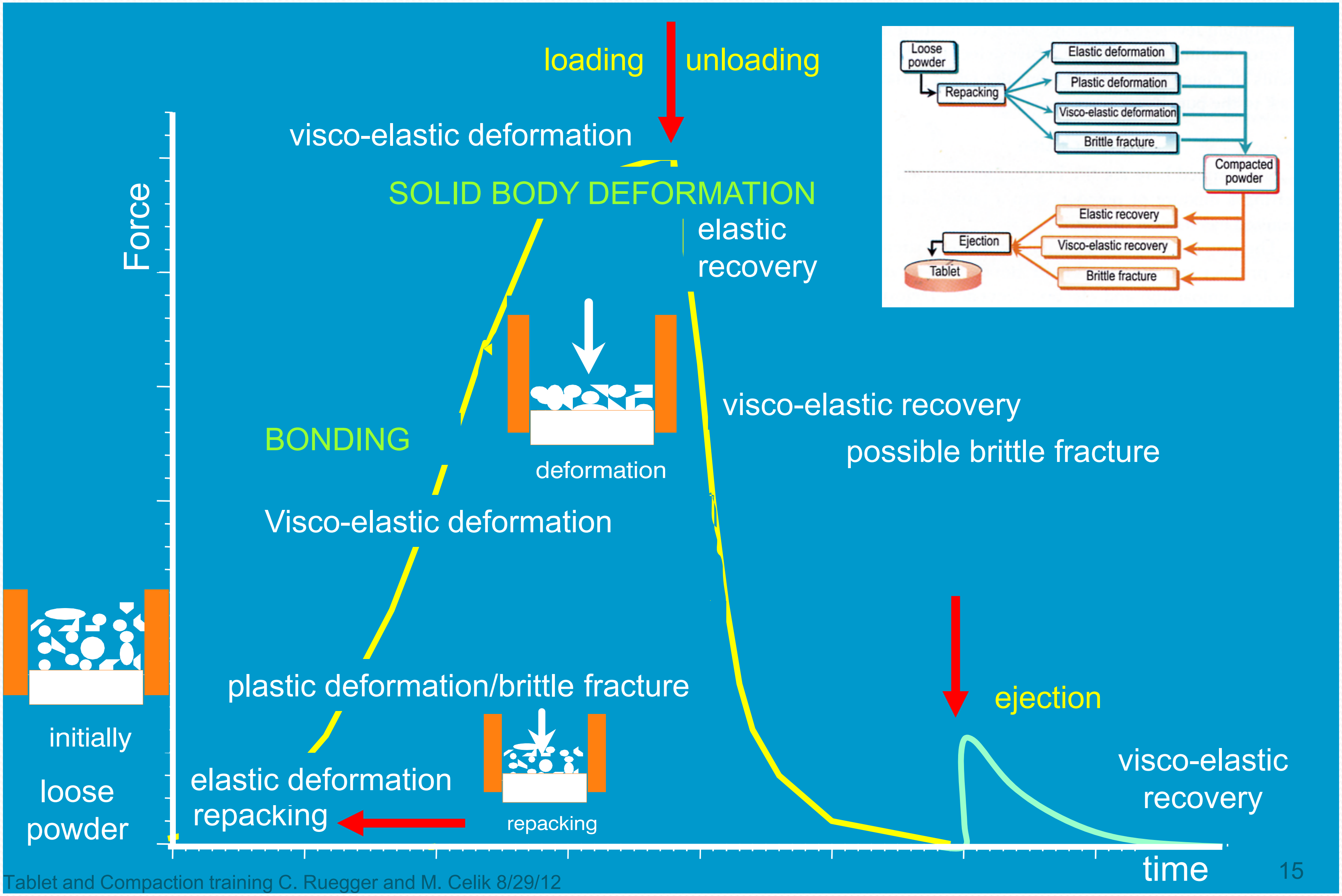
Stages of Compaction

- Deformation of the Solid Body
  - As pressure increases, the bonded solid is consolidated toward a limiting density by plastic and/or elastic deformation.

Stages of Compaction

- Recovery
  - The compact is ejected, allowing radial and axial recovery.
  - Elastic character tends to revert the compact to its original shape.

Stages of Compaction



loading

unloading

visco-elastic deformation

SOLID BODY DEFORMATION

elastic
recovery

Force

visco-elastic recovery

BONDING

deformation

possible brittle fracture

Visco-elastic deformation

plastic deformation/brittle fracture

ejection

initially

loose
powder

visco-elastic
recovery

elastic deformation

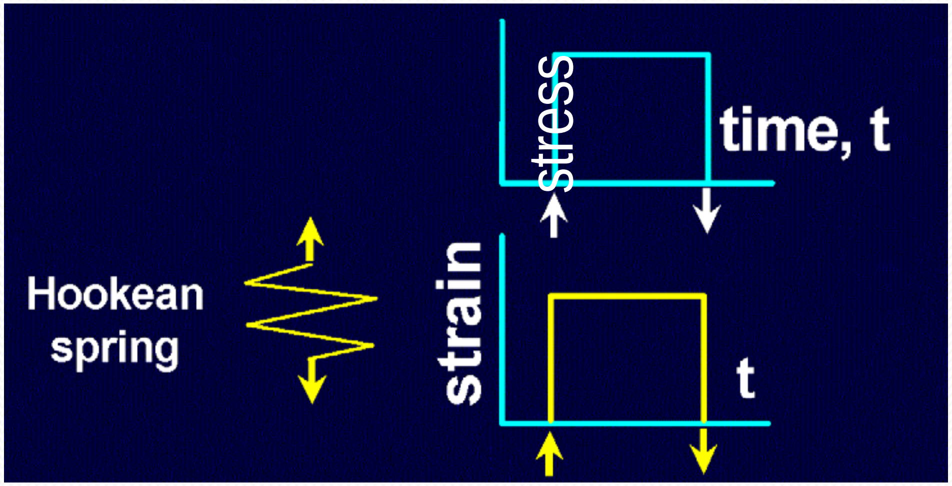
repacking

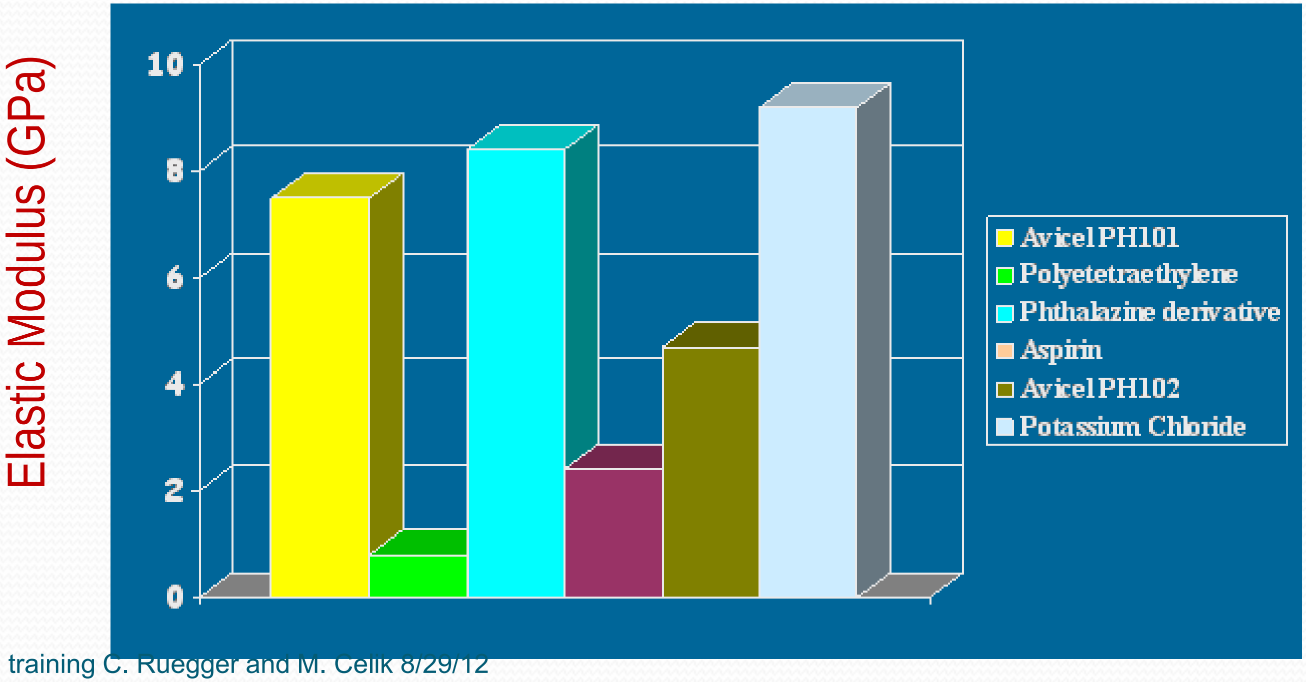
repacking

time

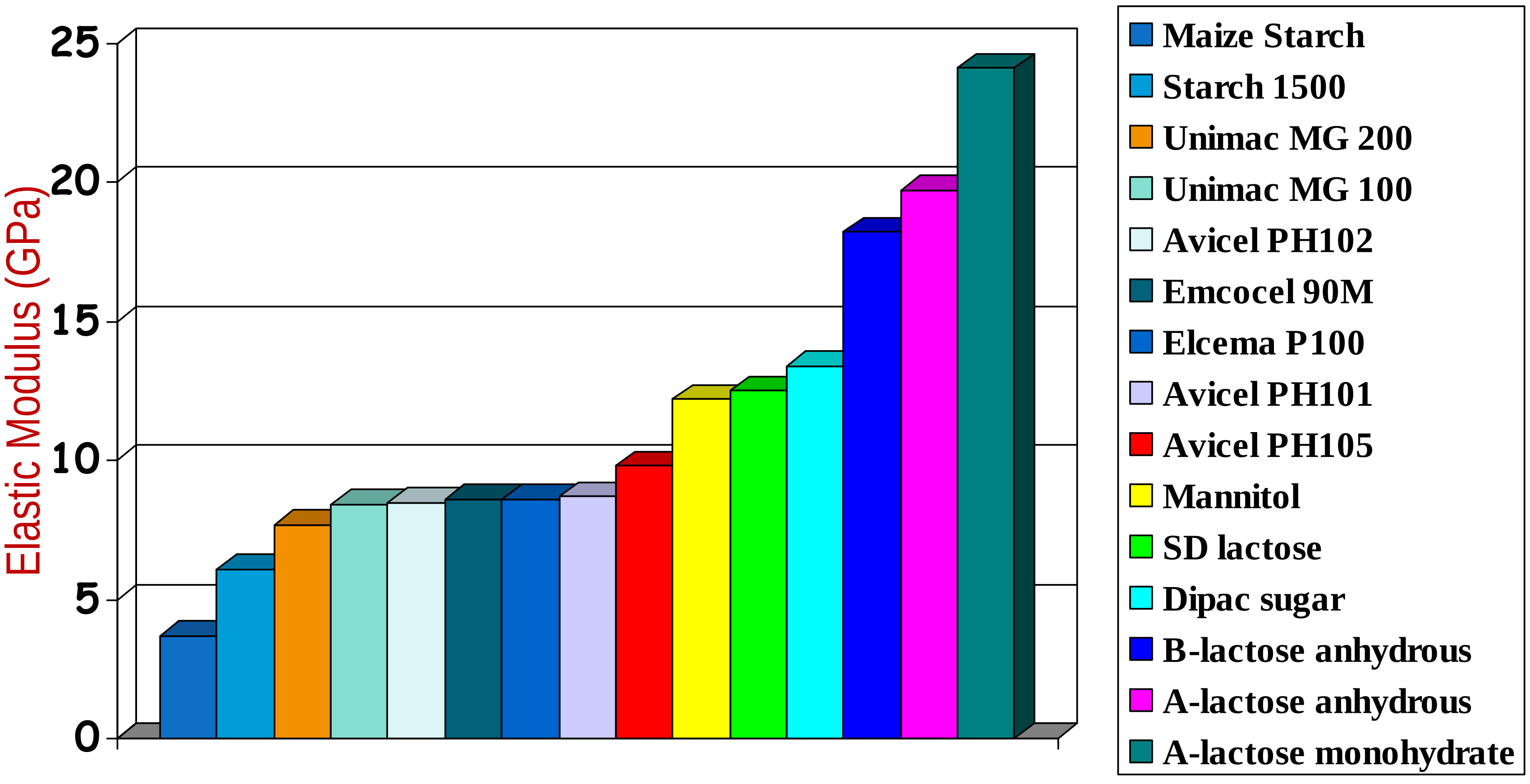
Young’s Modulus

For a a constant value of stress, a smaller Young’s modulus value will result in more deformation (strain) than a high Young’s modulus value, i.e.,a greater amount of elastic recovery occurs and lower tablet strength is expected due to structural failure (breakage of bonds)



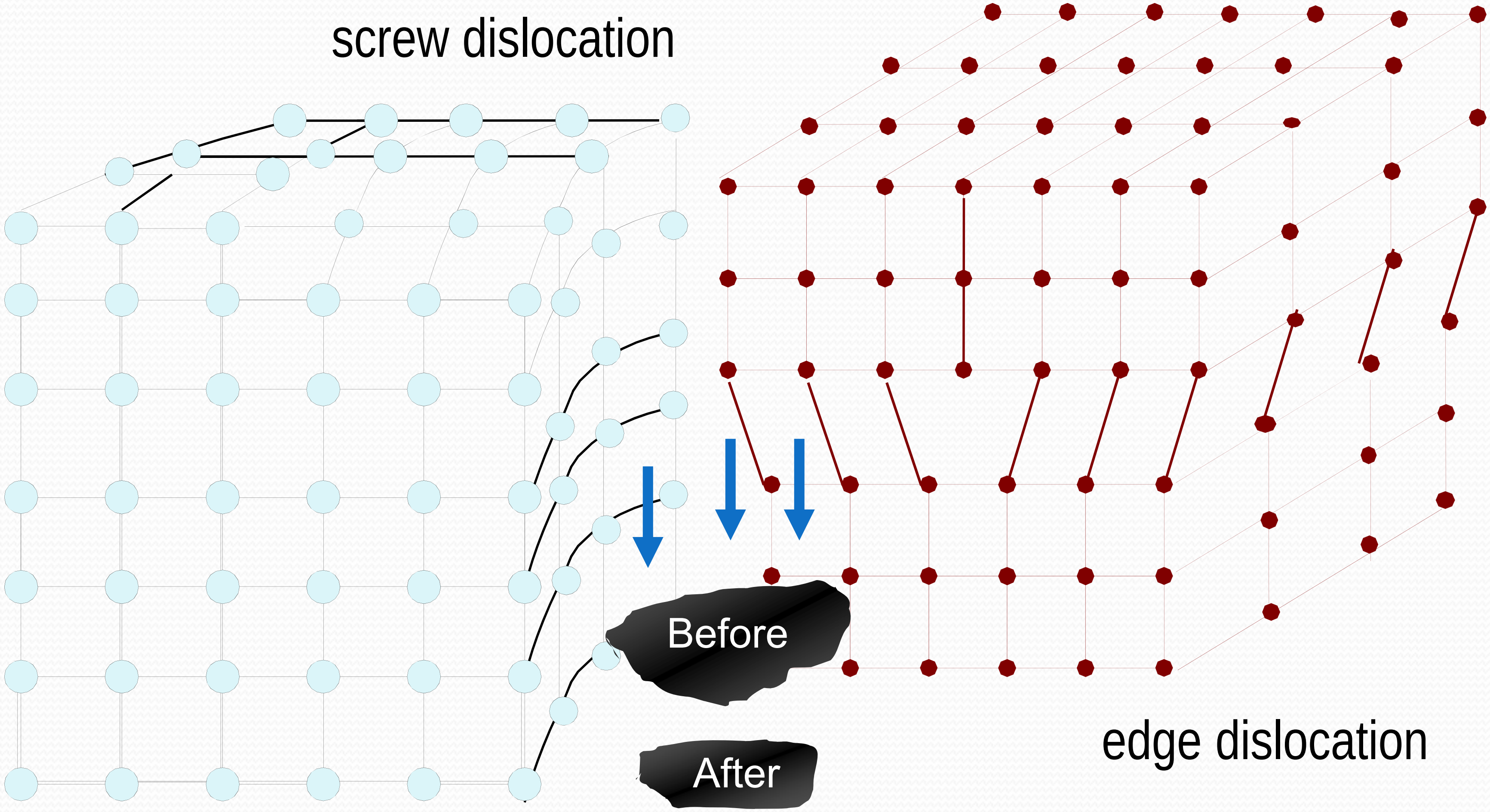


Young’s Modulus



Plastic Deformation

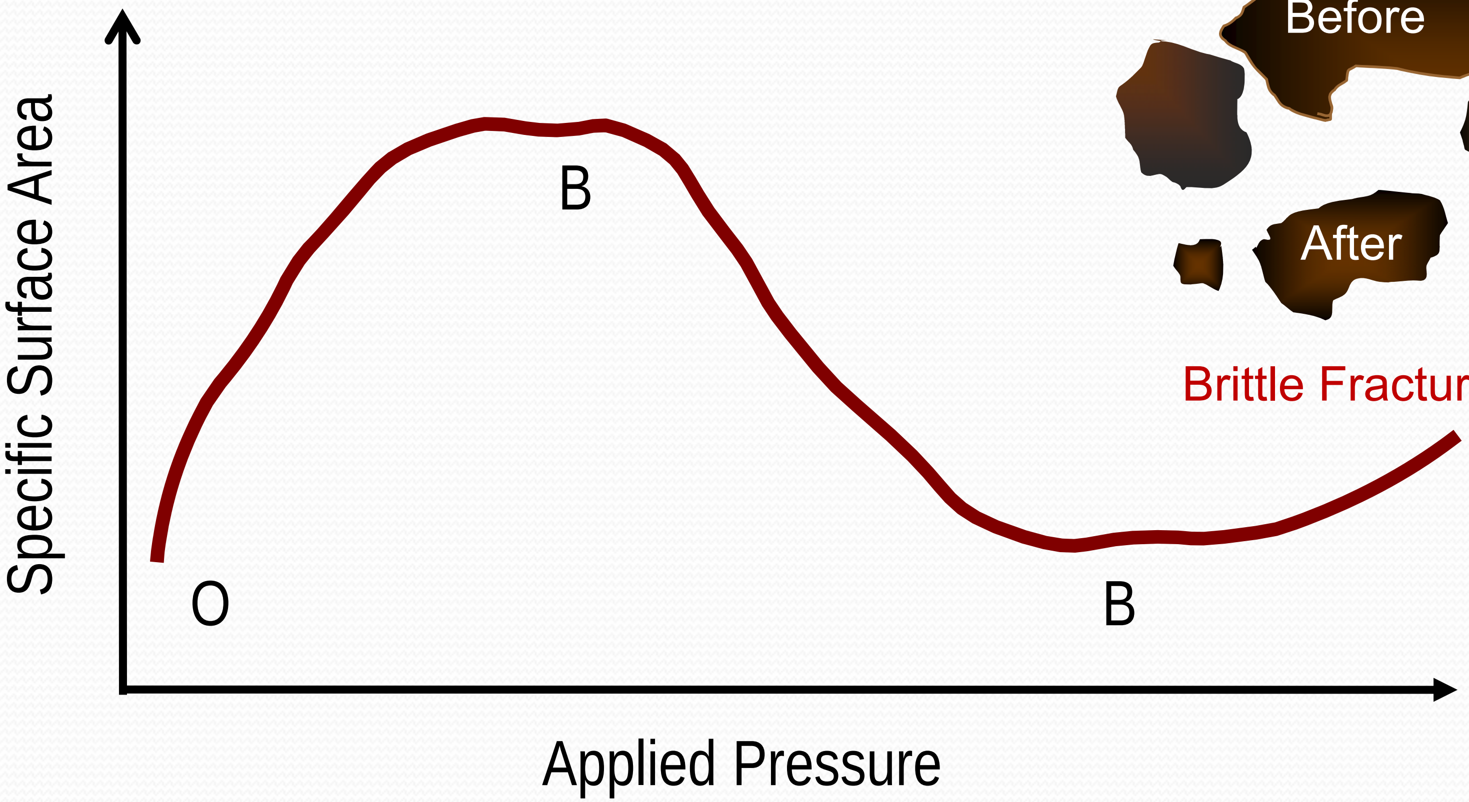
occurs primarily by the movement of crystal imperfections

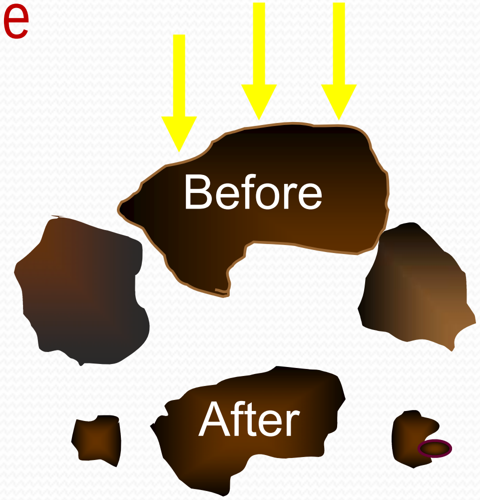


Plastic or Viscous

Fragmentation

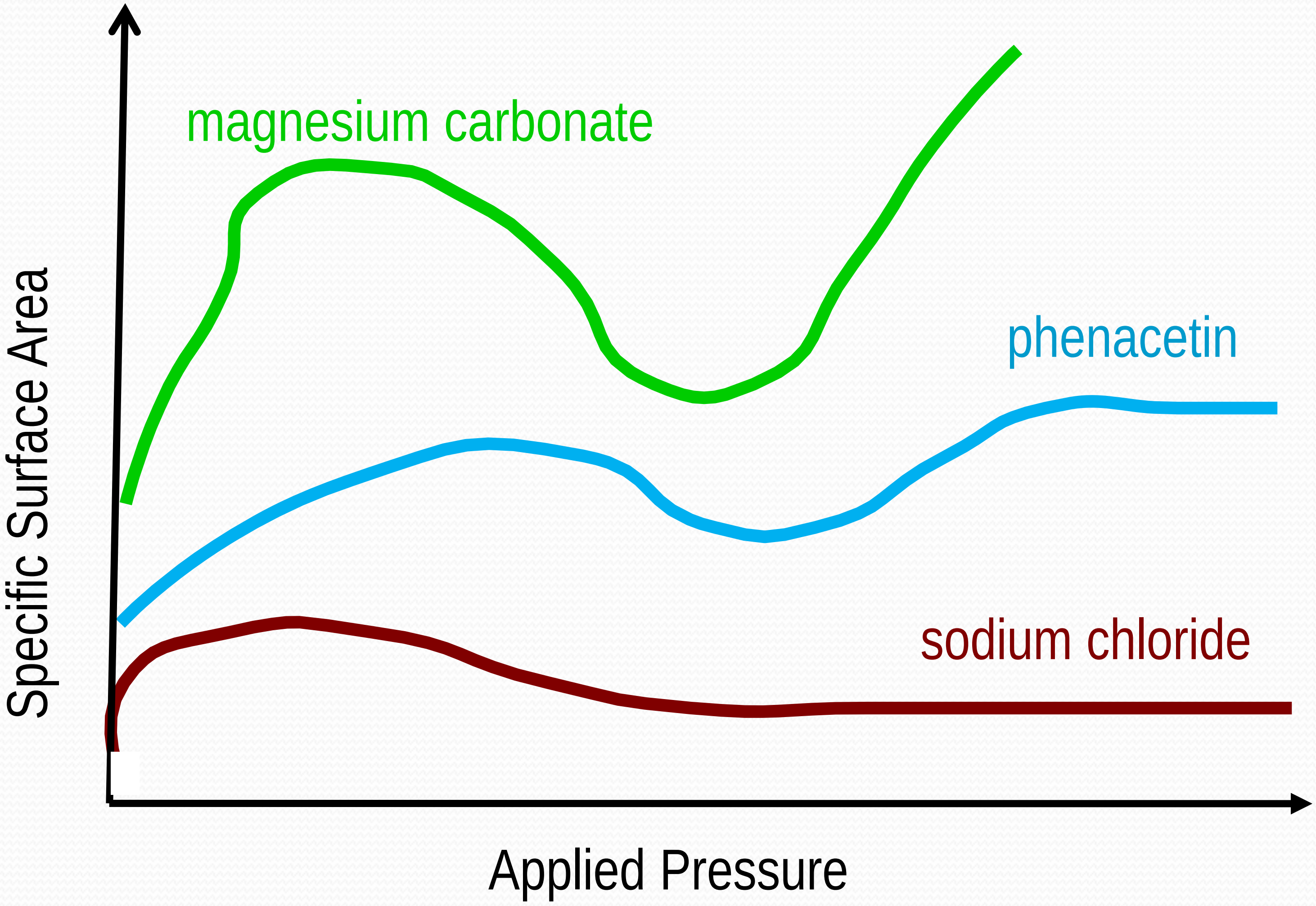
is the separation of a body under stress into two or more parts and is usually characterized as either brittle or ductile



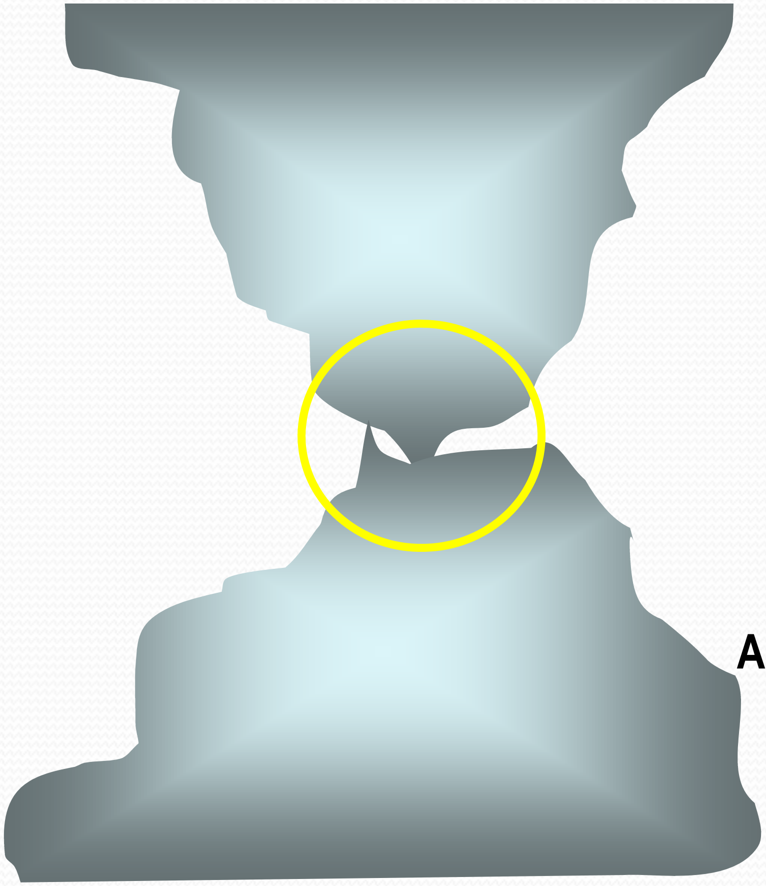


Brittle Fracture

Fragmentation



Fusion - Cold Welding



Pressure = Force/Area

As Area ↓ Pressure ↑

As Pressure ↑ Local Temperature ↑

As Local Temperature ↑ Local Meting may occur

As Local Melting occurs Area ↑, Pressure ↓ and Temperature ↓ and COLD WELDING occurs as the over all tablet temperature is relatively low during this process.

Temperature changes during tabletting

Magnitude of temperature increase depends on:

- Frictional Effects
  - Type of material
  - Lubricant efficiency
- Magnitude of Compaction Forces
- Machine Speed

Typical temperature increase is from 4C ° to 30C°

- The estimated transient temperatures are maximum at the end of compaction at the center of the tablet and close to the die wall next to the powder/die interface [Ref: "Temperature evolution during compaction of pharmaceutical powders", Antonios Zavaliangos et al., Published Online: 29 Oct 2007 (J. Pharm. Sci)]

As tablet temperature increases:

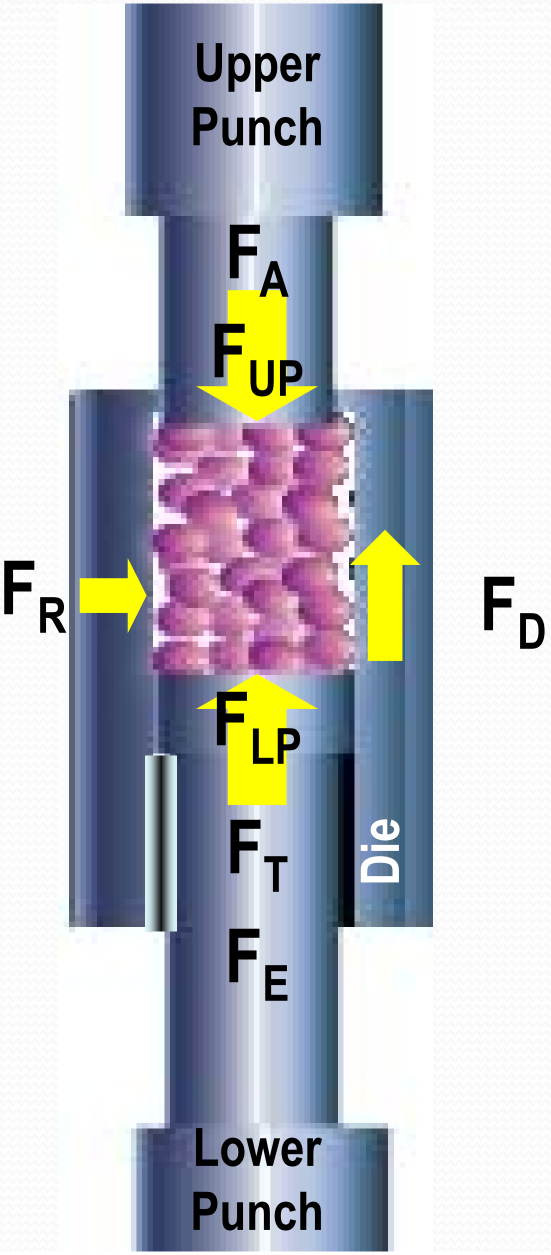
- Stress relaxation increases
  - Plasticity increases
  - Elasticity decreases

Main Factors Governing Tabletting

1. Intrinsic Material Properties
    a) Mechanical nature of the material to be tabletted, i.e., viscous, plastic, or elastic.
    b) Material properties, i.e., values of its viscosity, plasticity, hardness etc.
    c) Properties and amounts of additives, lubricants and binders
2. Particulate Properties
    a) Mean size and size distribution
    b) Shape
    c) Agglomerate porosity
    d) Moisture Content
3. Applied Load
    a) Amount
    b) Rate (of load application and removal)
4. Die Geometry
    a) Length
    b) Diameter
    c) Shape complexity, regions of different depth or thickness, etc.

Compaction Parameters
and
Common Equations

Compaction Parameters



CRITICAL PARAMETERS

FORCE
DISPLACEMENT
TIME

- ☐ punch displacement (UP & LP)
- ☐ machine operating speed
- ☐ pre-compaction force
- ☐ main-compaction force
- ☐ die-wall force
- ☐ UP pull up force
- ☐ LP pull down force
- ☐ ejection force
- ☐ scrape off force
- ☐ die & punch temperature
- ☐ miscellaneous

Compaction Equations

Year	WORKER	EQUATION
1923	Walker	$V_r = C - K \log P_a$
1930	Athy	$(V-V_n)/V = [(V_o - V)/V_o]\, e^{-cP}$
1938	Balshin	$\ln F = -c_1 (V + V_n) + c_2$
1948	Smith	$1/V - 1/V_o = cP$
1956	Kawakita	$(V_o - V)/V_0 = (c_1 c_2 P)/(1 + c_3 P)$
196	J	$\ln P = -c_1 (V_n) c_2$
19		n[1 P

Cooper and Eaton

Lawrence

Torre

Unckel

Wakabayashi

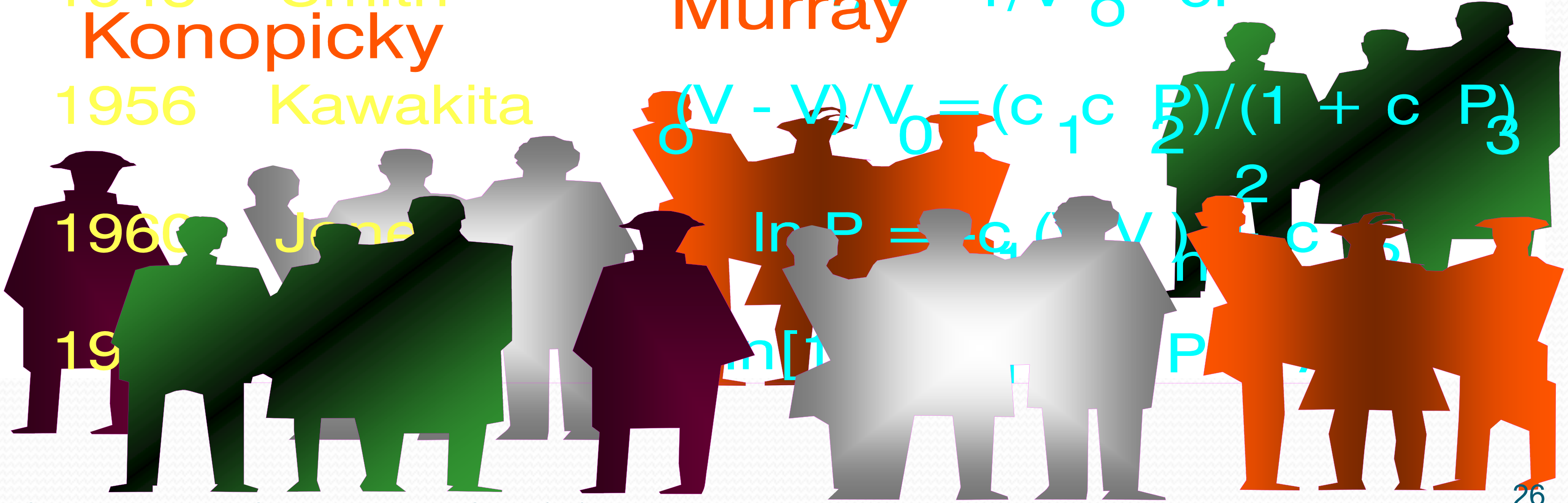
Shapiro

Cooper

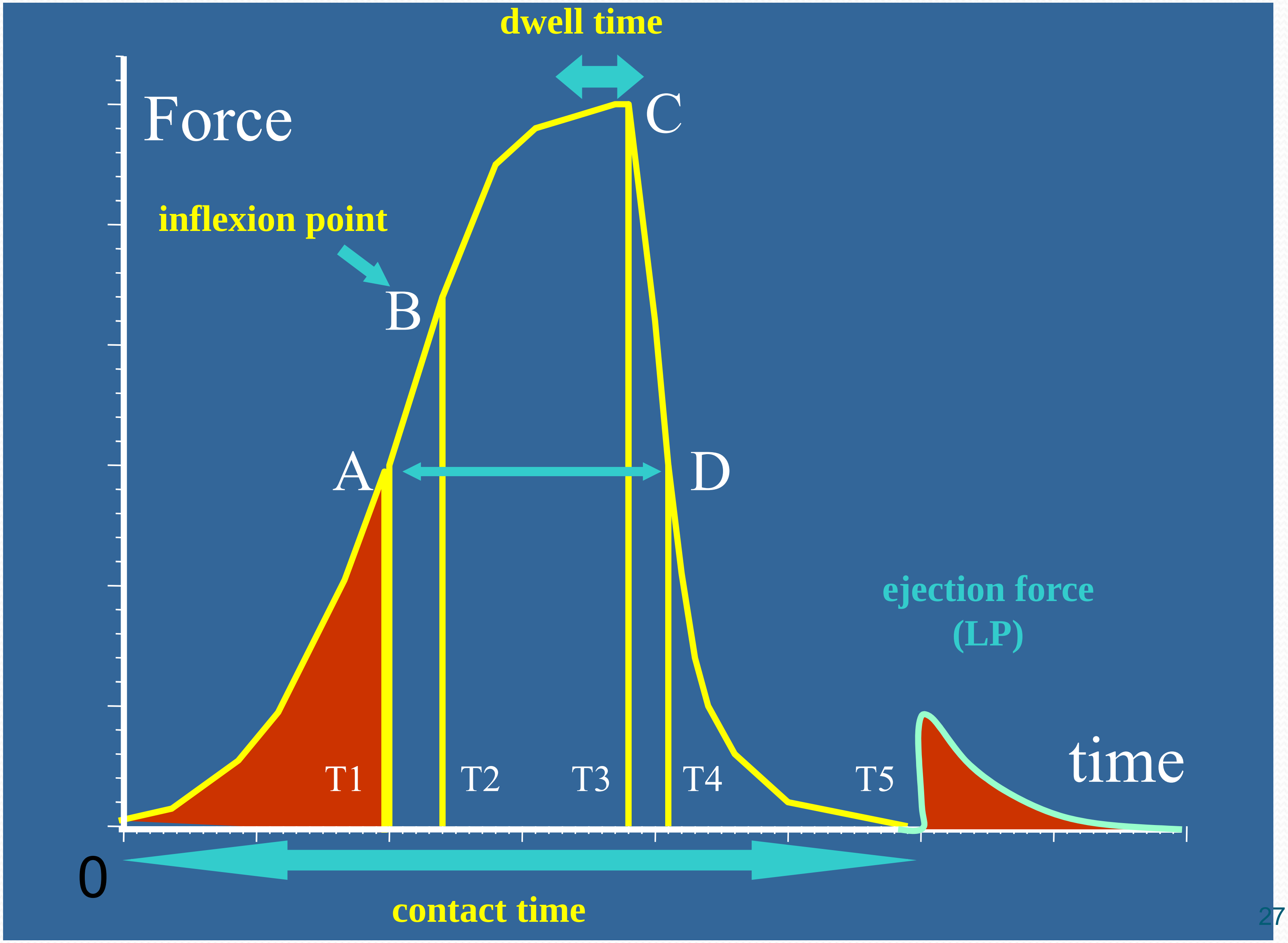
Toor and Eagleton

Murray

Konopicky



F-t Curves:

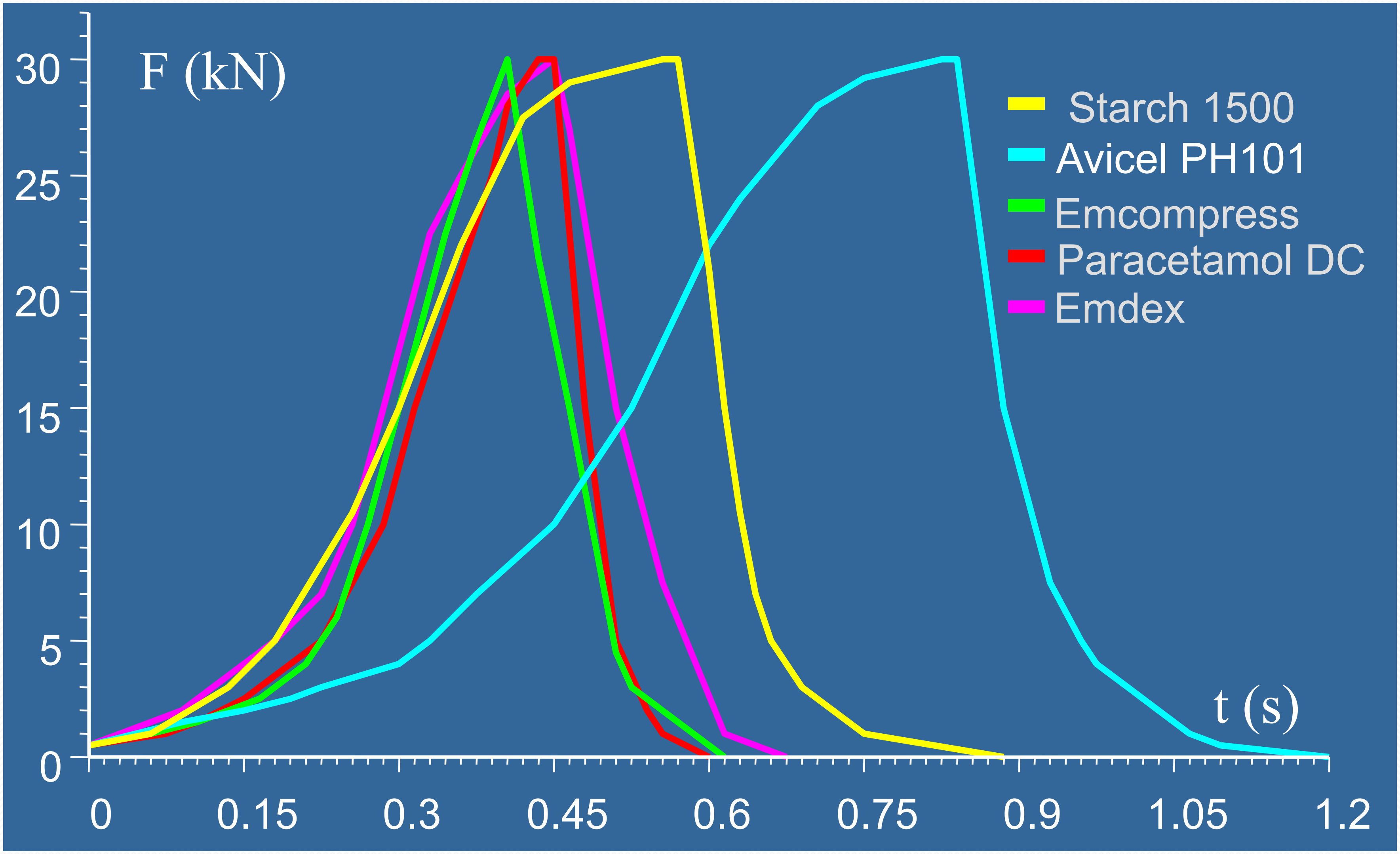

dwell time
Force
C
inflexion point
B
A
D
ejection force
(LP)
T1
T2
T3
T4
T5
time
0
contact time

AUC (kN.s) Values For the F-t Curves:

Material	OAT1	OBT2	OCT3	CT3T4
Avicel PH101	2.41	3.39	10.69	1.73
Starch 1500	1.34	2.11	8.76	1.82
Emdex	1.25	1.73	6.29	1.69
Paracetamol DC	1.13	1.76	4.06	1.76
Emcompress	1.18	1.69	3.61	1.69

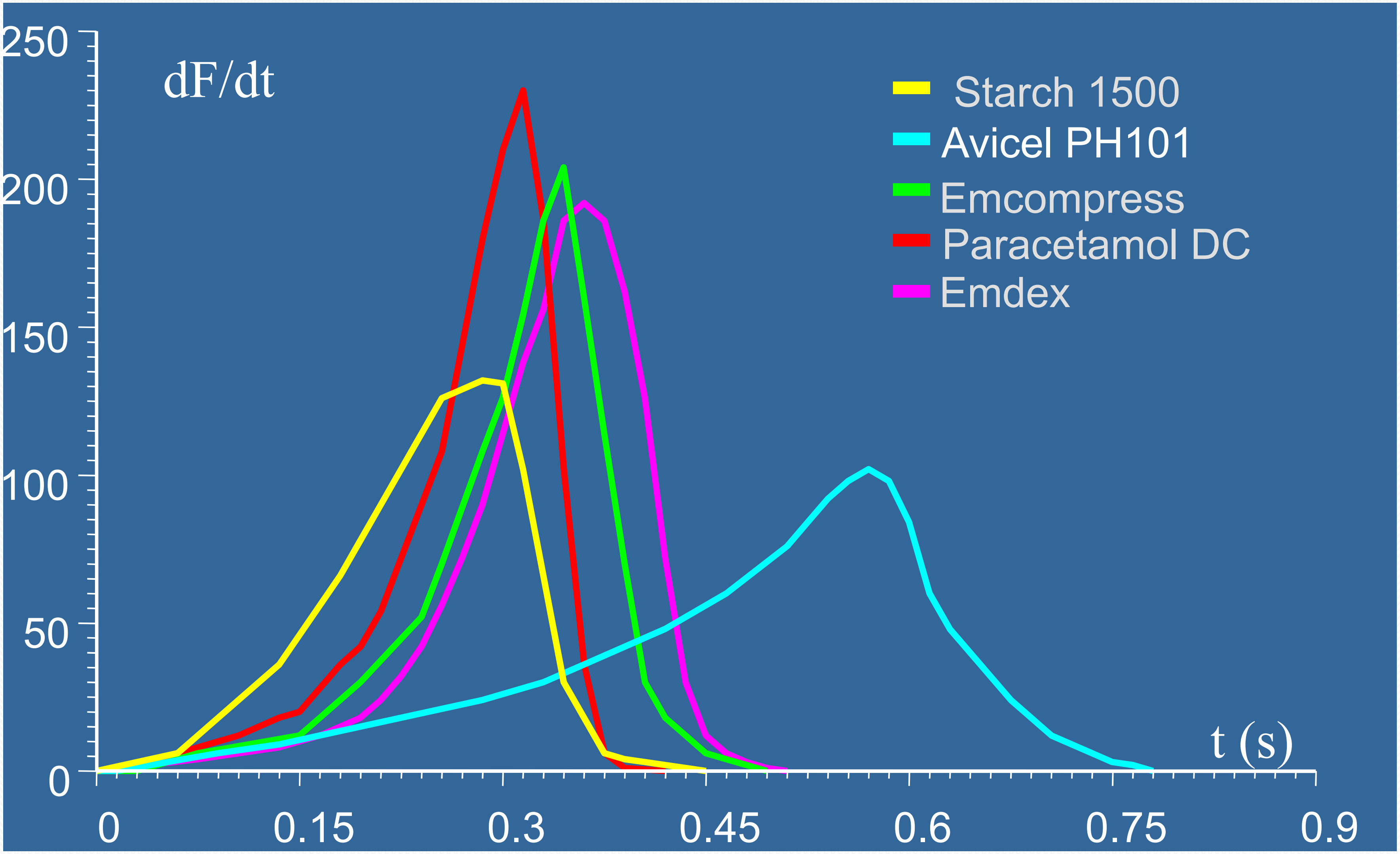
M. Çelik, Ph.D. Thesis, 1984

F-t Curves:



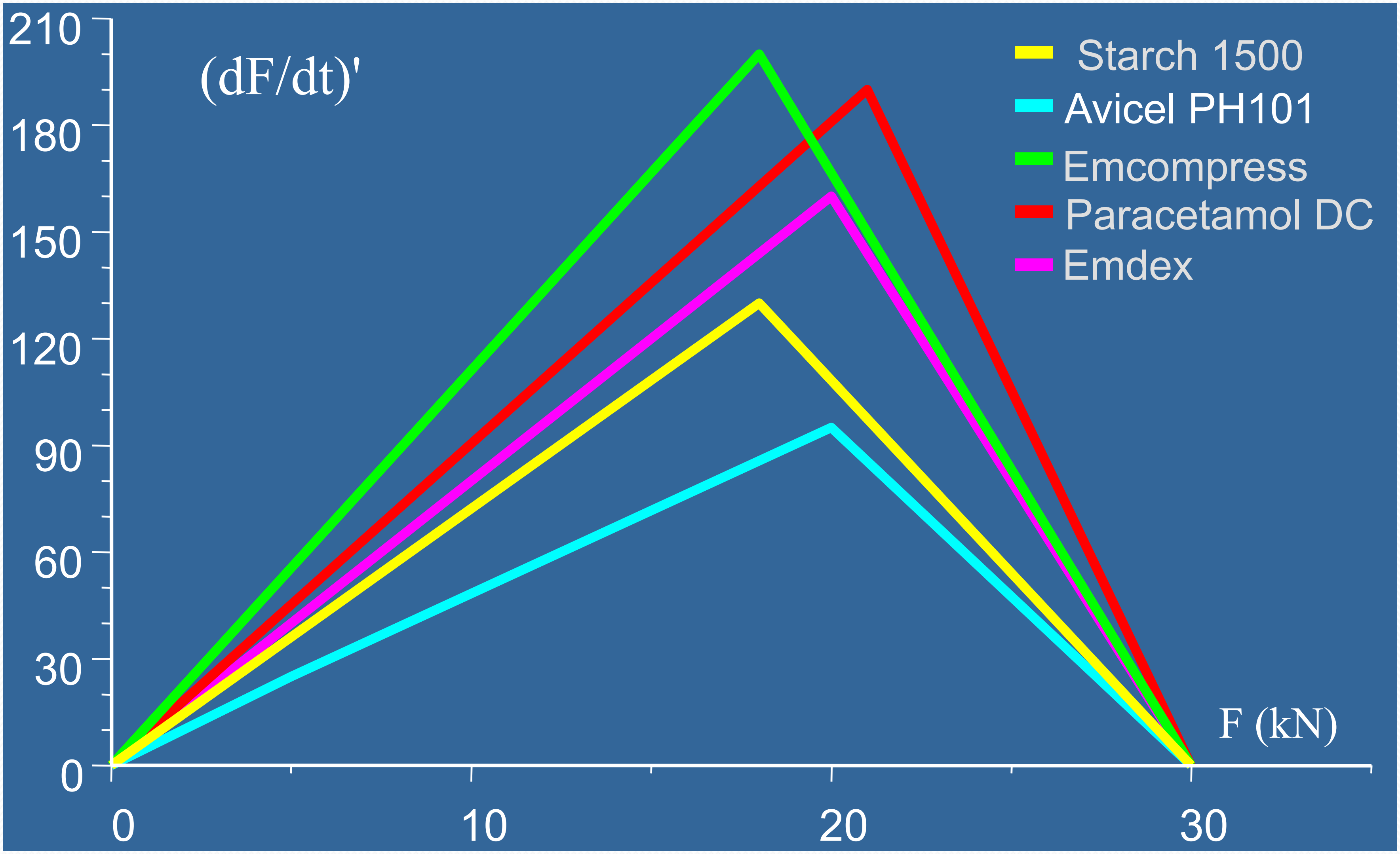
M. Çelik, Ph.D. Thesis, 1984

First Derivative of F-t Curves:



M. Çelik, Ph.D. Thesis, 1984

Second Derivative of F-t Curves:



M. Çelik, Ph.D. Thesis, 1984

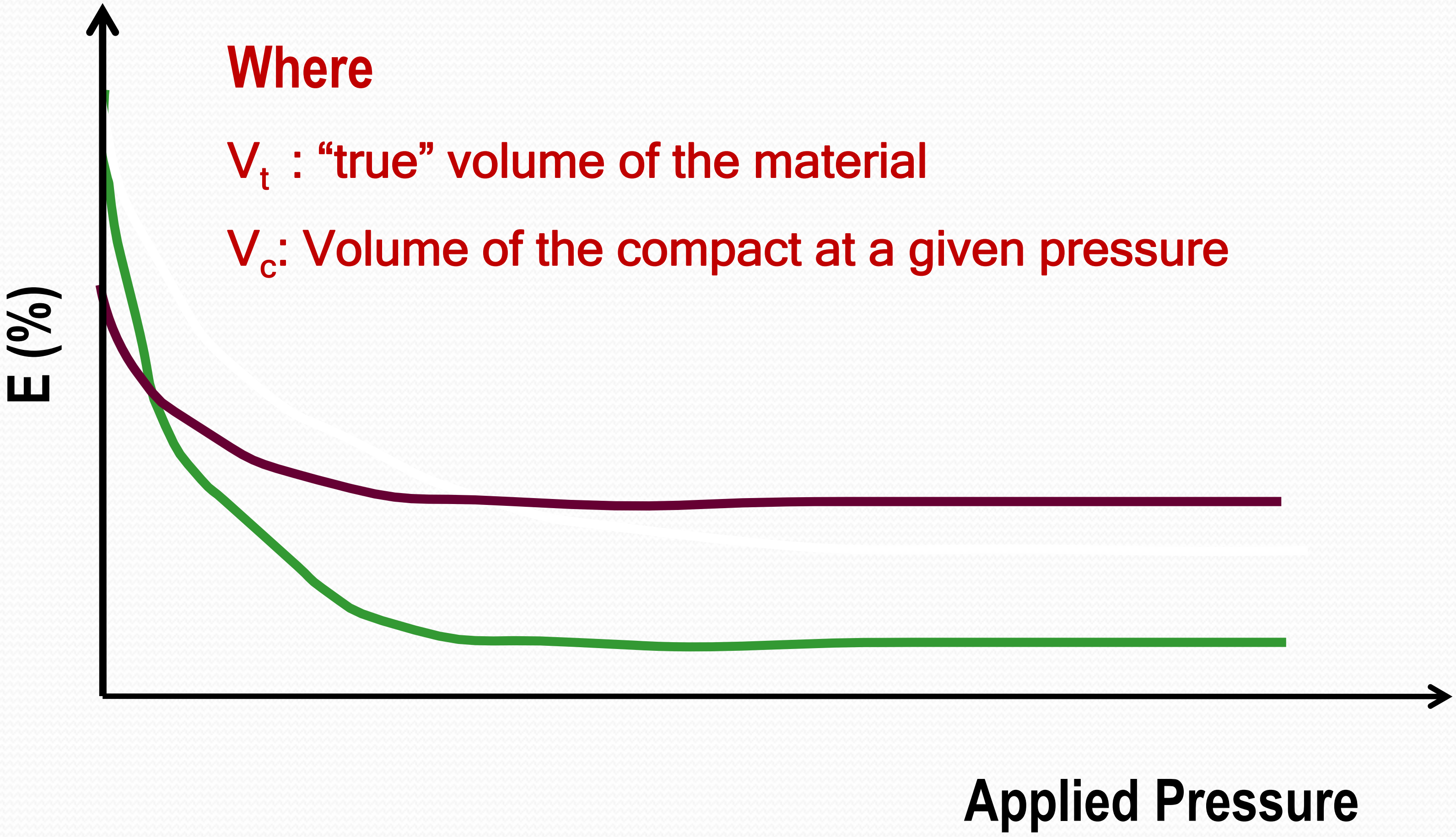
Porosity % Change Plots

$$E\ (\%) = 100 - [\,1 - (V_t - V_c)]$$

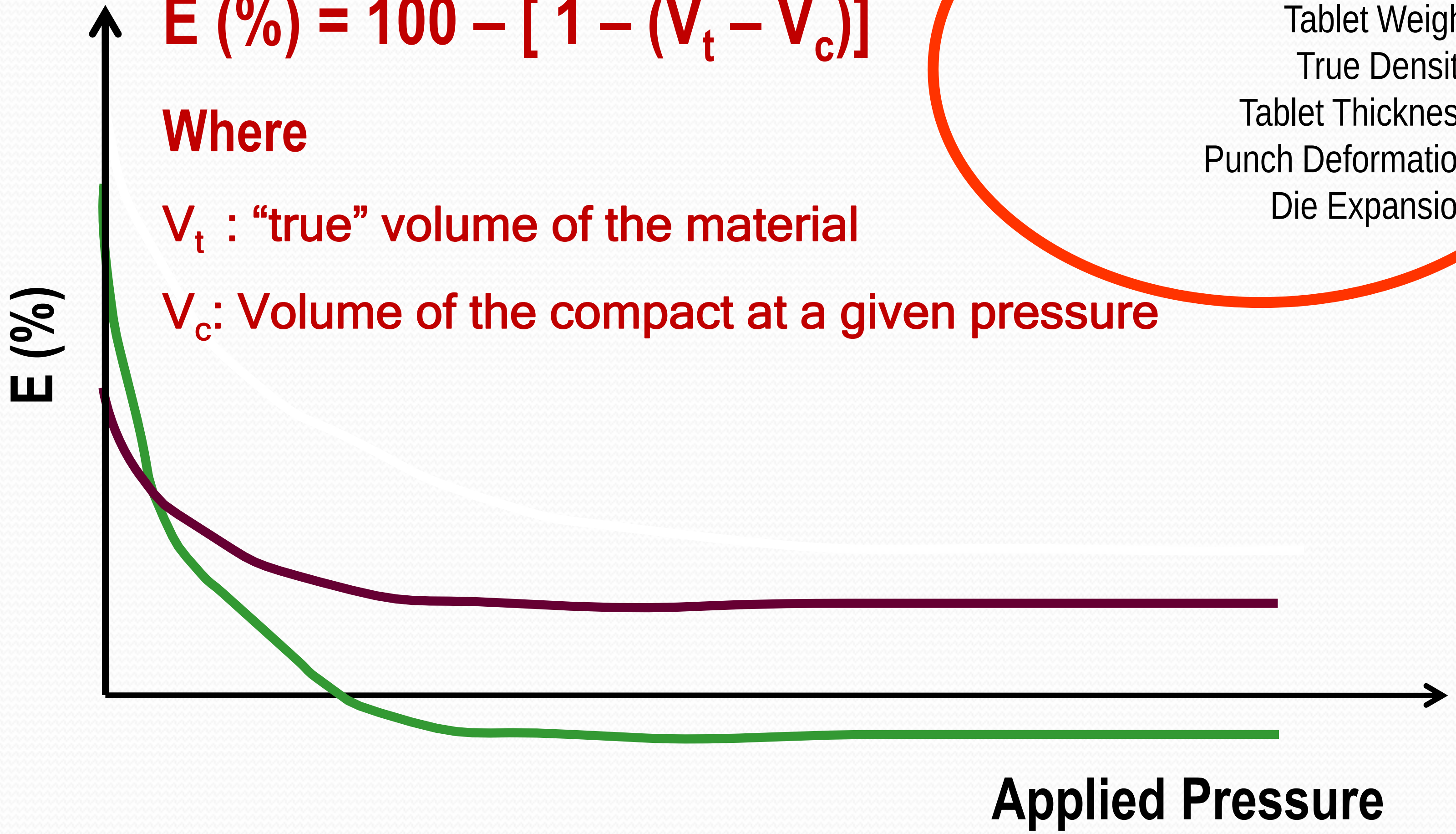
Where

V_t : “true” volume of the material

V_c: Volume of the compact at a given pressure



Porosity % Change Plots



$$E(\%) = 100 - [\,1 - (V_t - V_c)]$$

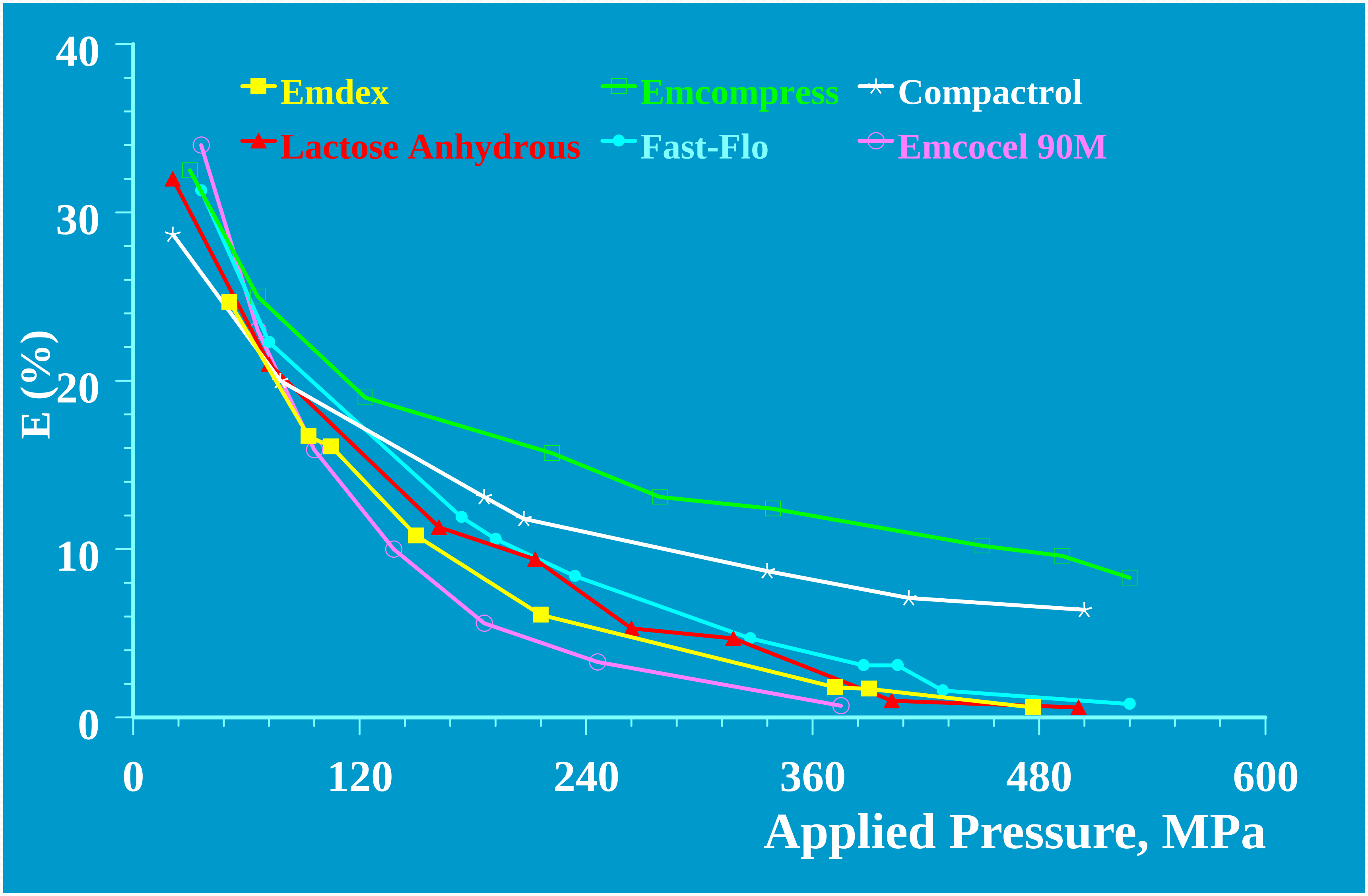
Where

V_t : “true” volume of the material

V_c: Volume of the compact at a given pressure

CRITICAL PARAMETERS
Tablet Weight
True Density
Tablet Thickness
Punch Deformation
Die Expansion

Porosity % Plots



100 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

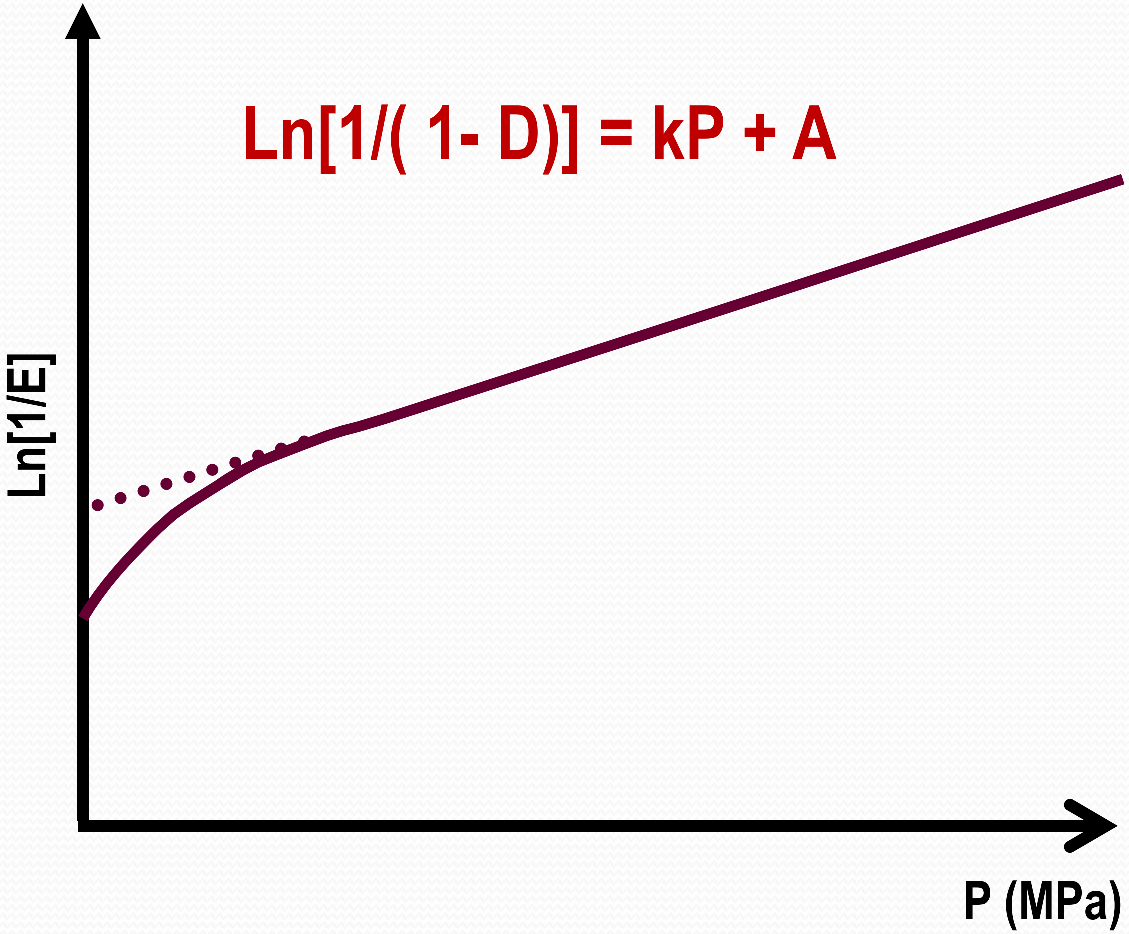
Porosity % Change Plots

Material	$E_{initial}$	E_{min}	$E_{ejected}$	TS_e
Avicel	82	8.3	12.9	15.15
Lactose	63	9.6	10.7	4.78
Emcompress	62	16.5	15.5	3.4
Acetaminophen	83	4.1	---	---

Heckel Plots

Where

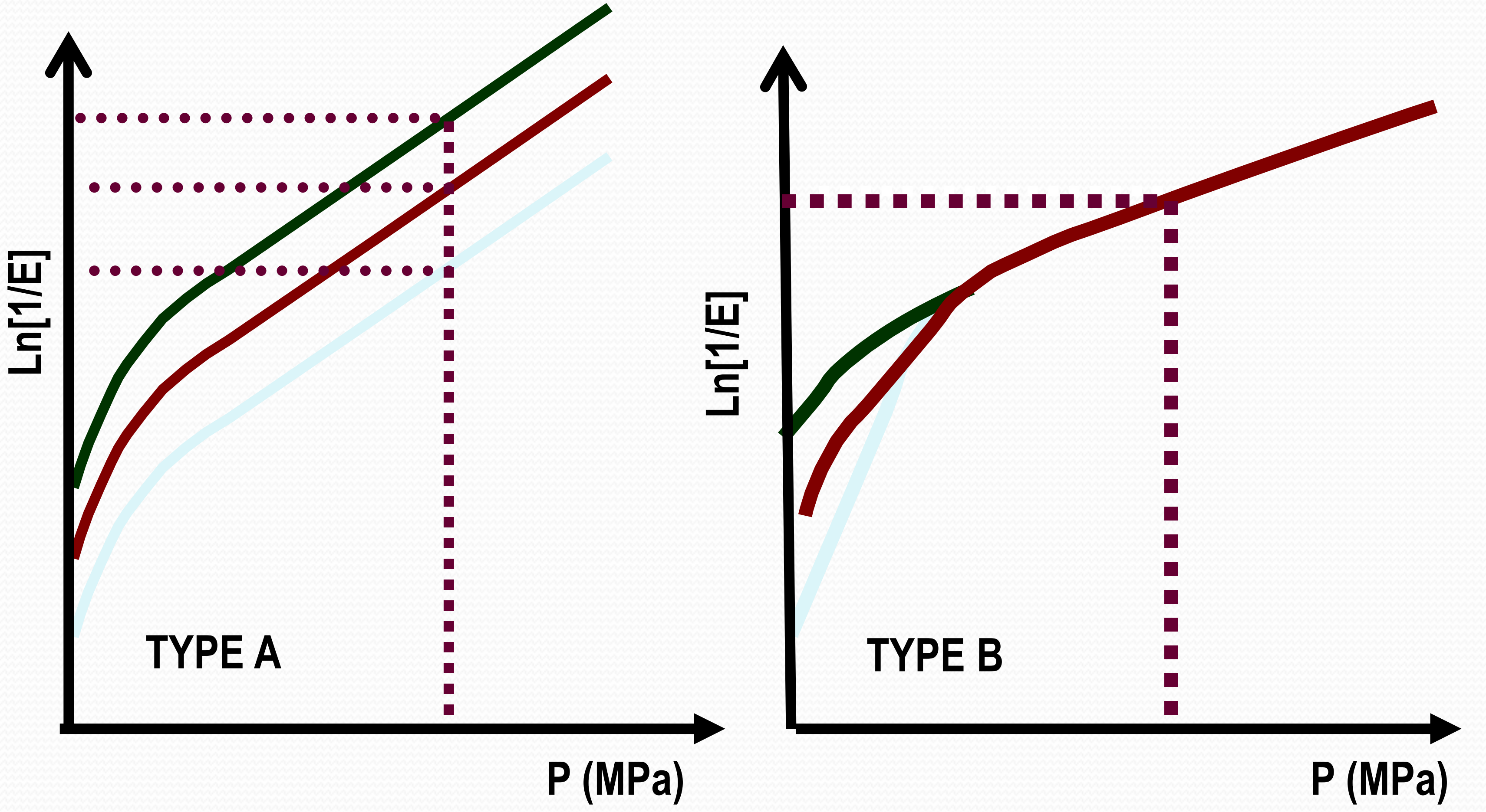
D : Relative Density; k : 1/Yield Stress; P : Applied Pressure; A : Intercept



$$\mathrm{Ln}[1/(1-D)] = kP + A$$

Heckel Plots

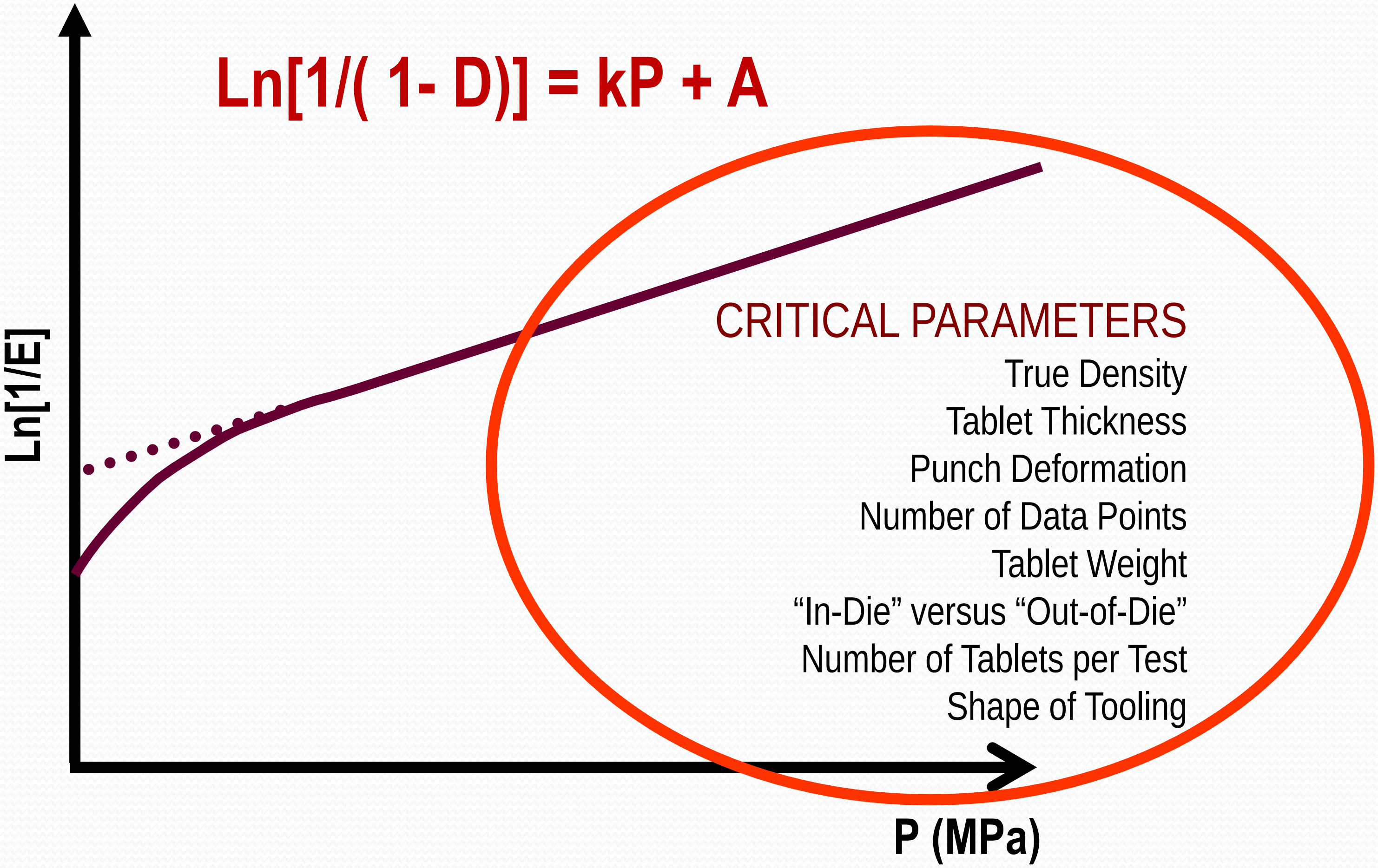
Ln[1/E] = kP + A



Heckel Plots

Where

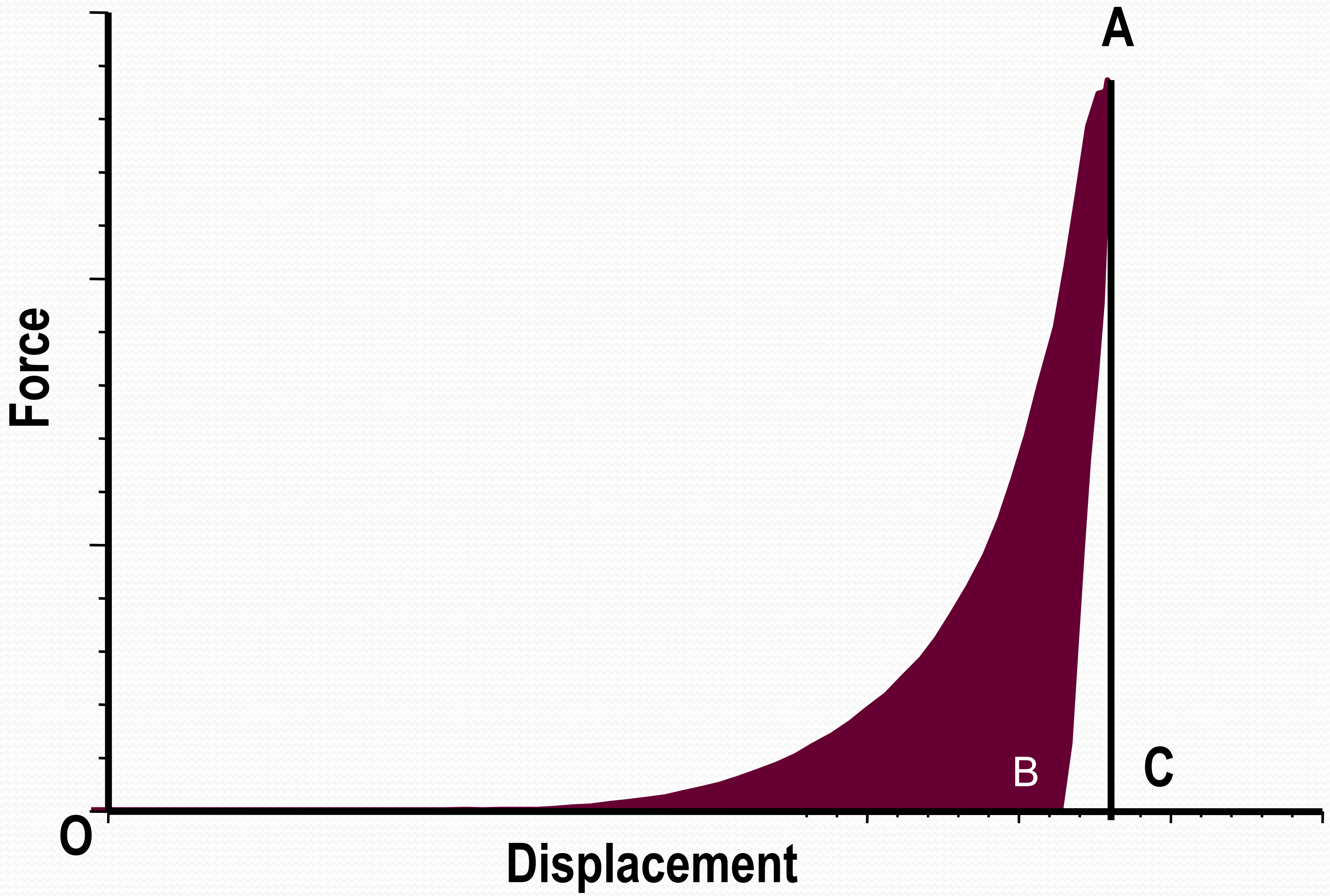
D : Relative Density; k : 1/Yield Stress; P : Applied Pressure; A : Intercept



$$\ln[1/(1-D)] = kP + A$$

CRITICAL PARAMETERS
- True Density
- Tablet Thickness
- Punch Deformation
- Number of Data Points
- Tablet Weight
- “In-Die” versus “Out-of-Die”
- Number of Tablets per Test
- Shape of Tooling

F-D Curves

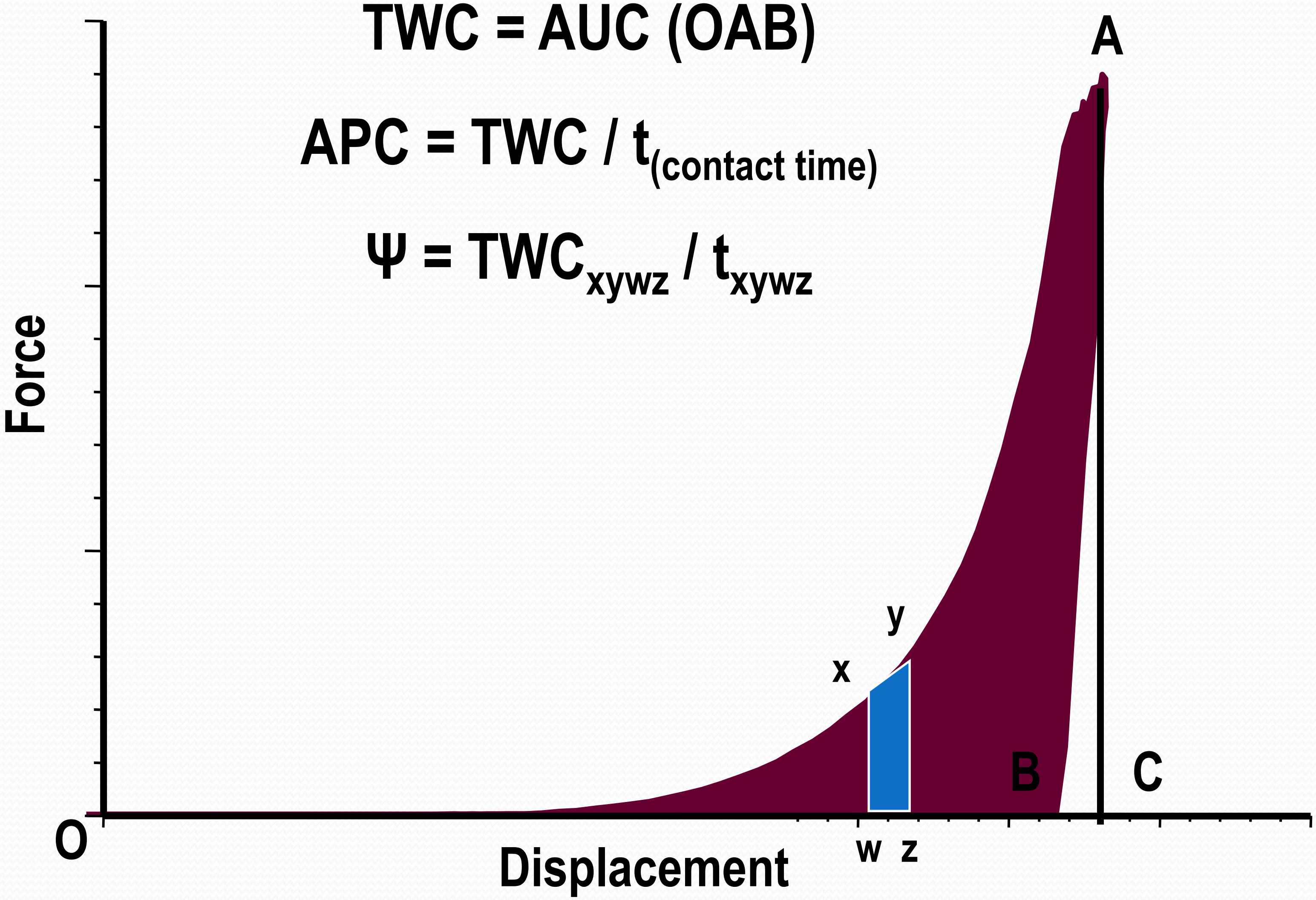


F-D Curves

$$TWC = AUC\ (OAB)$$

$$APC = TWC / t_{(contact\ time)}$$

$$\Psi = TWC_{xywz} / t_{xywz}$$



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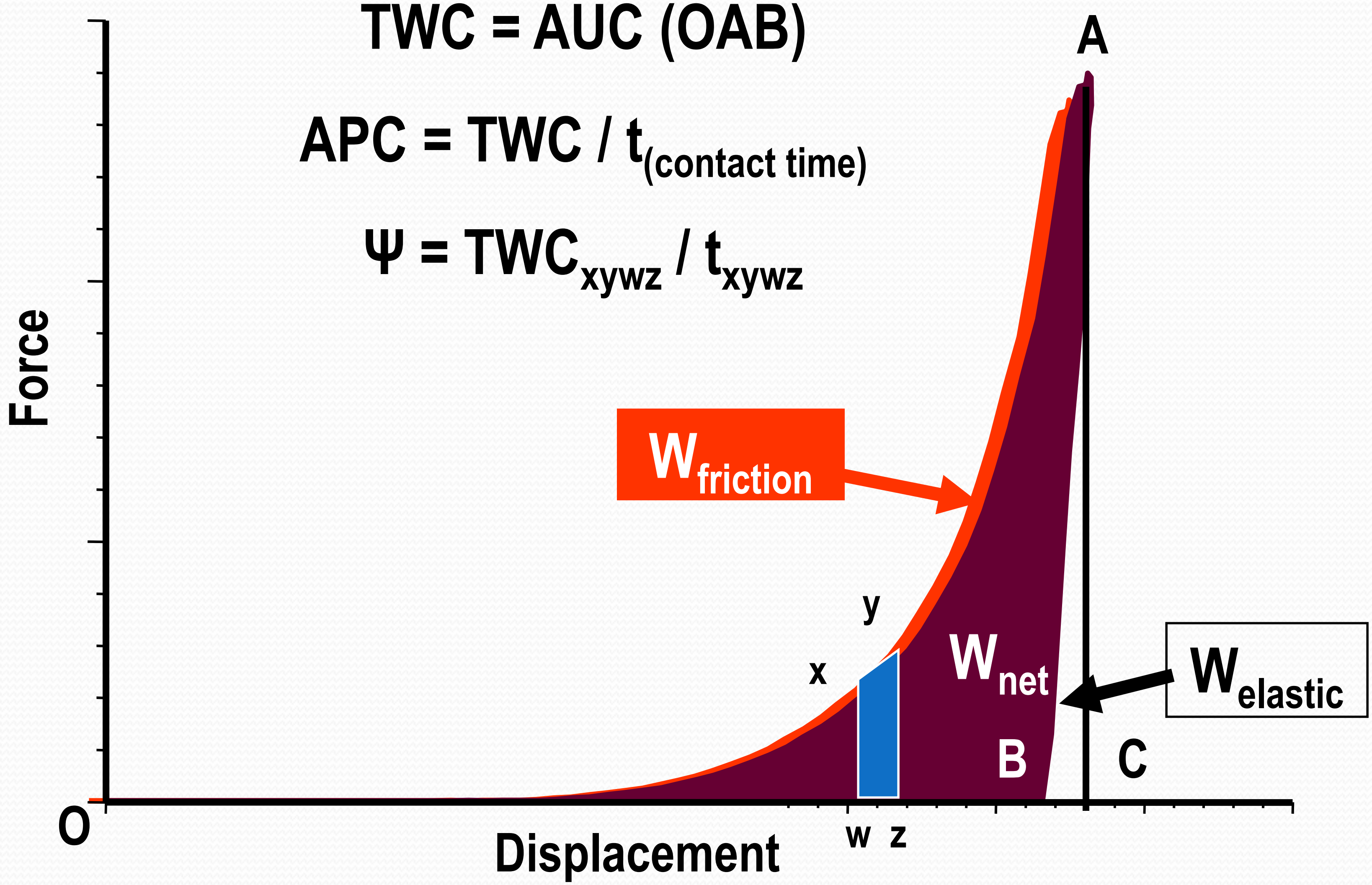
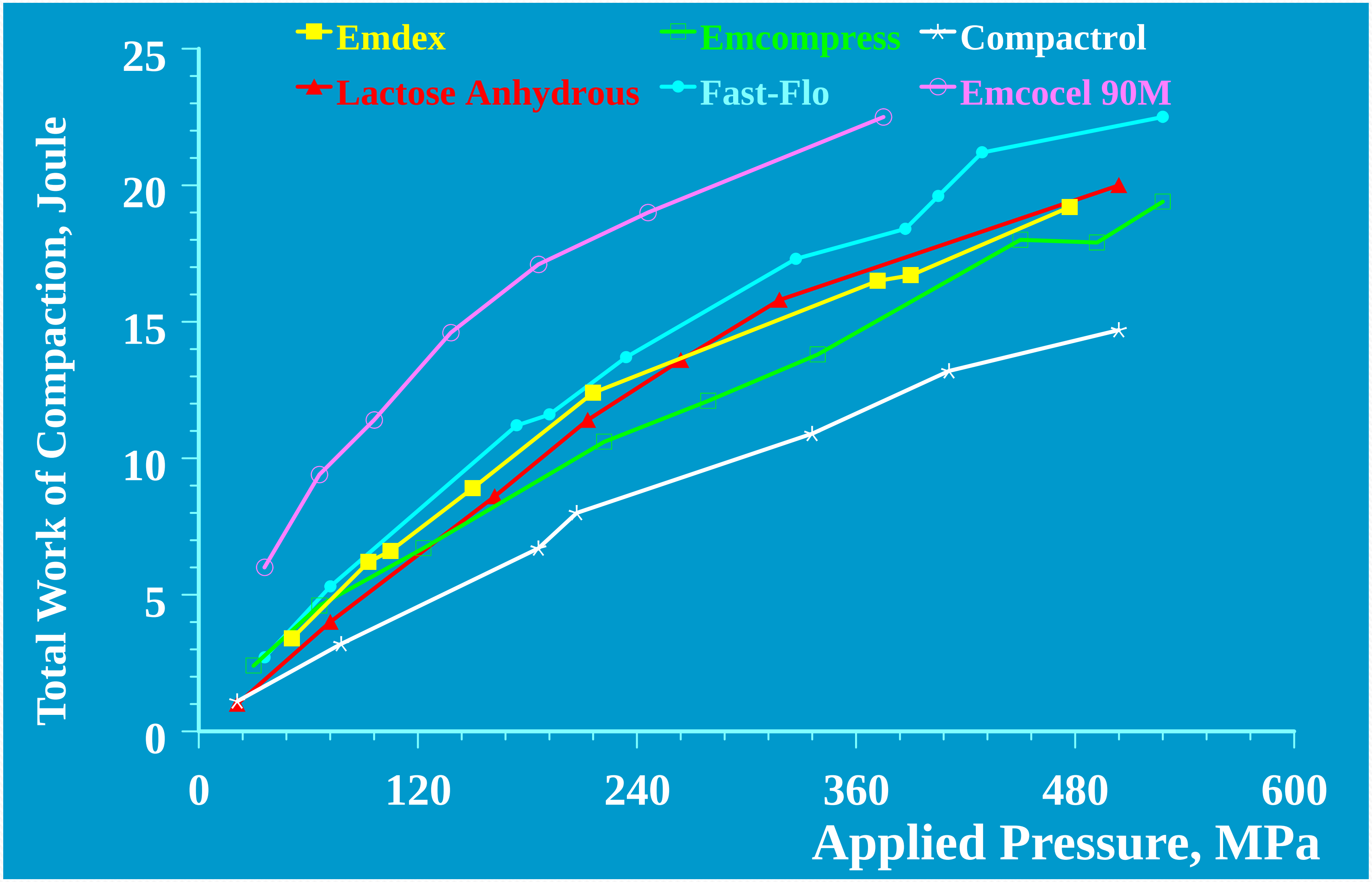


TWC vs P Plots



100 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

Energy (Joule) expended during compaction of 400 mg sulphatiazole granulation

Part of Compaction	Unlubricated	Lubricated
Compression	6.28	6.28
Die wall friction	3.35	negl.
Upper punch withdrawal	5.02	negl.
Tablet ejection	21.36	2.05
Totals	36.00	8.37

Elastic Expansion

$$ER\ (\%) = \frac{H_e - H_c}{H_c} \times 100$$

where

H_c = Height of the compact at P_a

H_e = Height of the compact after ejection

Remarks:

out of die measurements at varying times after ejection

Elastic Expansion: Better to call (Visco-elastic Strain)

$$ER\,(\%) = \frac{H_e - H_c}{H_c} \times 100$$

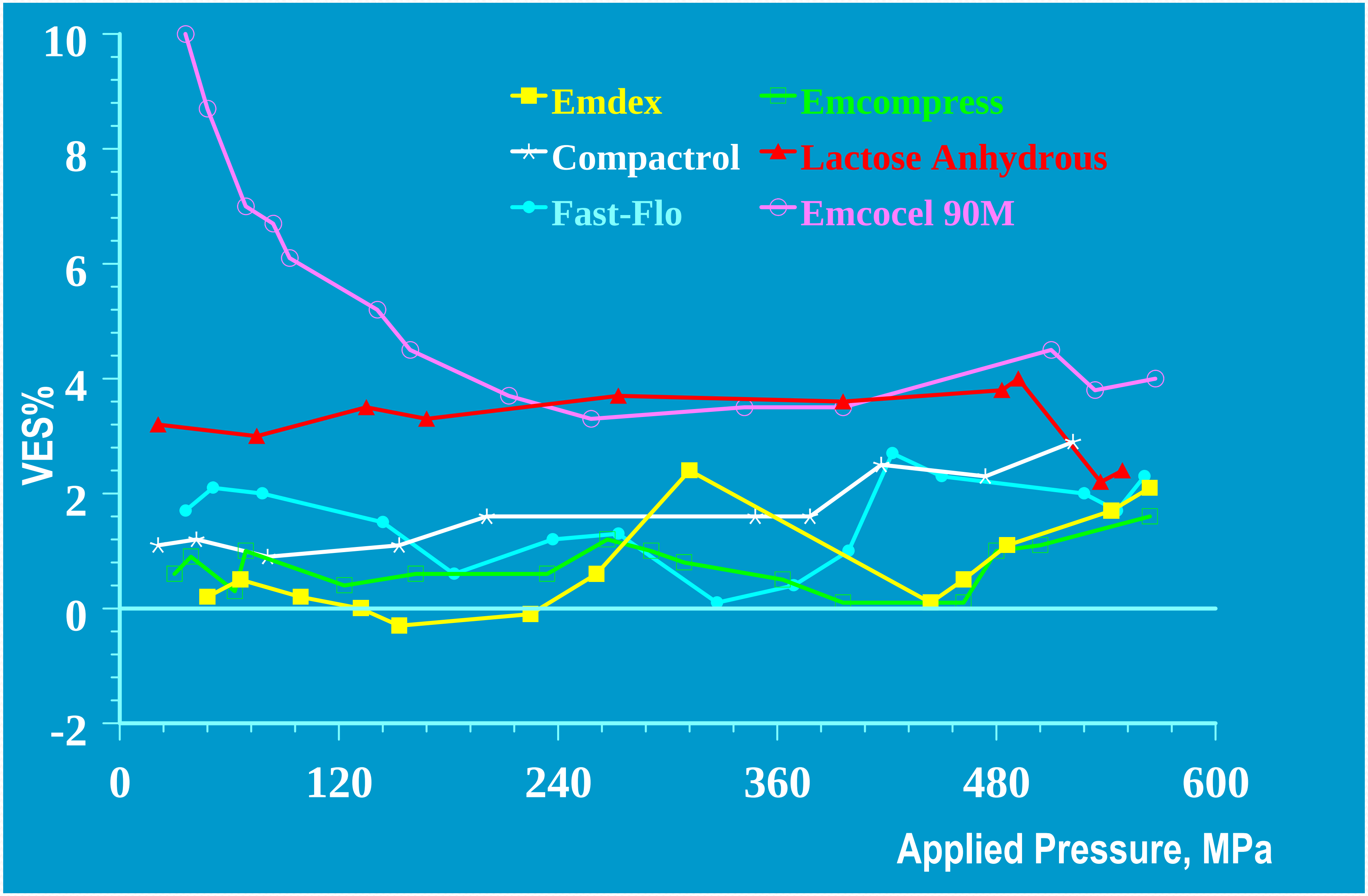
$$VES\,(\%) = \frac{D_e^2\ H_e - D_c^2\ H_c}{D_c^2\ H_c} \times 100$$

where

D_c H_c = Diameter and Height of the compact at P_a

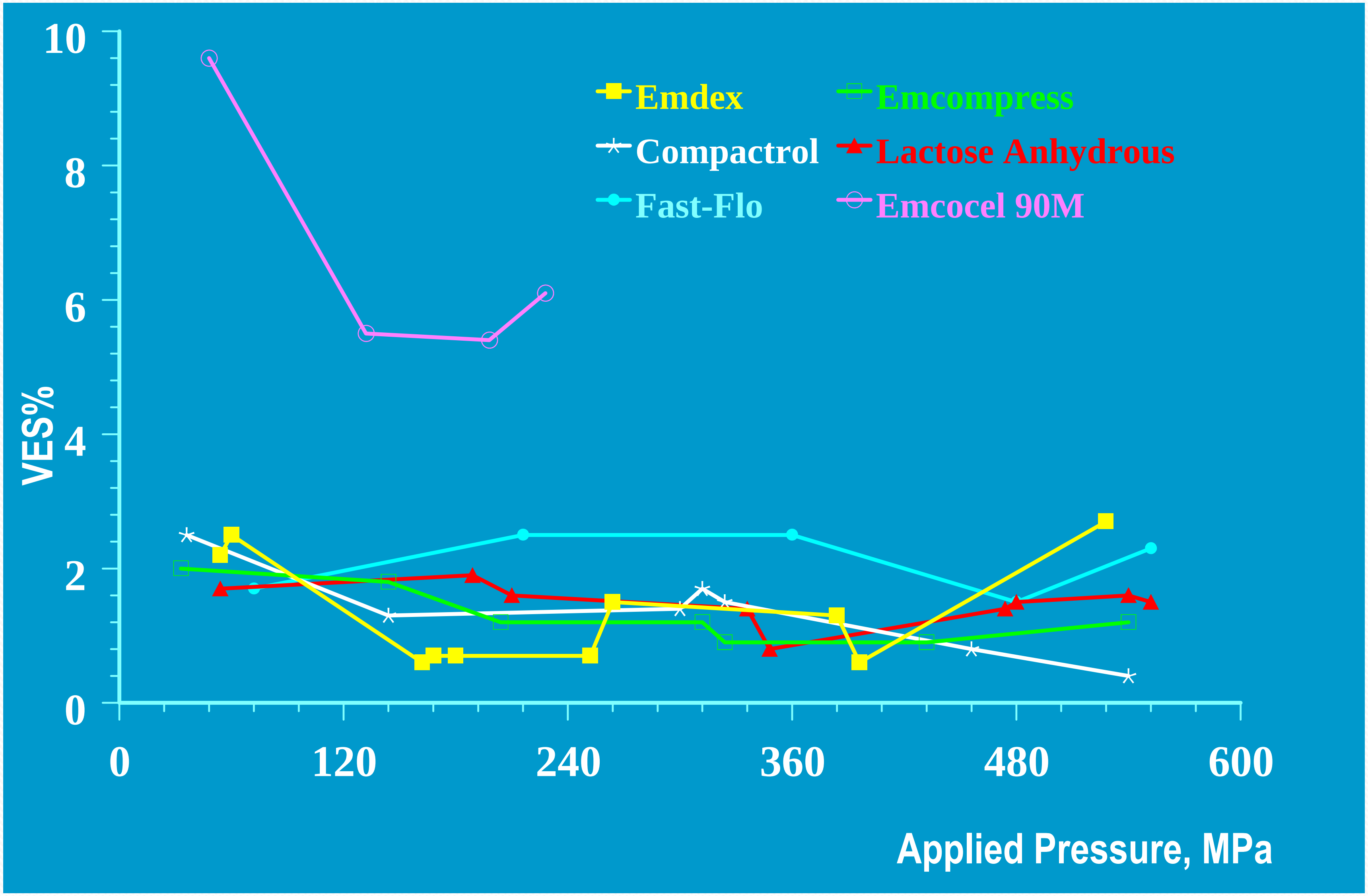
D_e H_e = Diameter and Height of the compact after ejection

VES – Examples (1)



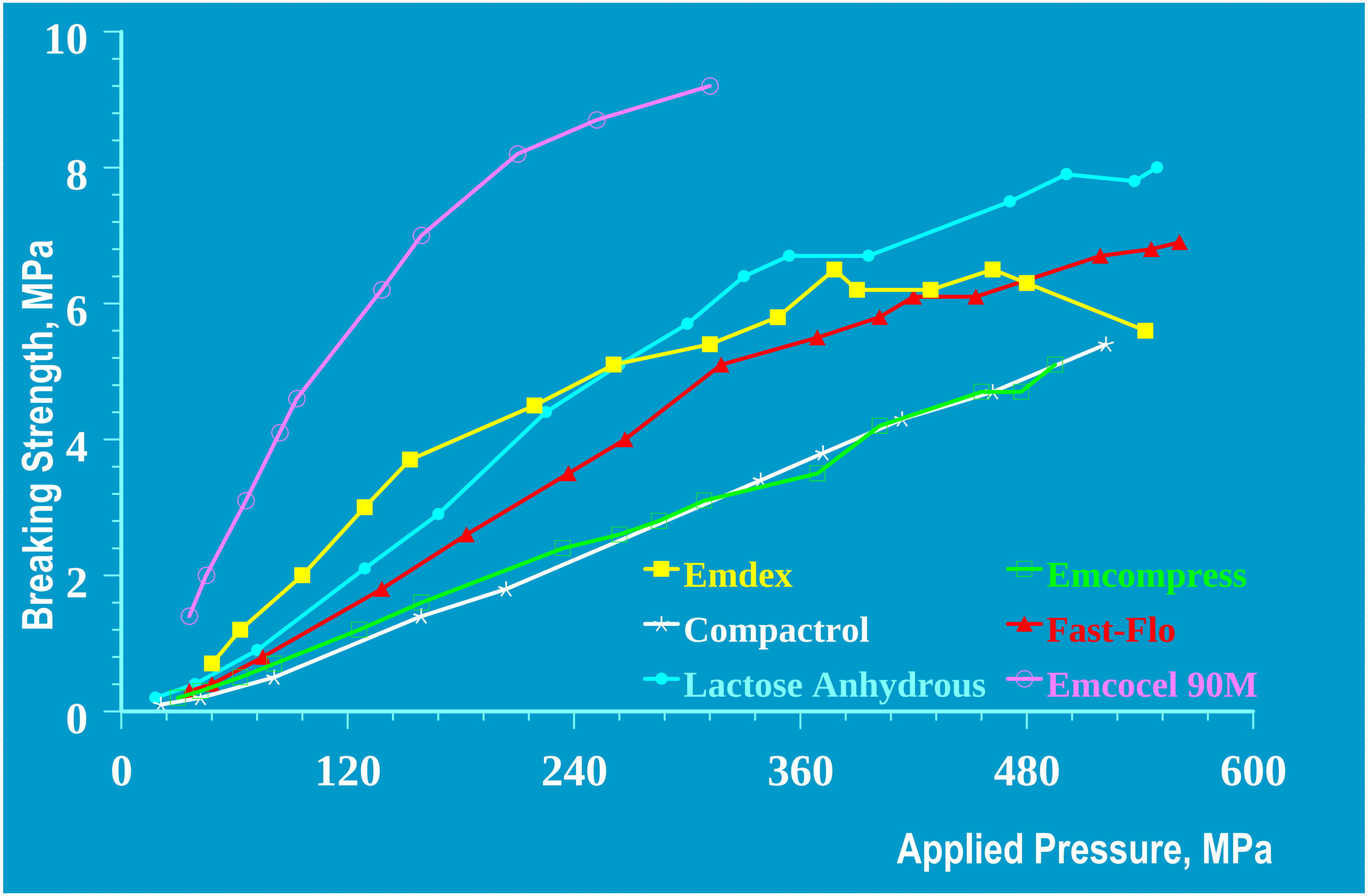
100 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

VES – Examples (2)



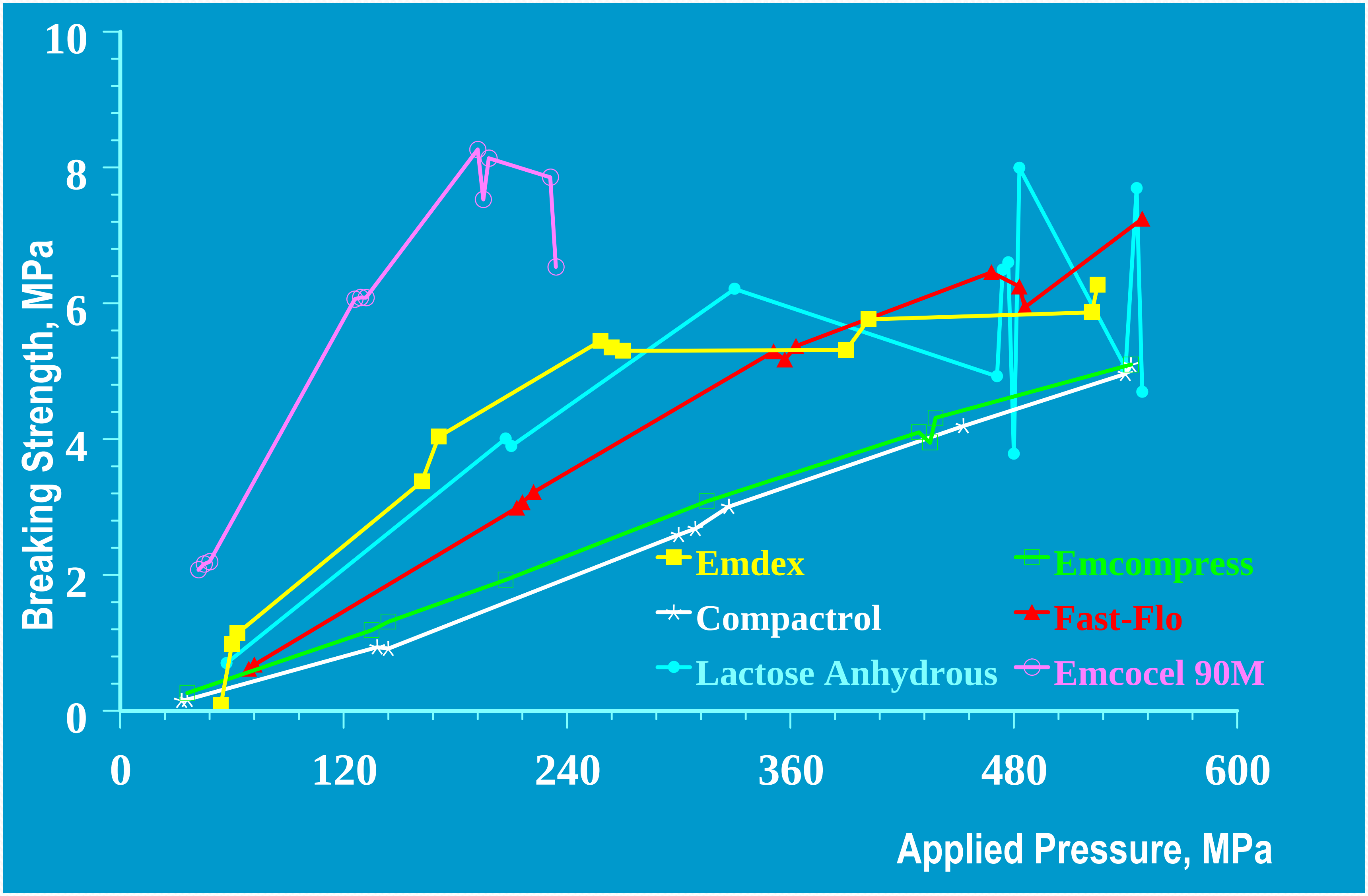
300 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

Breaking Strength Profile (1)



100 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

Breaking Strength Profile (2)



300 mm/sec, 0.5% magnesium stearate, 10 mm, Flat-Faced, Round, BB

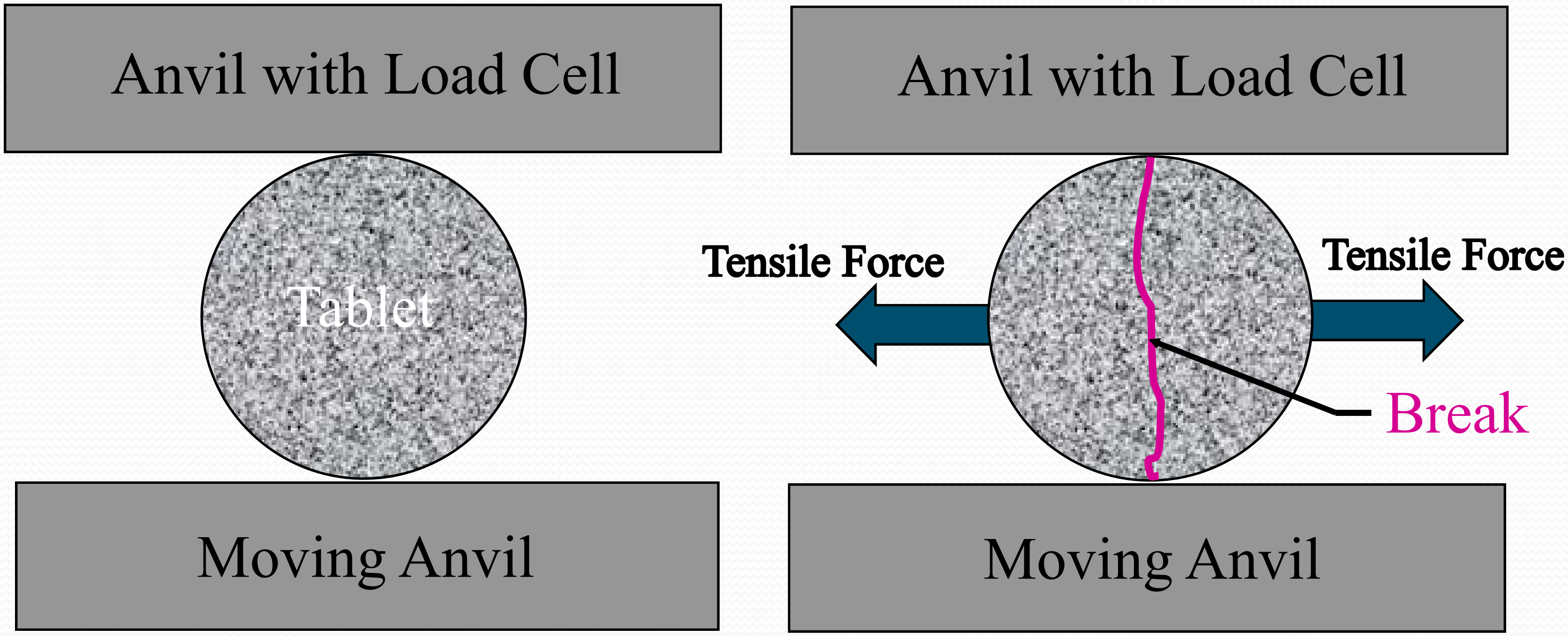
Constant True Volume v. Constant Weight

	True Density (g/cc)	Weight (mg) (V_t-0.250 cc)	V-true (cc) (W=300 mg)
Emcompress	2.329	582.0	0.129
Compactrol	2.309	577.0	0.130
Emdex	1.513	378.0	0.198
Lactose Anhydrous	1.570	393.0	0.190
Fast-Flo	1.537	384.0	0.195
Emcocel 90M	1.552	388.0	0.193

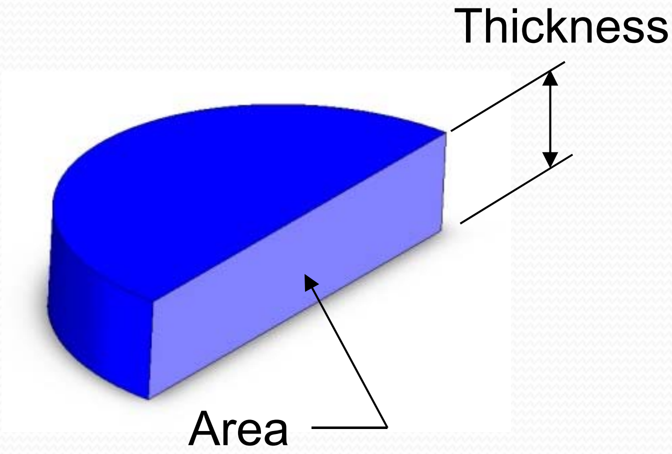
Compaction Studies

- Measure force applied to the powder bed to form the tablet.
- Measure the physical properties of the tablet for different applied forces.
  - Tablet strength
  - Friability
  - Tablet disintegration time
  - Tablet dissolution time
- Graph the applied force vs. the physical properties.

Breaking Force



Tensile Strength



Tensile Strength = (2 * Breaking Force)/π Fracture Area

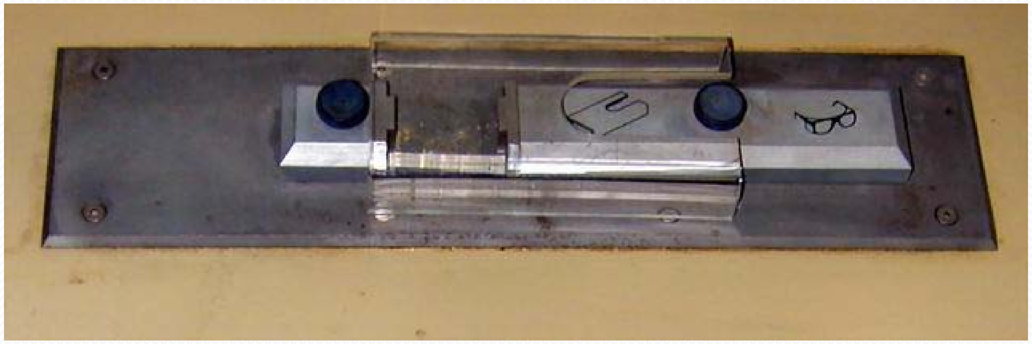
Rees, Hersey, and Cole Tensile strength equation for round convex tablets

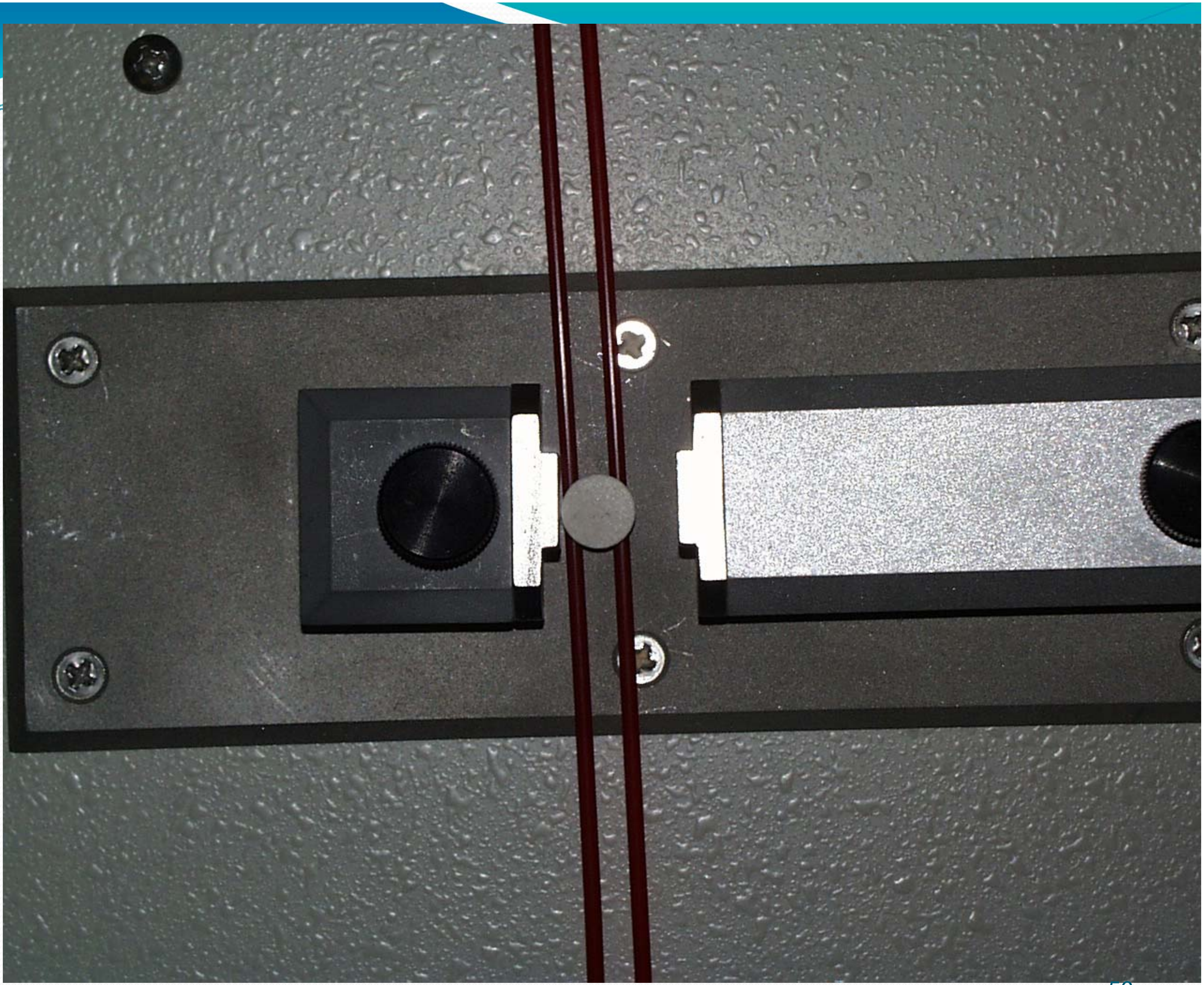
$$TS = \frac{10F}{\pi d^2}\left(2.84\frac{t}{d} - 0.126\frac{t}{c_l} + 3.15\frac{c_l}{d} + 0.001\right)^{-1}$$

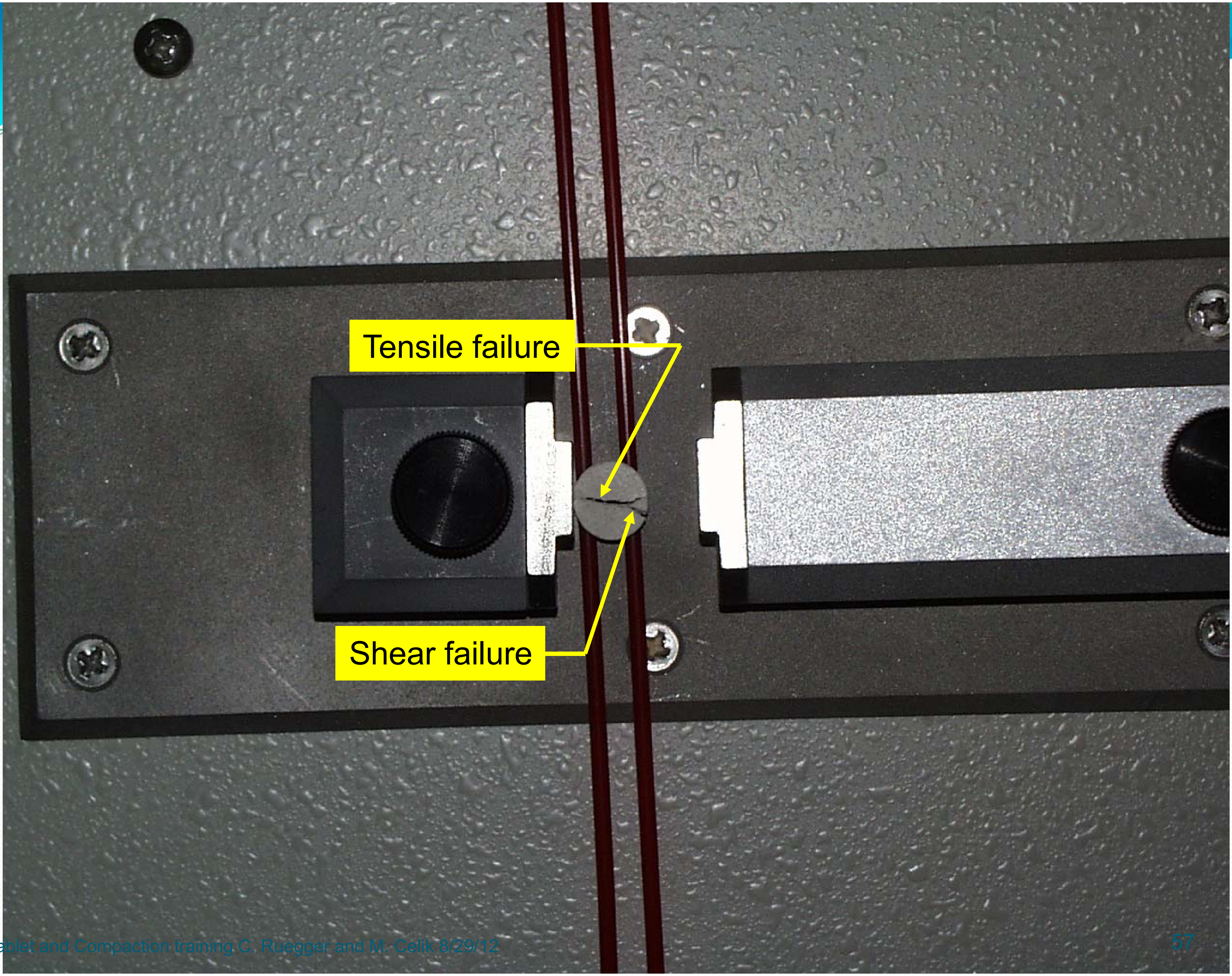
Where:

TS = tensile strength
F = breaking force
d = tablet diameter
t = overall tablet thickness
c = thickness of the belly band

Hardness Tester



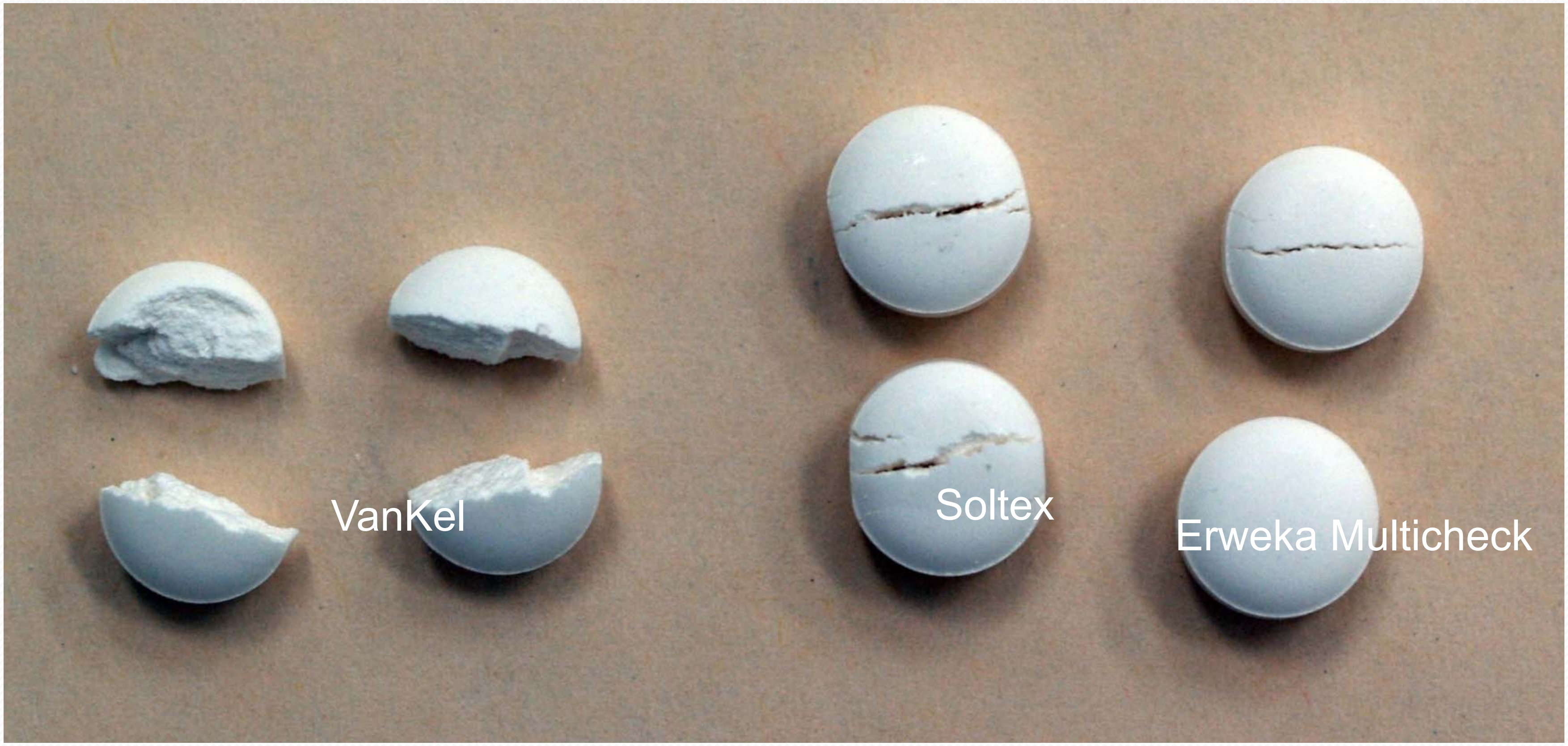




Tensile failure

Shear failure

Tablets broken from three different hardness testers



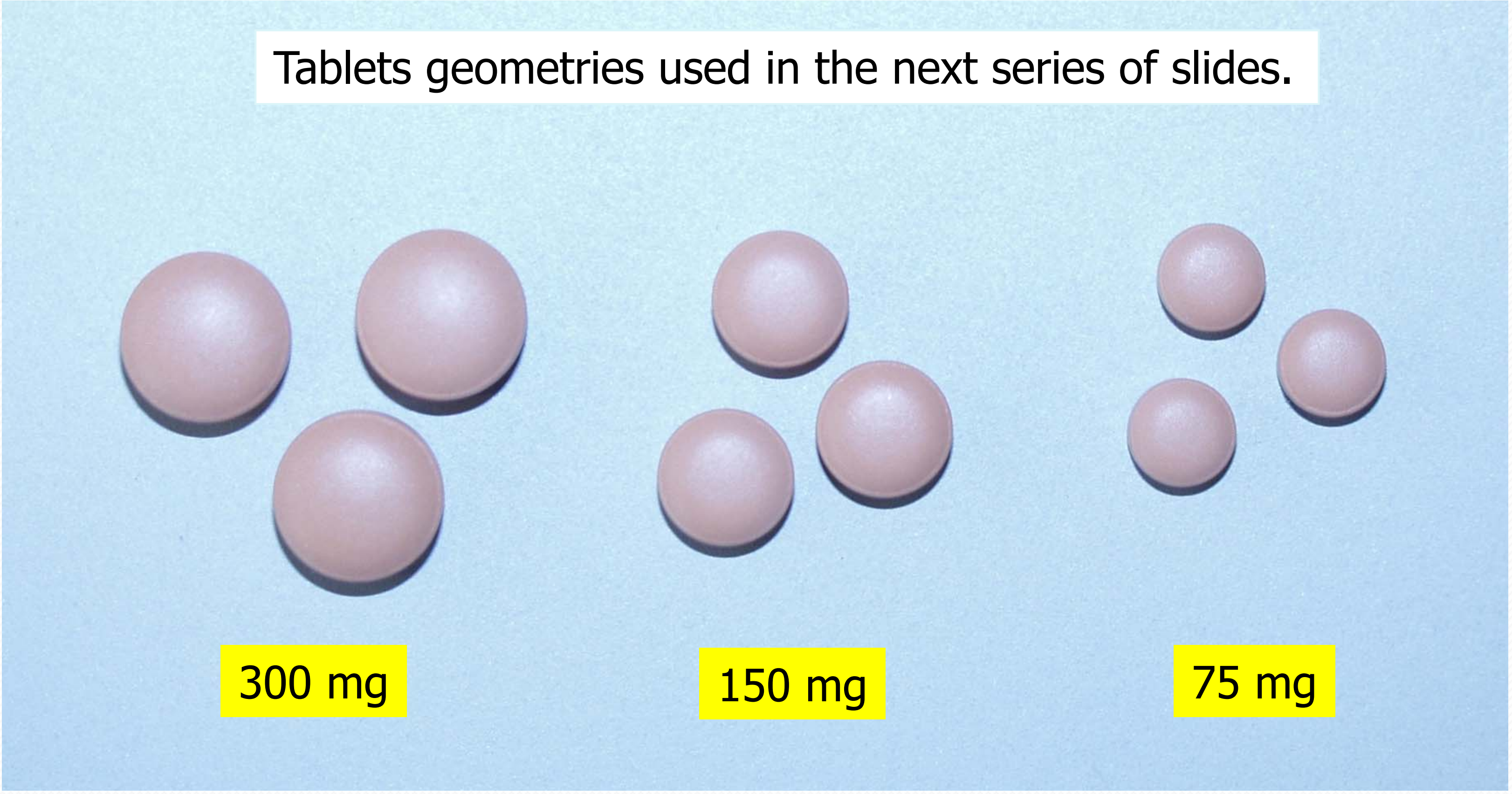
All tablets taken from the same tablet press and cured for 24 hours

Limited API ! Use smaller tooling

- Normalize… use tensile strength and compaction pressure, not hardness and force.

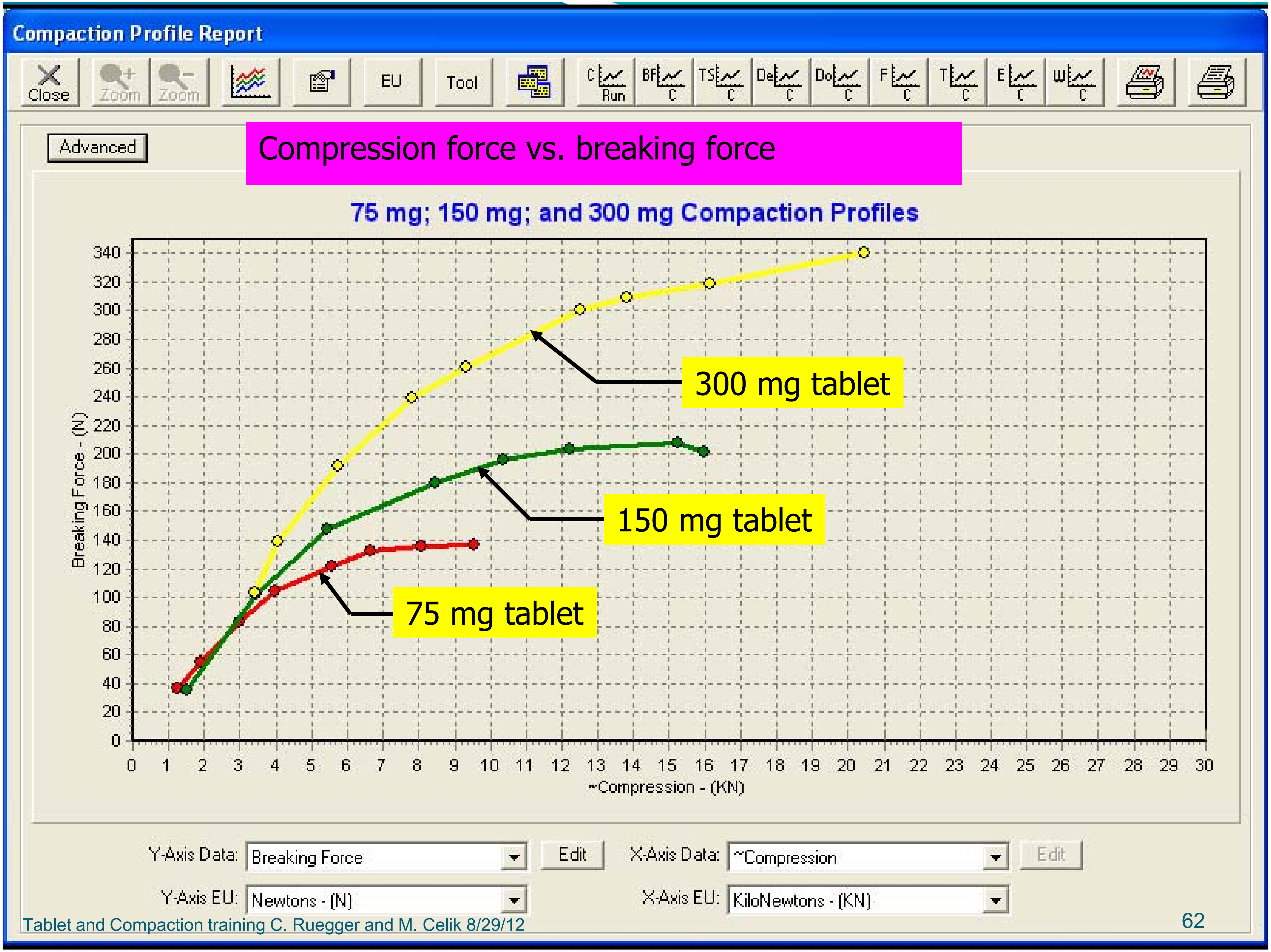
- Example 5 mm vs. 15 mm tooling:
  - Diameter is factor of 3, area is factor of 9.
  - Aspect ratio is linear, factor of 3.
  - Therefore tablet weights will be 27 times more with the 15 mm tooling.

Punches used in the experimental study



Tablets geometries used in the next series of slides.

Compression force vs. breaking force



300 mg tablet

150 mg tablet

75 mg tablet

Y-Axis Data: Breaking Force

X-Axis Data: ~Compression

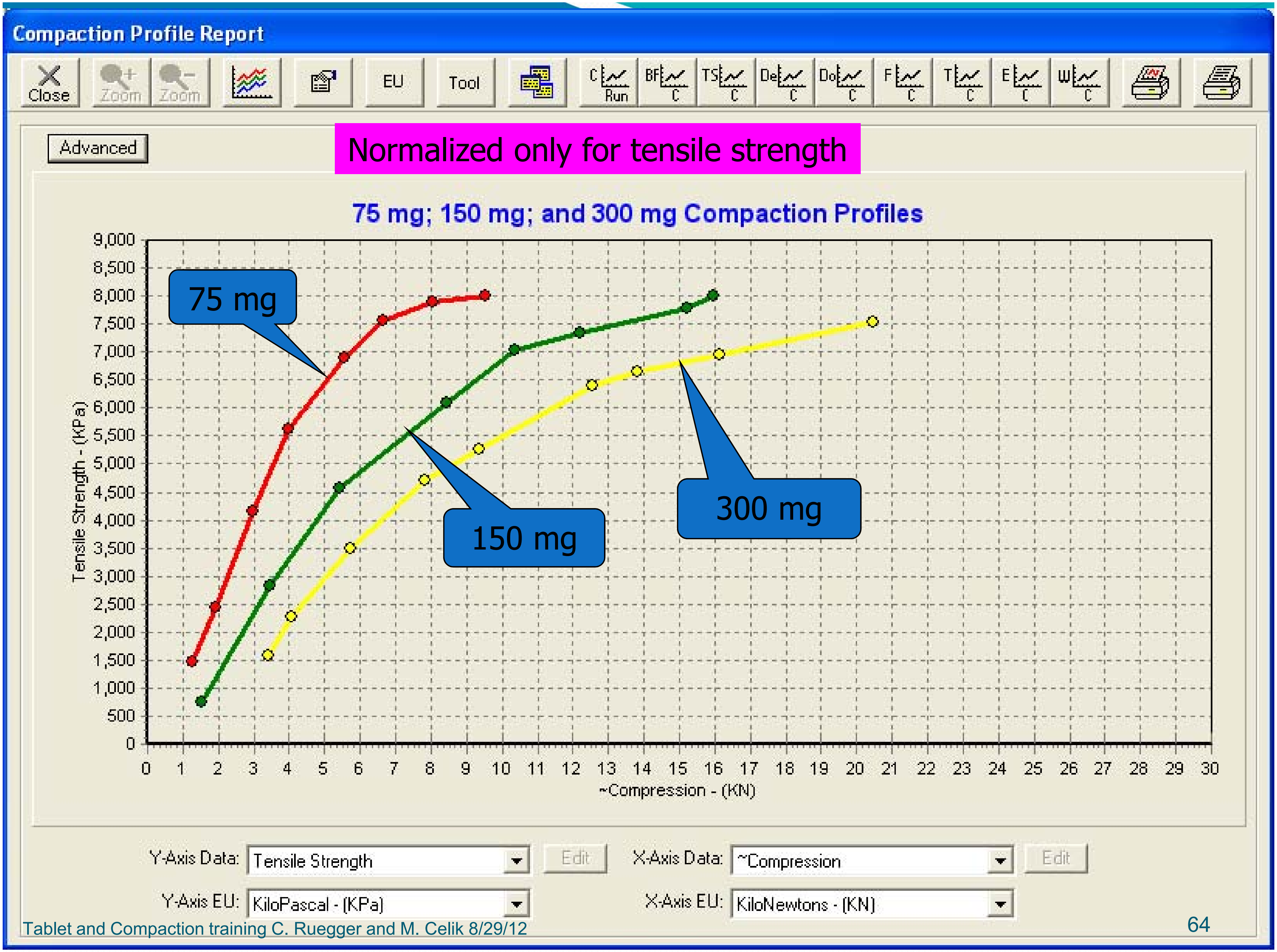
Y-Axis EU: Newtons - (N)

X-Axis EU: KiloNewtons - (KN)

Relationship between compaction pressure and tensile strength.

Pressure = Force/Cross sectional area
Cross sectional area = (п)(Φ)^2/4
Pressure is inversely proportional to the diameter squared.

Tensile strength = (2 * Breaking Force)/(п) (Fracture Area)
Fracture area = (Φ)(tablet thickness)
Tensile strength is inversely proportional to the diameter and thickness.



Normalized only for tensile strength

Y-Axis Data: Tensile Strength

X-Axis Data: ~Compression

Y-Axis EU: KiloPascal - (KPa)

X-Axis EU: KiloNewtons - (KN)

Normalized: Compaction pressure vs. tensile strength

Compaction Profile Report

75 mg; 150 mg; and 300 mg Compaction Profiles

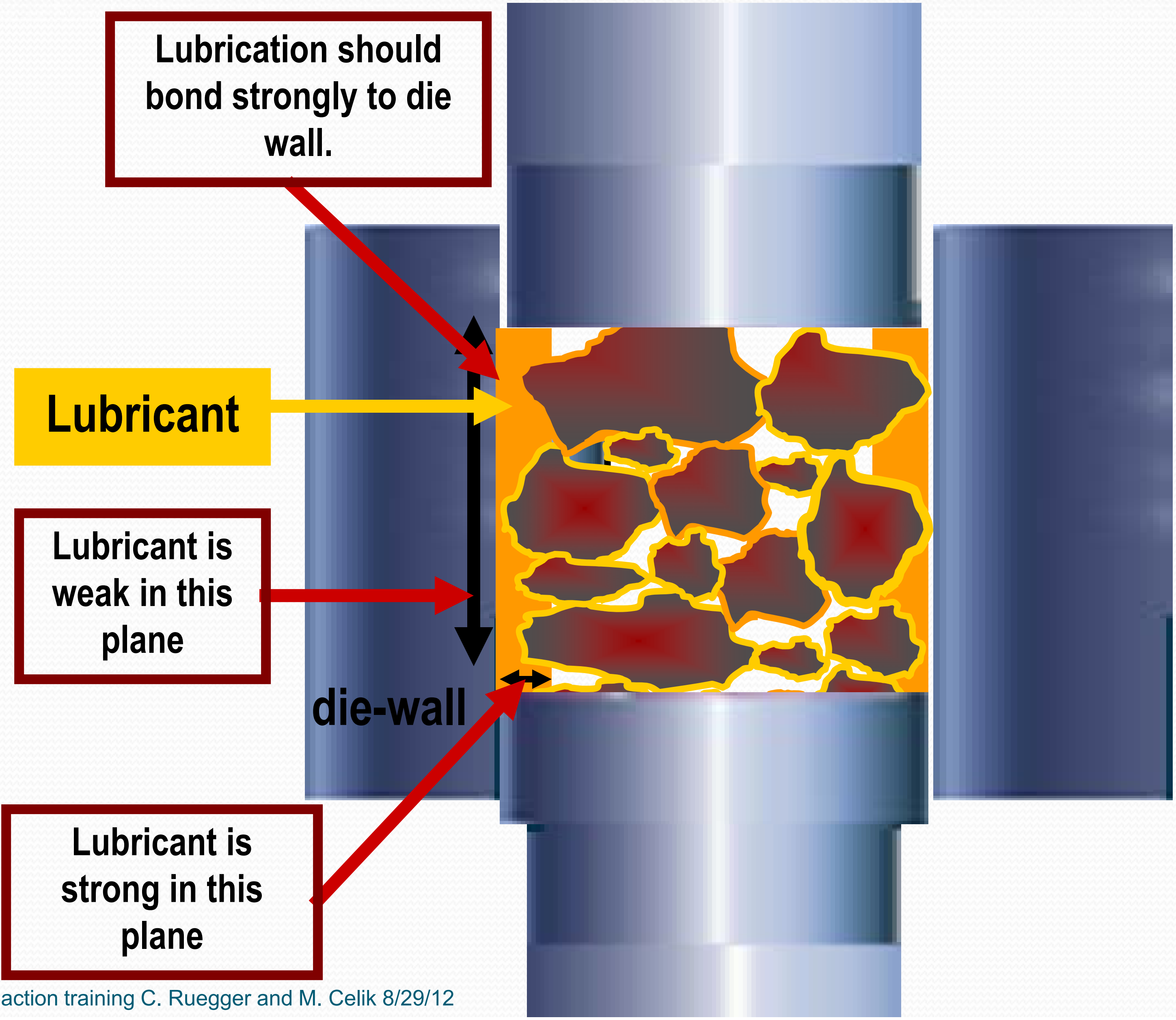
Y-Axis Data: Tensile Strength

X-Axis Data: ~Compression

Y-Axis EU: KiloPascal - (KPa)

X-Axis EU: Mega Pascal - (MPa)

Lubrication function



Lubrication should bond strongly to die wall.

Lubricant

Lubricant is weak in this plane

Lubricant is strong in this plane

Lubricity

Ejection Force

R Ratio [R= Fl / Fa= Pl / Pa]

Shaxby-Evans Equation

Unckel’s Equation

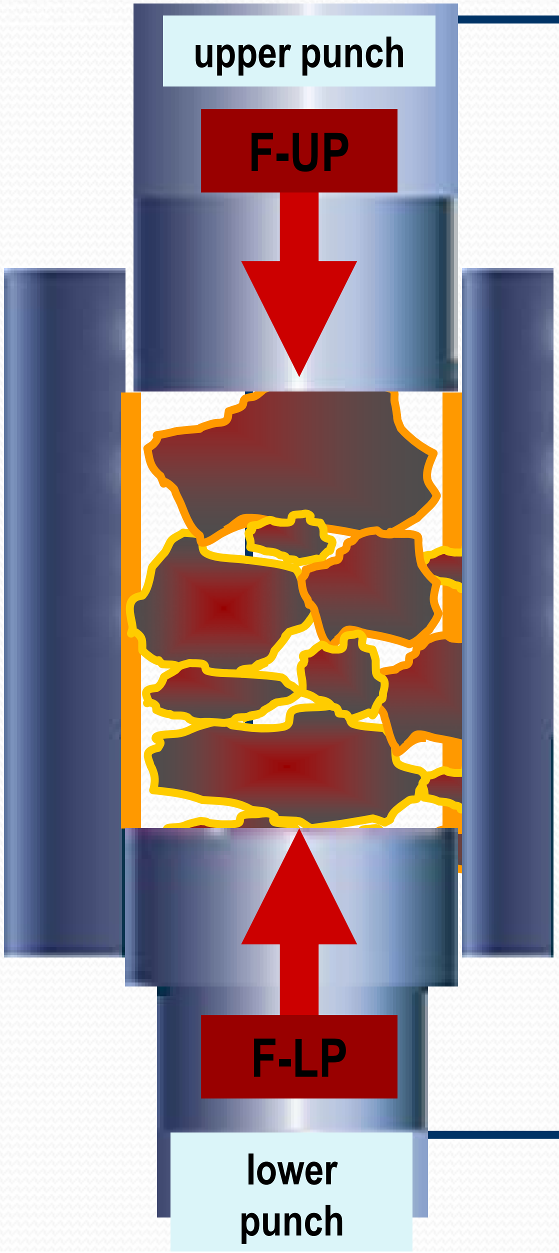
Compression Cycles

Compressibility Index

Etc.

Lubrication efficiency

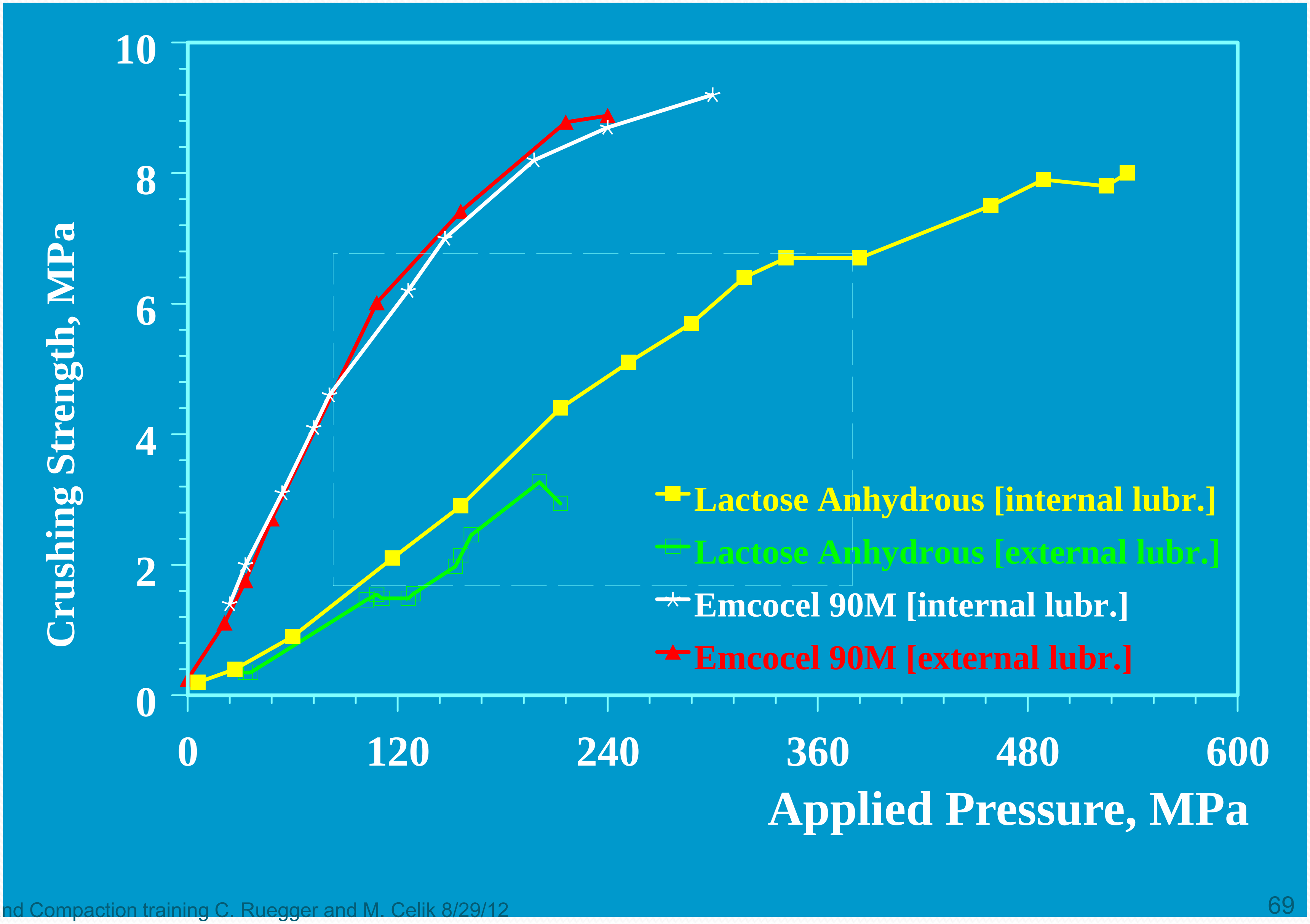
Coefficient of Lubricant Efficiency [R= Fl / Fa= Pl / Pa]



Material	0%	0.5%	1%	2%
None	0.63	-	-	-
Calcium Stearate	-	0.96	0.98	0.99
Sodium Stearate	-	0.86	0.94	0.95
Spermaceti	-	0.56	0.66	0.68
Veegum	-	0.62	0.63	0.59
PEG 4000	-	0.76	0.79	0.74
Talc	-	0.60	0.60	0.63
Mg Stearate	-	0.83	0.86	0.88

* formulation contains sulphatiazole

Internal versus External Lubrication



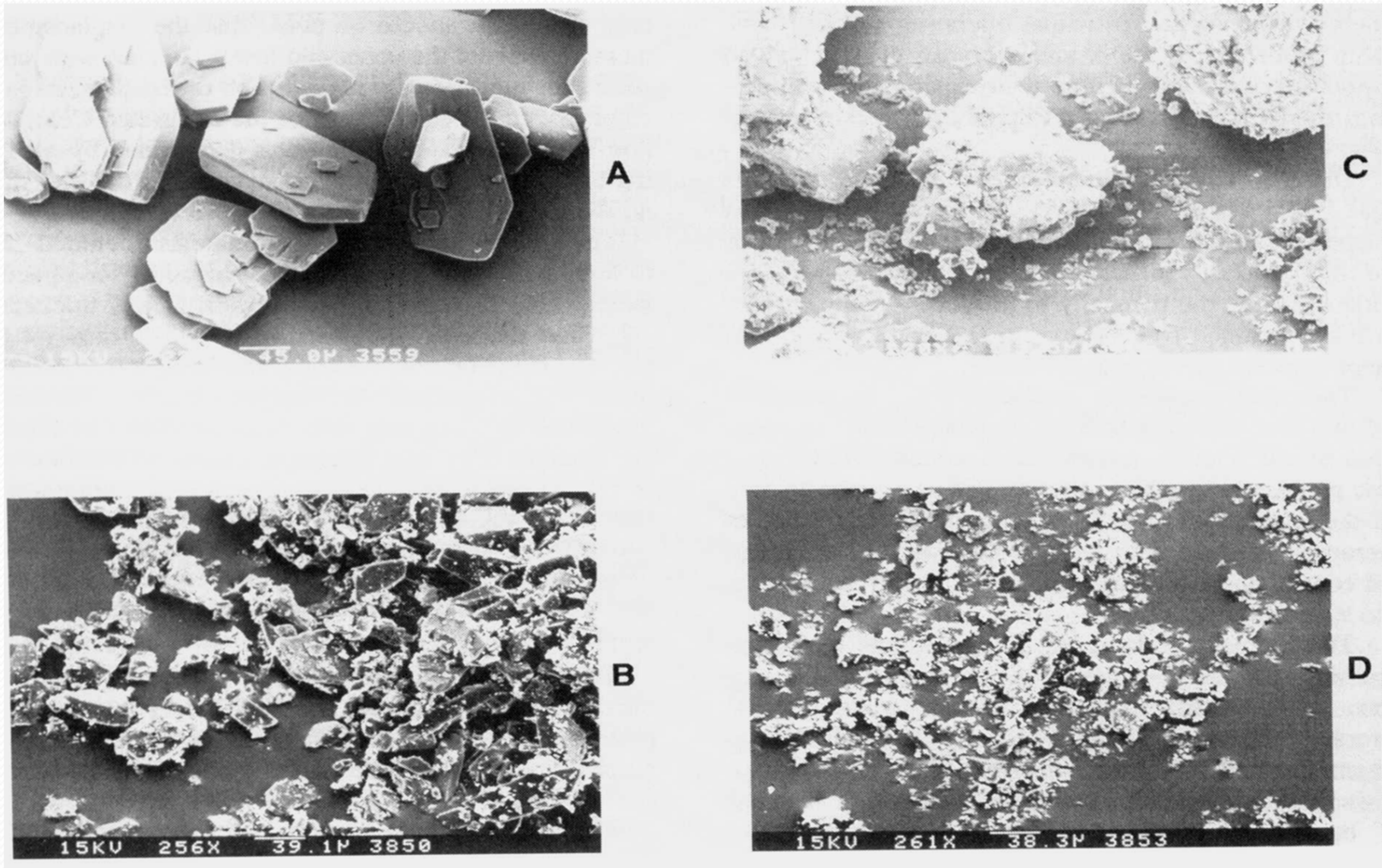
Particle Properties

Particle Properties

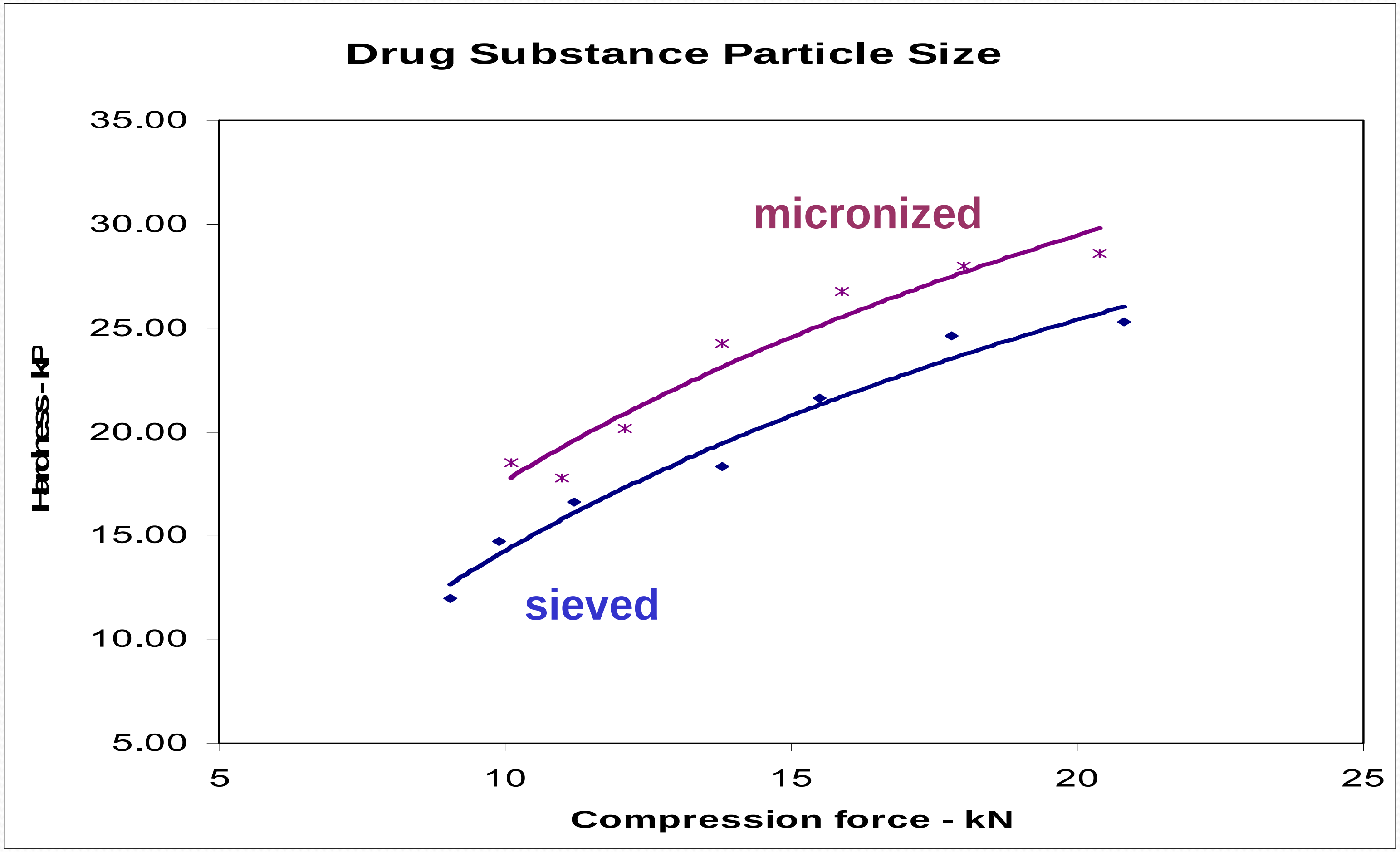
- Is there an ideal particle property for tableting?
- Important to characterize particle properties
  - Bulk/tap density
  - Particle size/morphology
  - Specific surface area
  - Flow
  - “stickiness”
  - Deformation characteristics
- Desirable particle/bulk properties:
  - Good flow
  - Good compactibility

Particle Properties

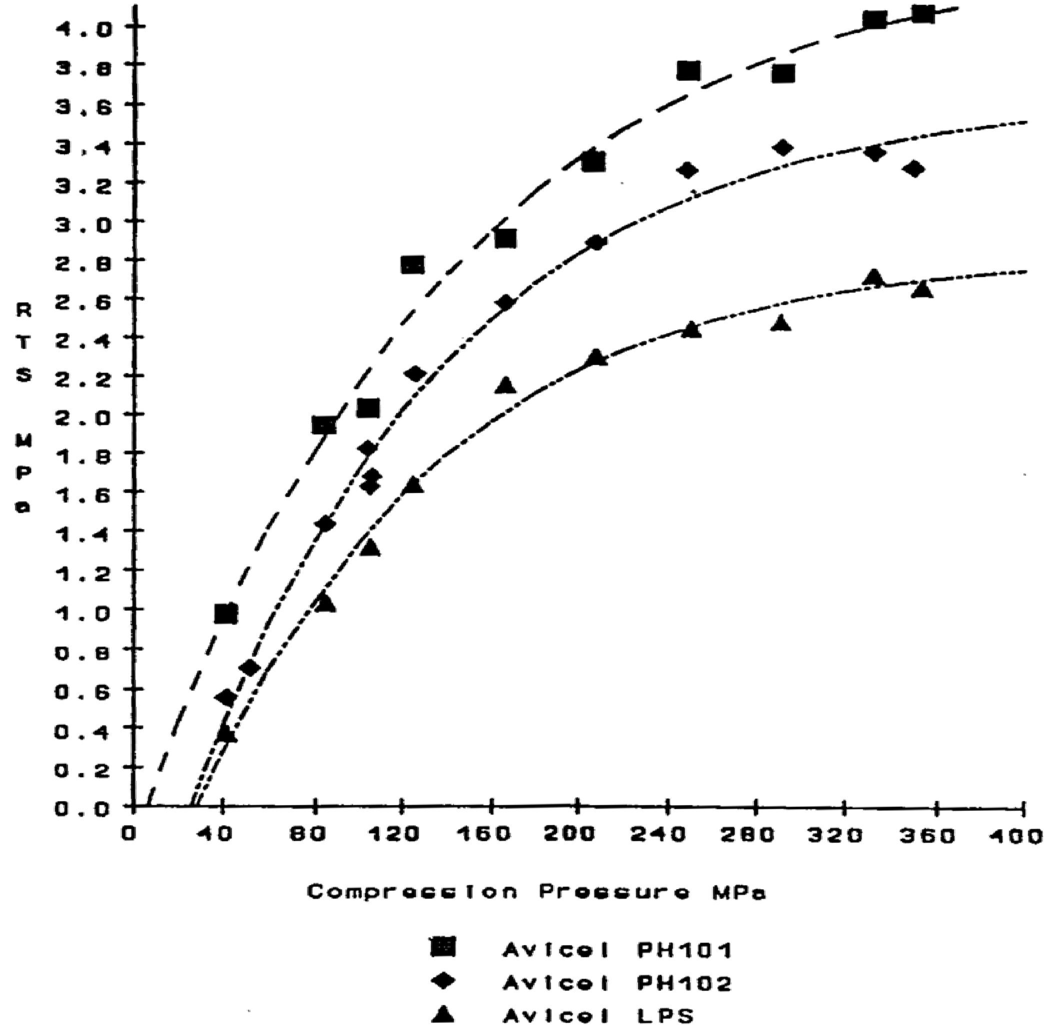
- SEM pictures of different DS



Particle Properties



Particle size - diluent selection



Troubleshooting

Troubleshooting

- Weight uniformity
- Low dose issues
- High dose issues
- Loss of material
- Sticking/picking/capping/lamination

Troubleshooting

- Weight uniformity
  - First confirmation of the correct content in each dosage unit

☐ Possible causes of non-uniformity

- Flow issues
- Particle size too large
- Particle size – wide distribution
- Non-uniform lower punch length

☐ Solutions

- Add a flow aid
- Adjust feeder rate
- Optimize screen size for milling
- Optimize blending time and external excipient ratio as well as particle size
- Storage conditions?
- Adjust tabletting speed
- Automatic weight regulation

Troubleshooting

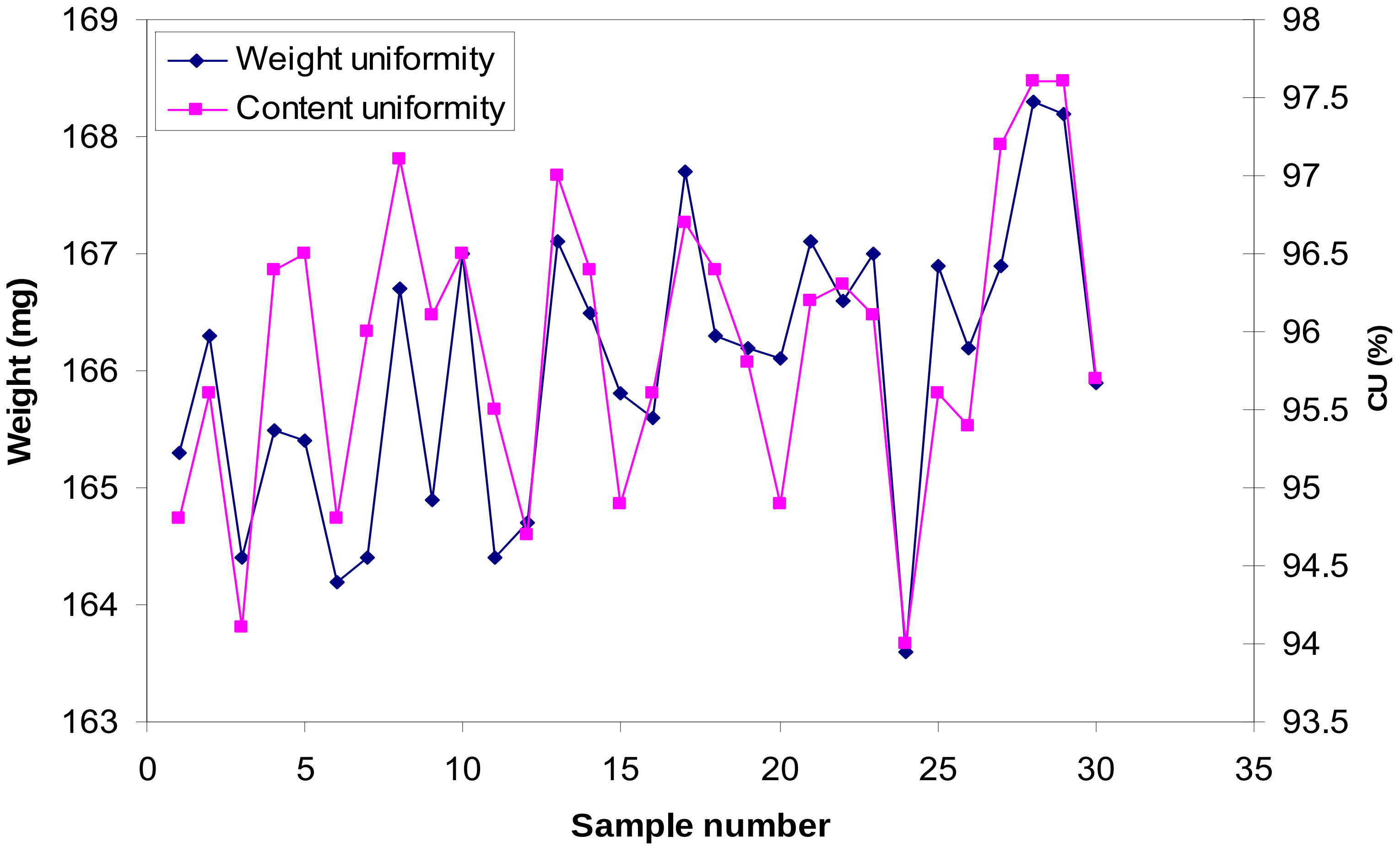
- Low dose products – content uniformity will be the major challenge
  - Drug substance particle size is critical
    - Micronization may be necessary
    - Ordered mixing or geometric dilution
  - Segregation concerns
    - Excipient considerations
    - Process impact
  - Adsorption of the drug substance to equipment or excipients

Low dose DOE results

RSD% content uniformity

Experiment	Screening steps	Blend revs	Screen size (mesh)	Lubricant level	Lubricant blend revs	RSD% CU
M	2	120	35	1.75	135	1.2
F	2	360	35	1.75	45	1.7
J	2	360	35	2.5	135	2.0
T	1	120	35	1.75	45	3.1
D	1	120	20	1.75	135	3.2
R	1	360	35	1.75	135	3.5
A	2	120	35	2.5	45	3.5
E	2	240	30	2	90	4.0
Q	2	240	30	2	90	4.2
S	1	360	35	2.5	45	4.4
I	2	240	30	2	90	4.7
N	2	240	30	2	90	4.7
G	2	120	20	1.75	45	4.8
O	1	120	35	2.5	135	4.9
P	1	360	20	1.75	45	5.8
B	1	360	20	2.5	135	6.2
H	2	360	20	2.5	45	6.6
L	2	360	20	1.75	135	6.8
C	1	120	20	2.5	45	9.7
K	2	120	20	2.5	135	10.1

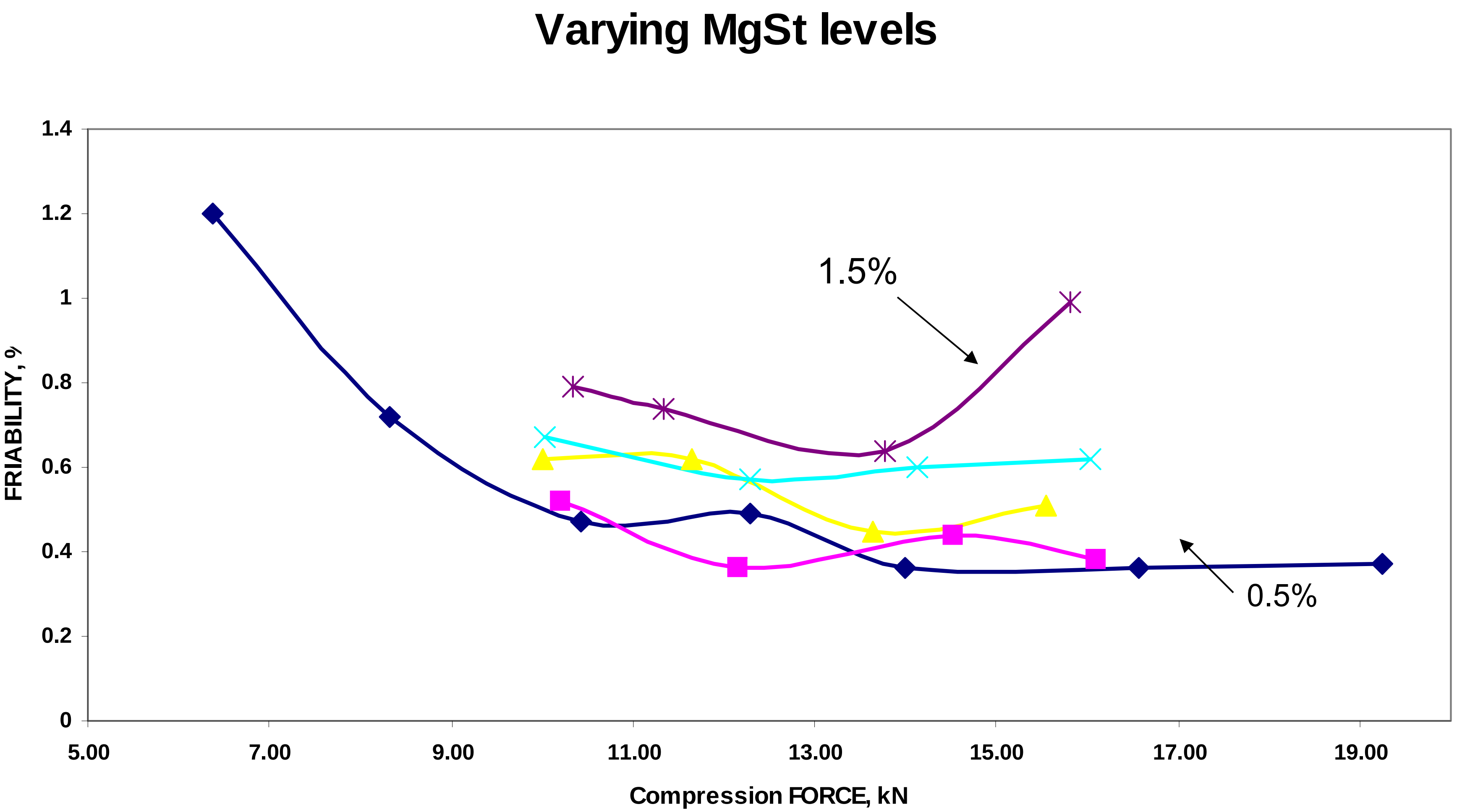
Content Uniformity – low dose product



Troubleshooting

- High dose - drug substance properties become more critical or tablet size could be excessive
  - Flow
  - Bulk density
  - Particle size
  - Compactibility
    - Weak tablets
    - Work hardening

Troubleshooting



Troubleshooting

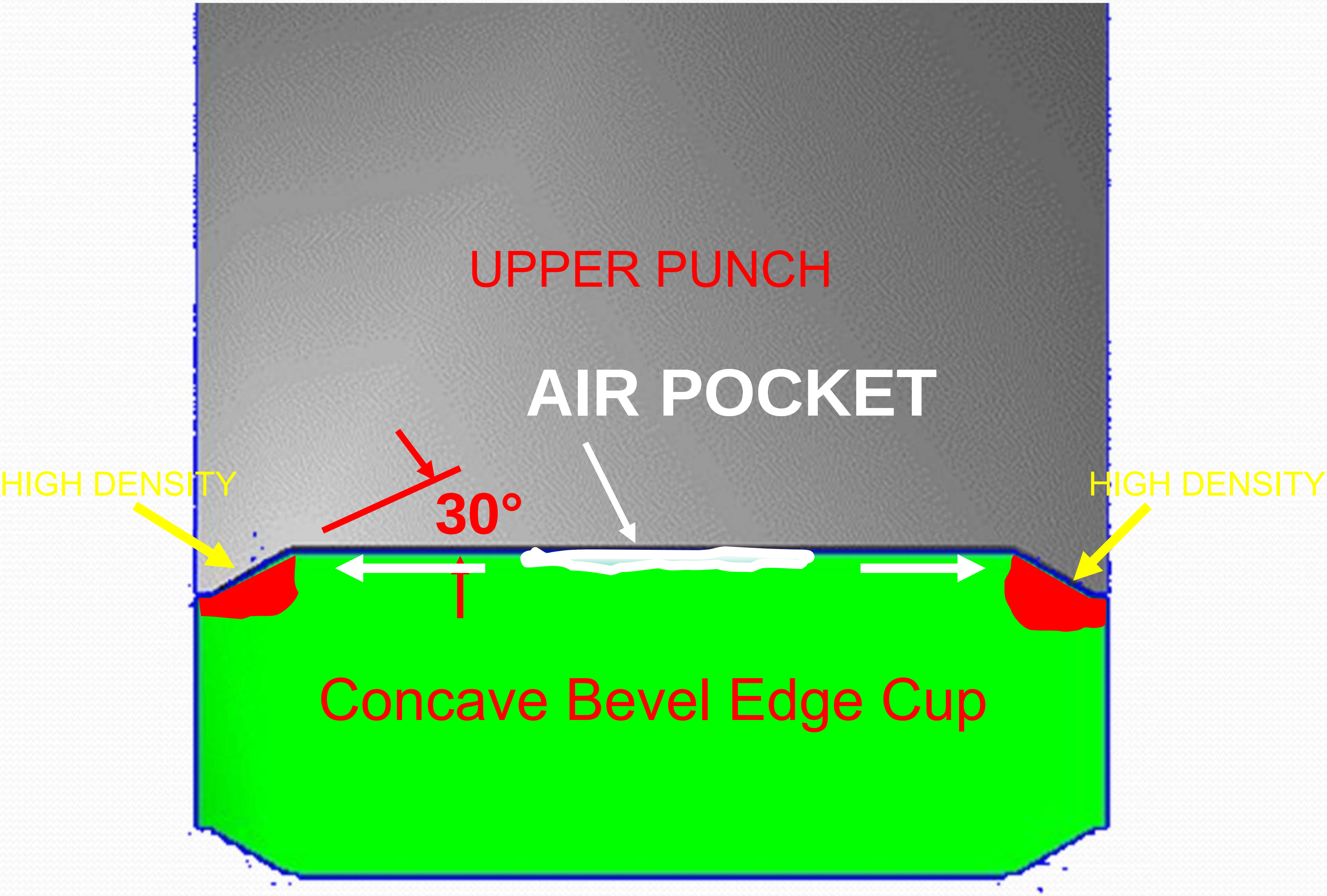
- Sticking/picking may be caused by:
  - Excess moisture
  - Punch face conditions
  - Insufficient compaction force
  - Underlubrication

  Troubleshooting:
    - Check tooling/change tooling
    - Check moisture content of formulation
    - Increase compaction force/decrease compaction speed
    - Lubricant level/antiadherent

F.F.B.E. cup with center picking

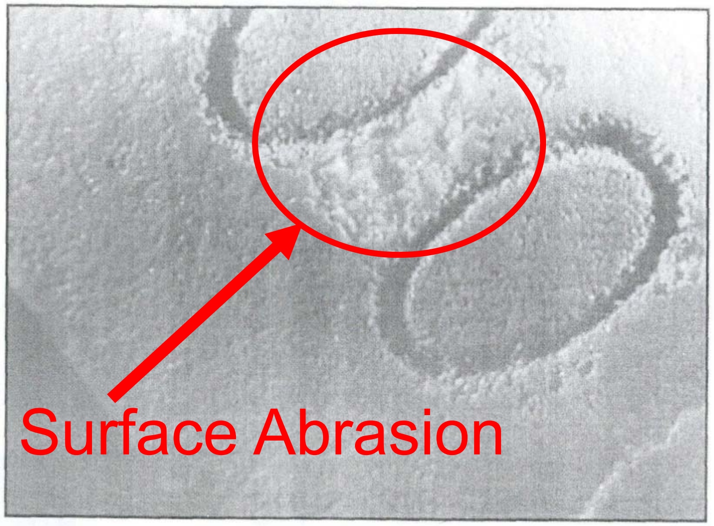
Ref: Elizabeth Carbide

Flat Face Bevel Edge Cup

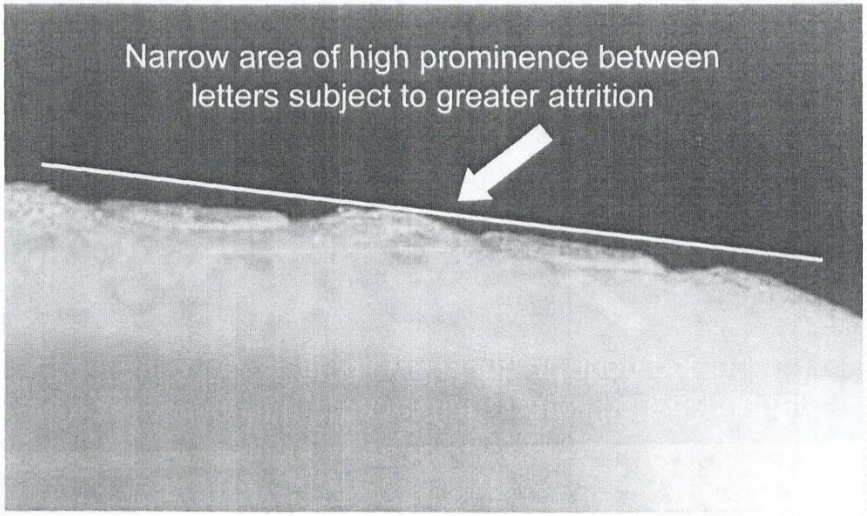


Ref: Elizabeth Carbide

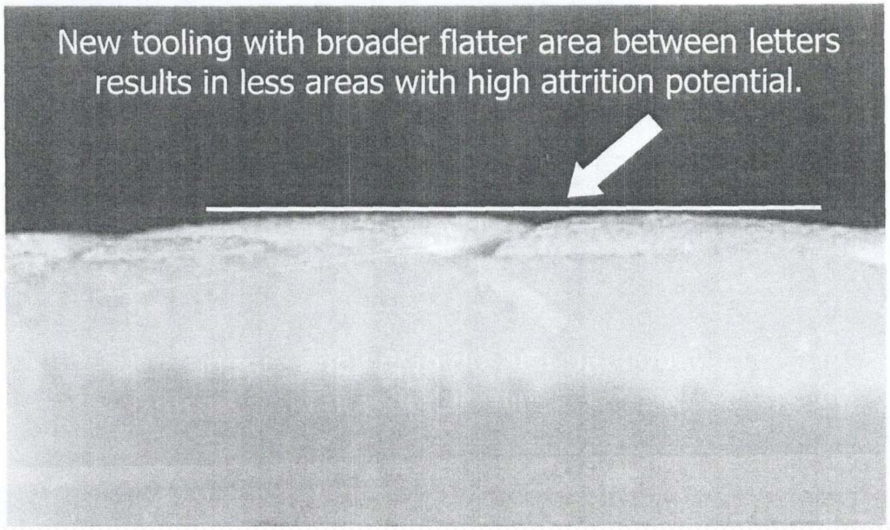
Text Spacing



Surface Abrasion



Narrow area of high prominence between letters subject to greater attrition



New tooling with broader flatter area between letters results in less areas with high attrition potential.

Ref: Elizabeth Carbide

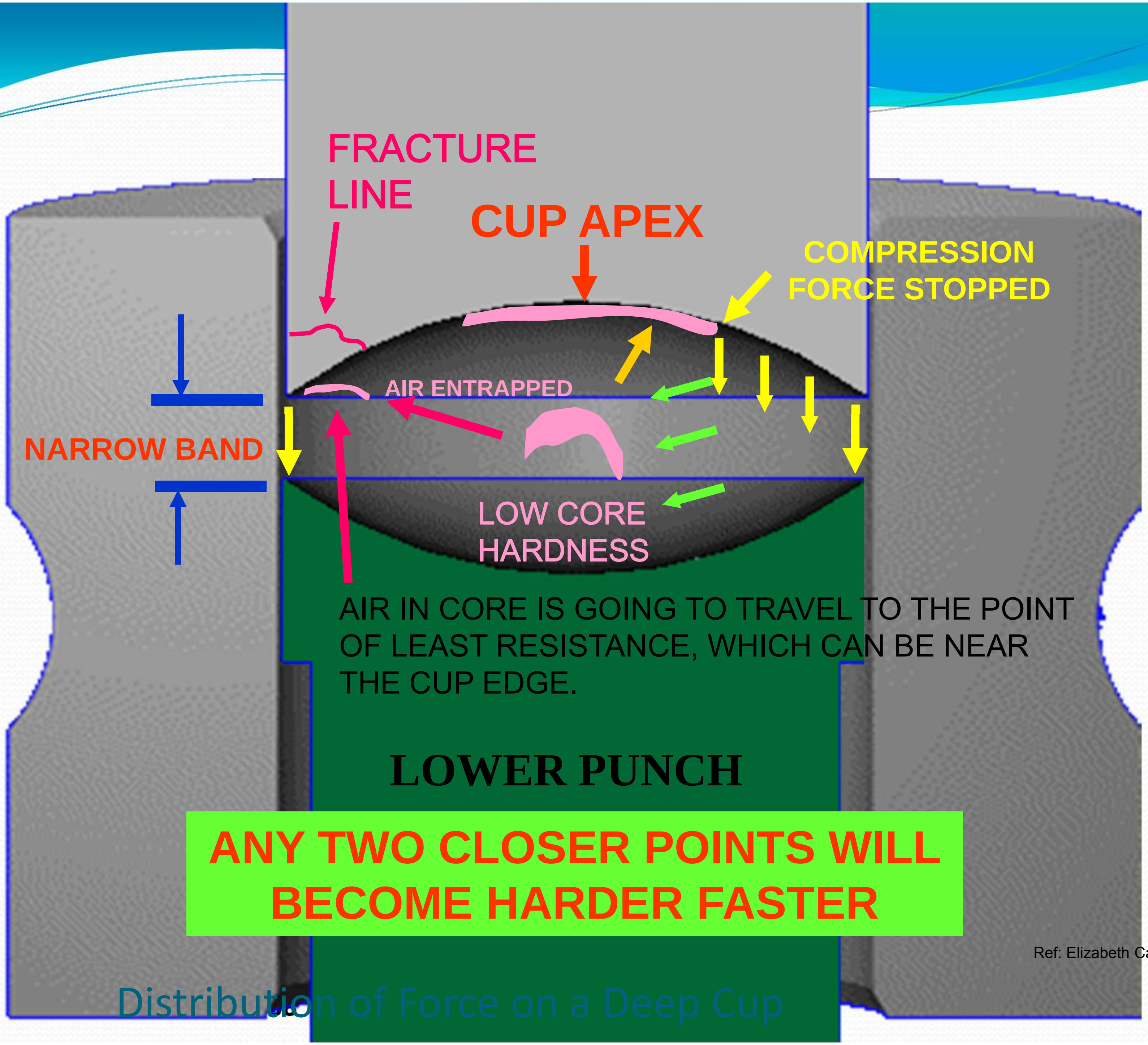
Troubleshooting

- Capping/lamination may be caused by:
  - Overcompression/high speed of compaction
  - Overmixing with lubricant or in the feedframe
  - Insufficient binder
  - Tooling defects/barreled die bore/incorrect press set up
  - Insufficient moisture level

Troubleshooting:

- Check tooling
- Reduce force/speed
- Reduce speed of feedframe
- Decrease lubricant level or lubricant mixing time
- Increase binder level/increase moisture level in granulation

Distribution of Force on a Deep Cup



FRACTURE LINE

CUP APEX

COMPRESSION FORCE STOPPED

AIR ENTRAPPED

NARROW BAND

LOW CORE HARDNESS

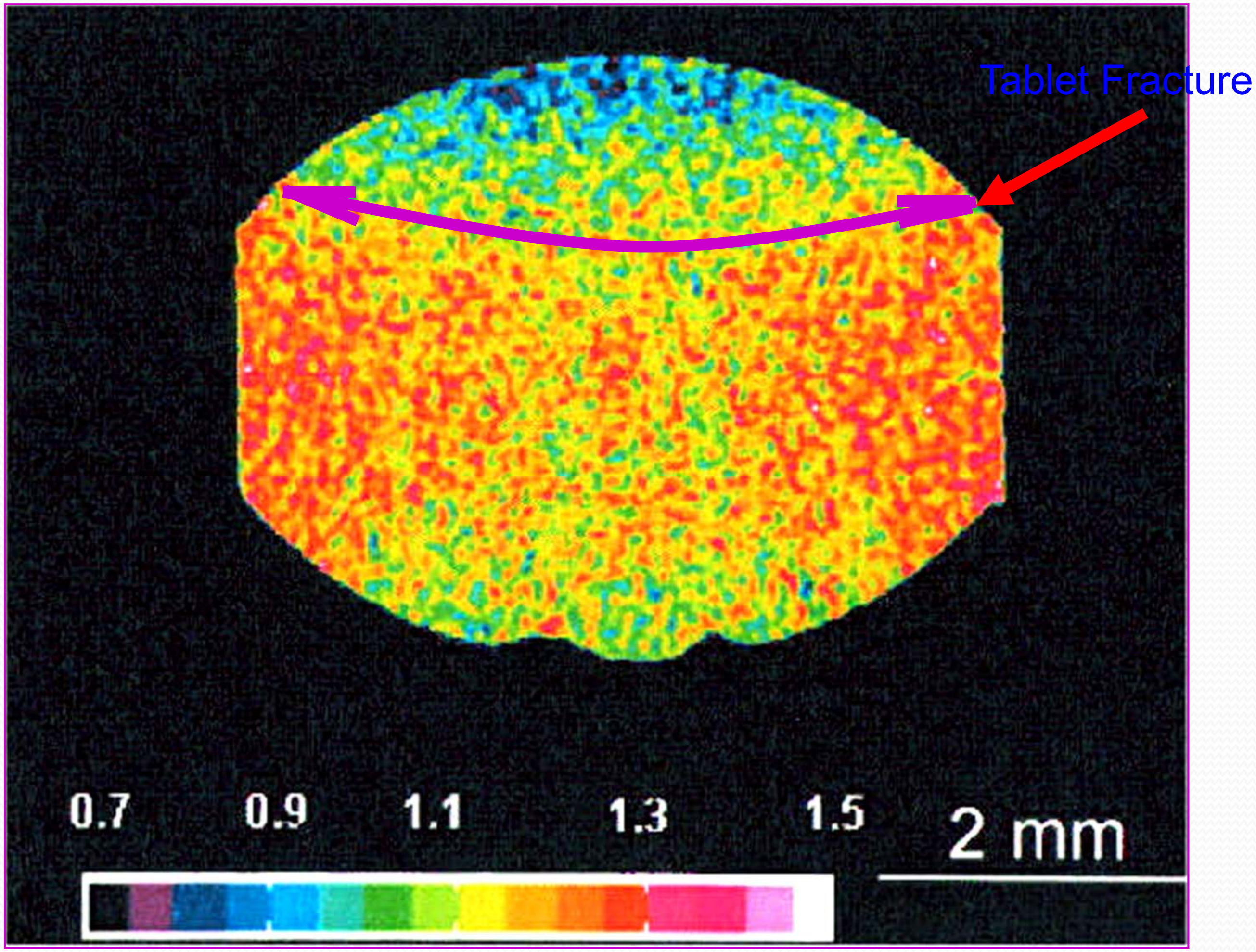
AIR IN CORE IS GOING TO TRAVEL TO THE POINT OF LEAST RESISTANCE, WHICH CAN BE NEAR THE CUP EDGE.

LOWER PUNCH

ANY TWO CLOSER POINTS WILL BECOME HARDER FASTER

Ref: Elizabeth Carbide

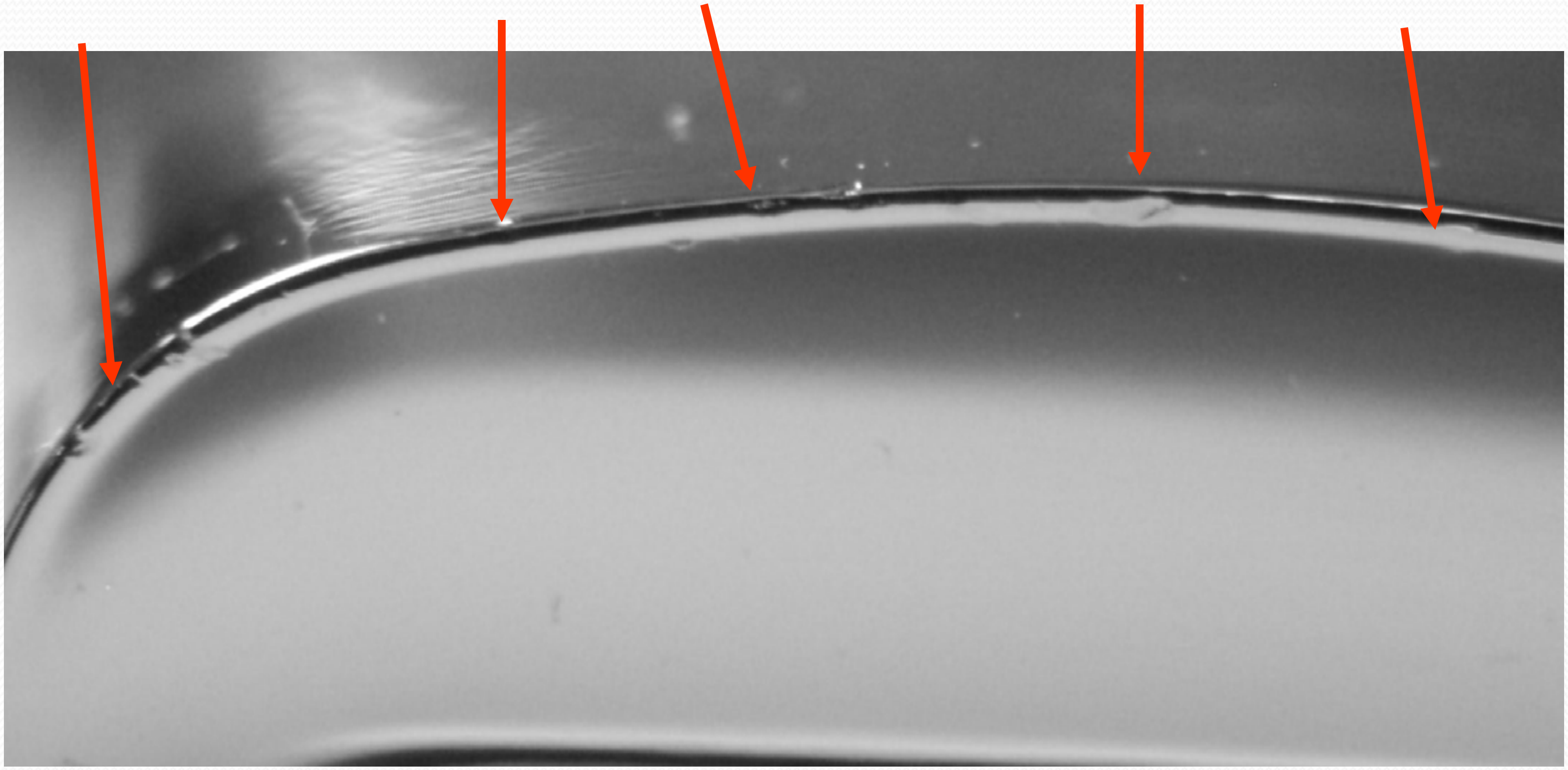
Capping



Ref: Elizabeth Carbide

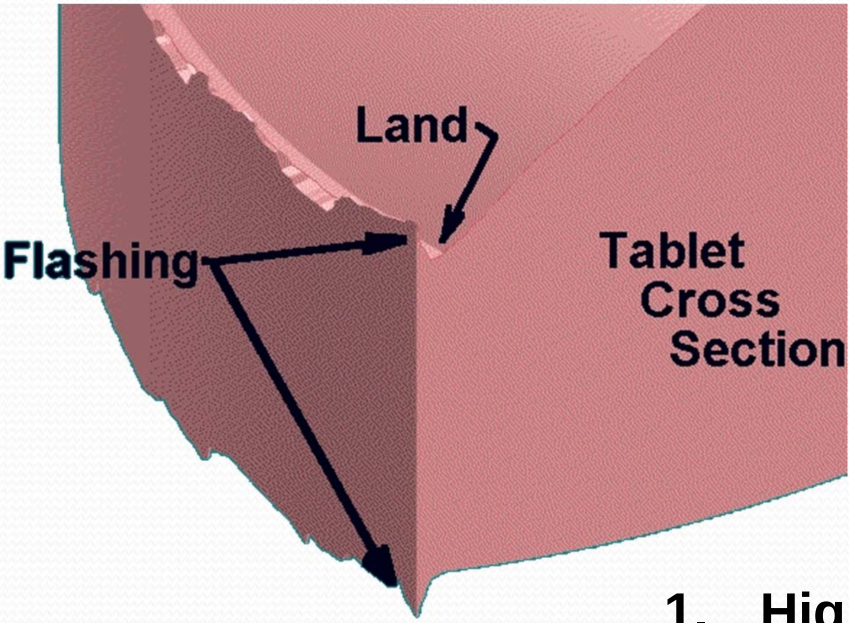
Lower punch nicks

Nicks all along the lower punch edge and land area, but no vertical wear lines on tip straight indicate a mishandling problem.



Ref: Elizabeth Carbide

Flashing



Possible Causes

1. **High Percentage of Fines in Formulation**
2. **Punch Tip to Die Clearance too Large**
3. **Outer Punch Edge Wear**

Ref: Elizabeth Carbide

Chipped Tablets

- Can be caused by any of the following:
- Lower punch ejection height too low: Adjust ejector
- Sharp or hooked tool tips: Polish tooling
- Soft tablet edge as a result of centrifugal force: Slow down press
- Take off bar adjustment: Raise or lower take off bar
- Discharge chute cover contact: Adjust cover
- Excessive ejection force: Raise penetration or granulation lubricant

Ref: Fette America

Bilayer compaction

Combination products

Layered tablets – Why make a bilayer tablet?

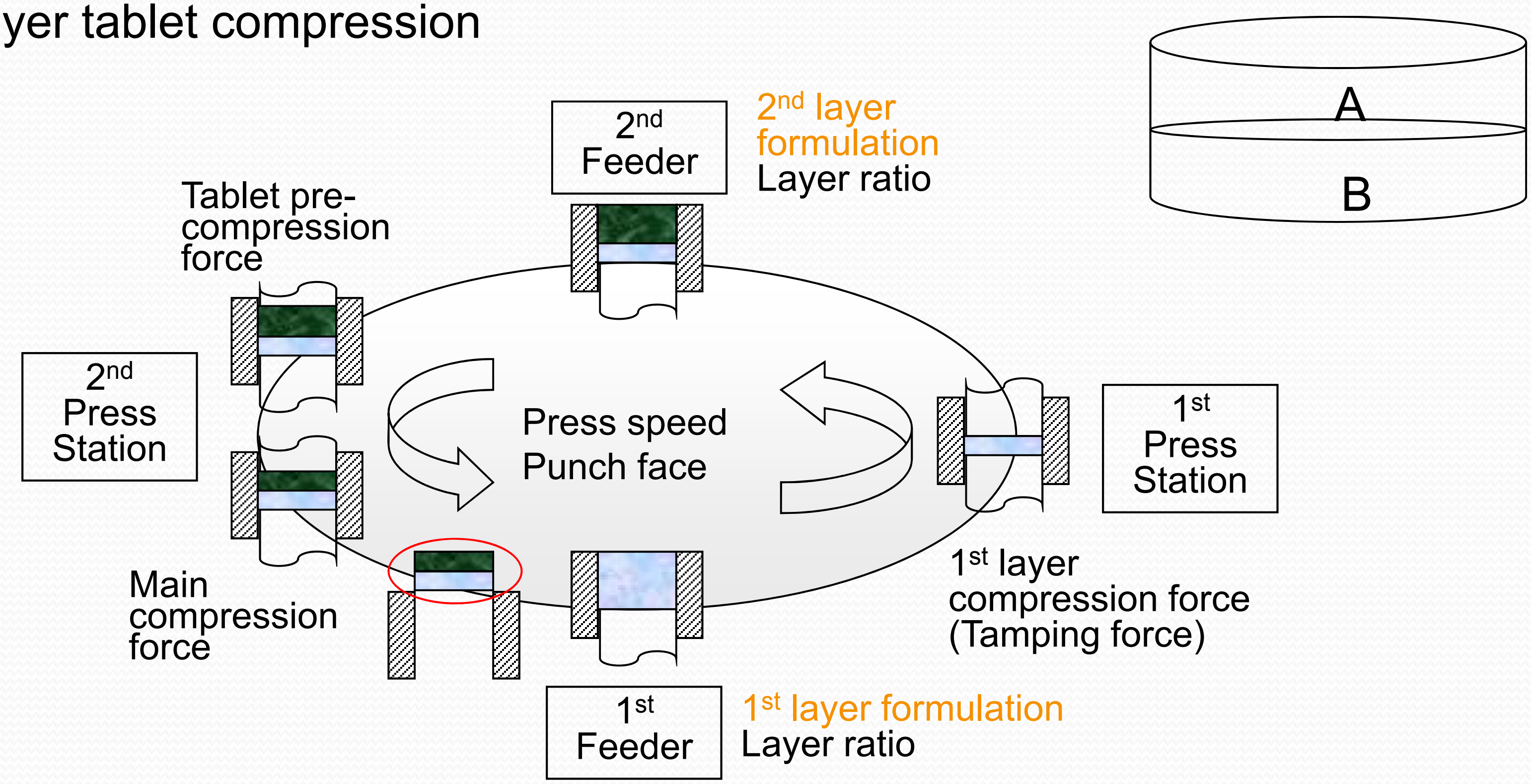
- Advantages of bilayer – similar to combination product in general plus…
  - Combine two incompatible ingredients into one tablet
  - Patient convenience and simplified dosing
  - Line extension/LCM
  - Modified release
  - When different release profiles are needed (IR/MR)
- Challenges specific to bilayer
  - Stability
  - Tablet size
  - Yield
  - Delamination potential

Bilayer Process Description

- Added complexity of bilayer *vs.* monolayer tableting
  - All compression parameters for first layer and bilayer
  - Parameters for each layer are not necessarily independent
  - All IPCs for bilayer, weight for first layer, second layer weight can not be determined directly
- Specific Bilayer Vocabulary
  - Layer ratio (weight by weight – no volume considerations)
  - Layer order
  - Delamination (separation of the 2 layers – adhesion strength)
  - Cracking (fine crack at layer interface – process induced)
  - First layer compression force (tamping)
  - Precompression (on bilayer only)

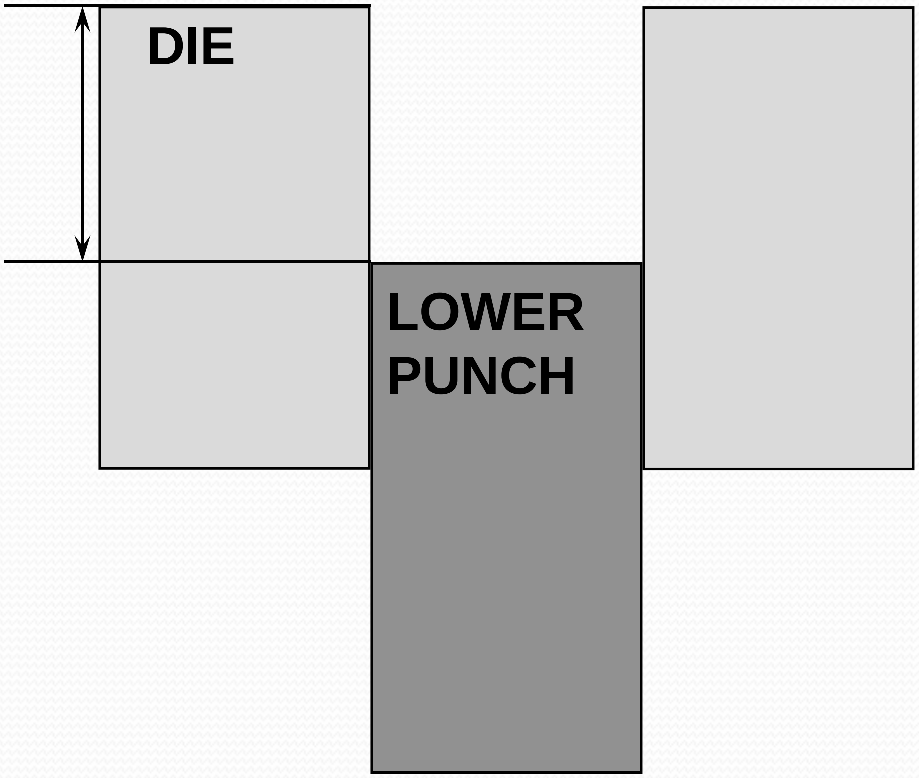
Bilayer Process Description

- Bilayer tablet compression



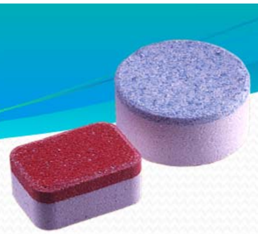
Main challenges for bilayer processing:
Delamination and 2nd layer weight control

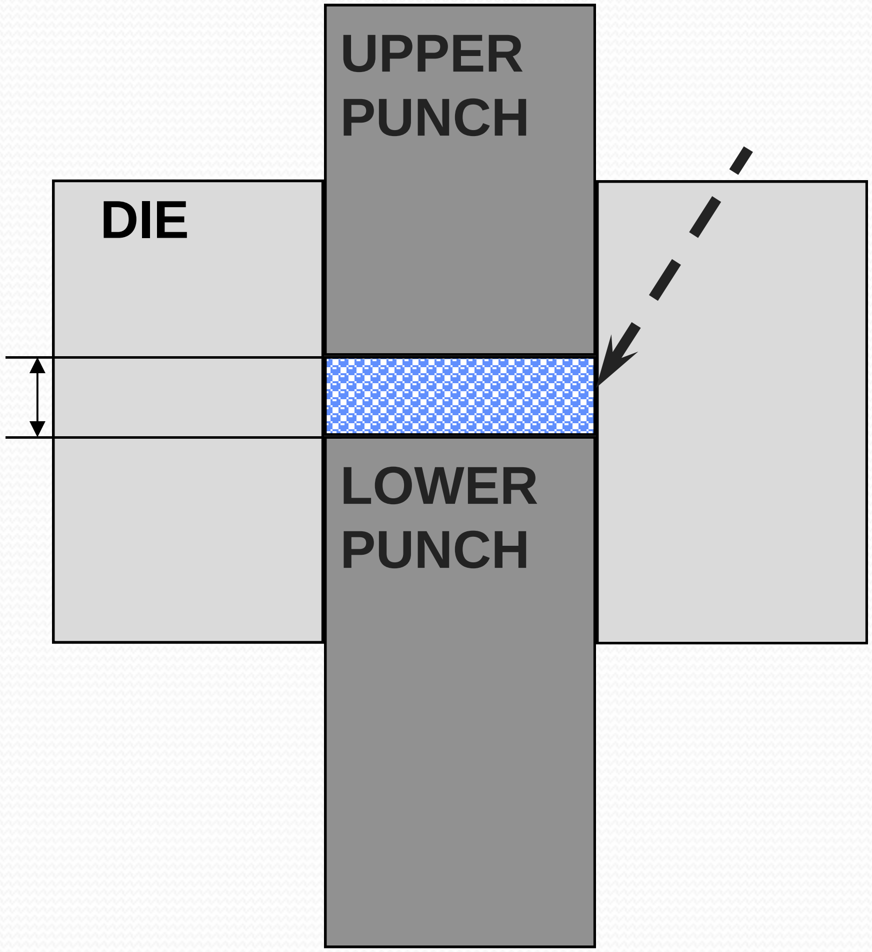
Bilayer tableting: Filling of the 1st layer



Ref: Fette America

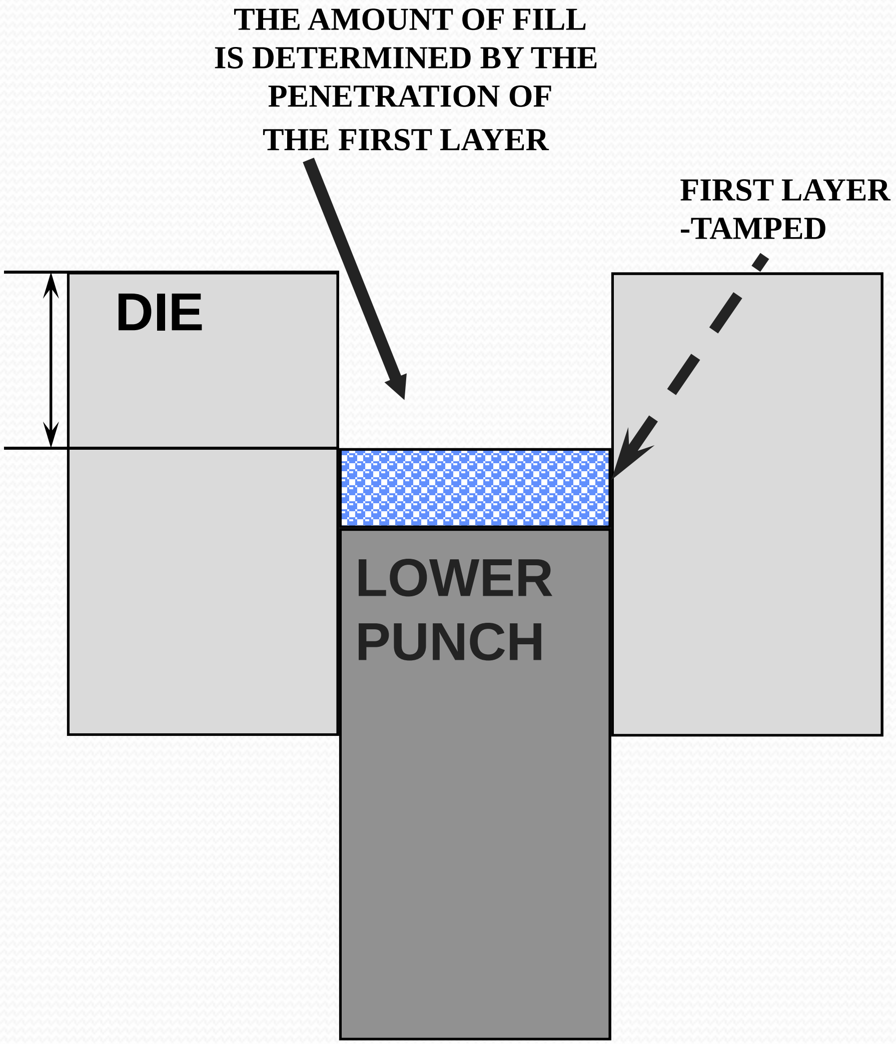
Bilayer tableting: Compressing the 1st layer





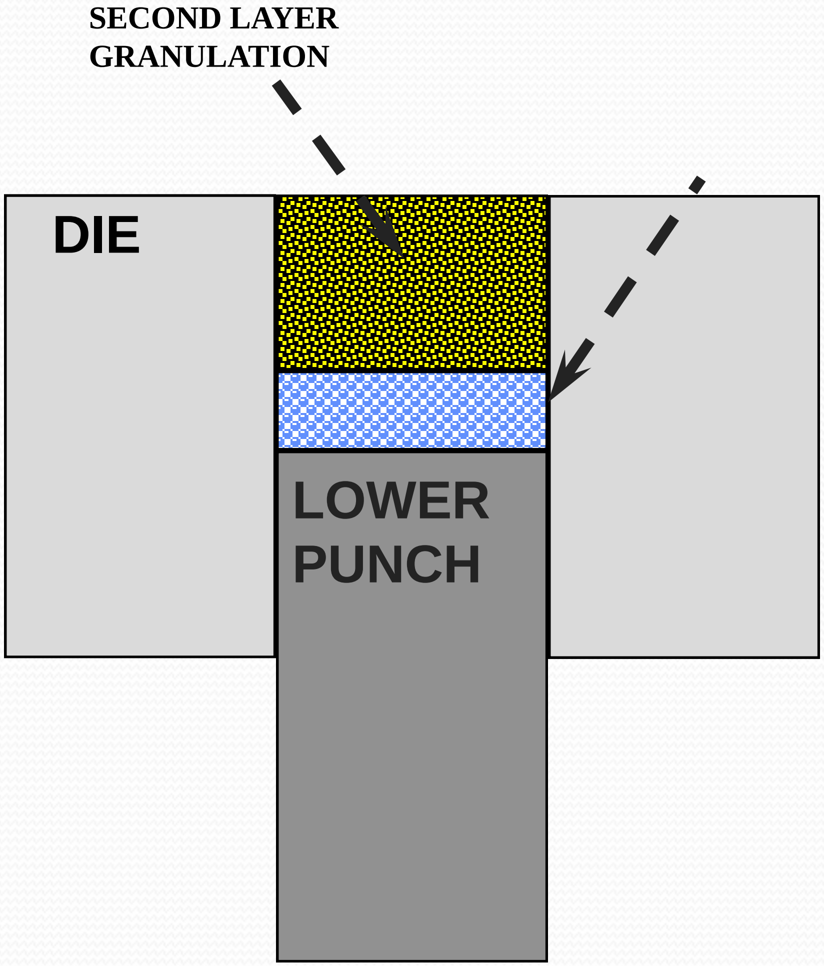
Ref: Fette America

Bilayer tableting: Filling of the 2nd layer



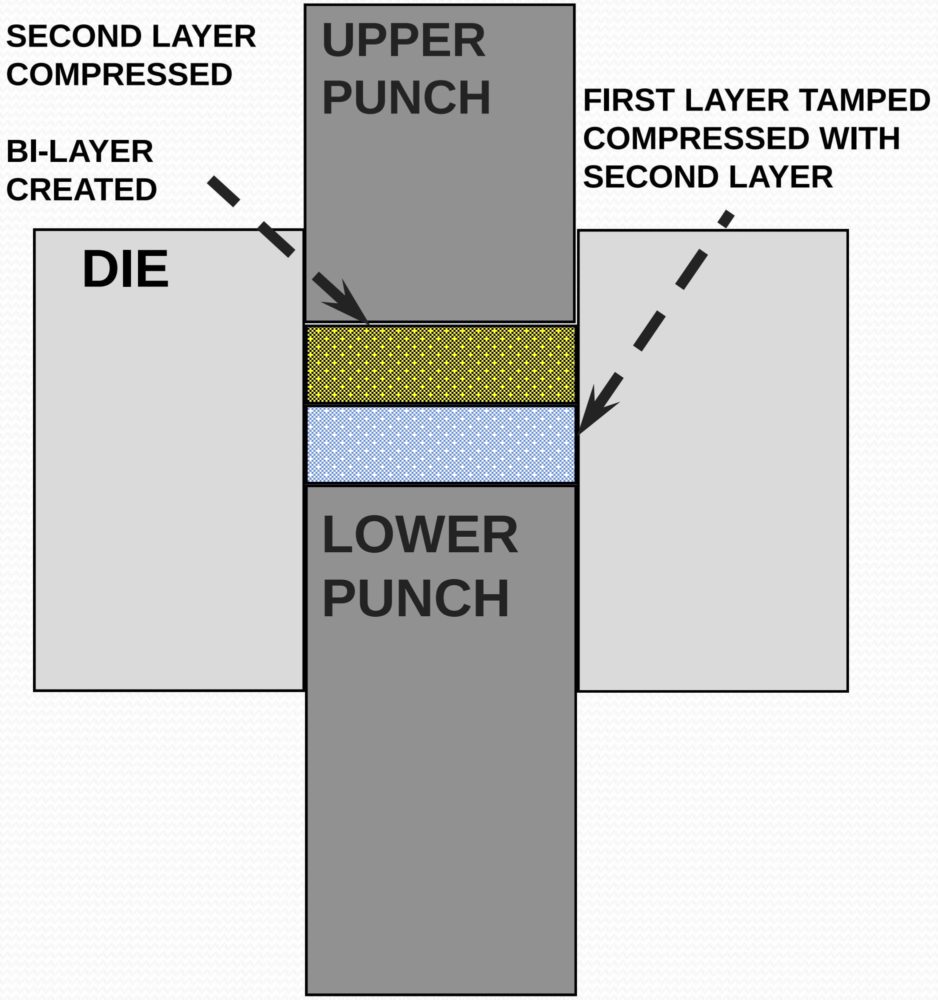
Ref: Fette America

Bilayer tableting: Filling of the 2nd layer



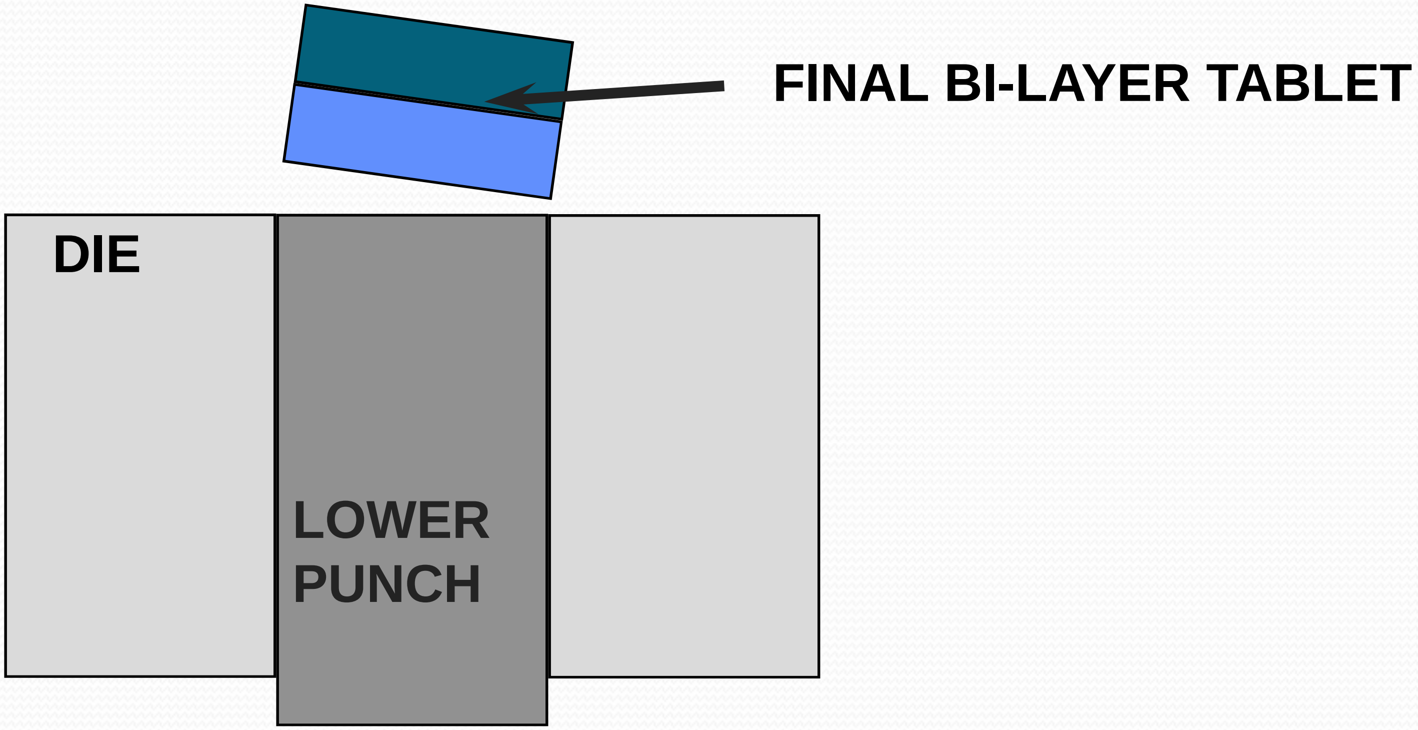
Ref: Fette America

Bilayer tableting: Compressing the bilayer tablet



Ref: Fette America

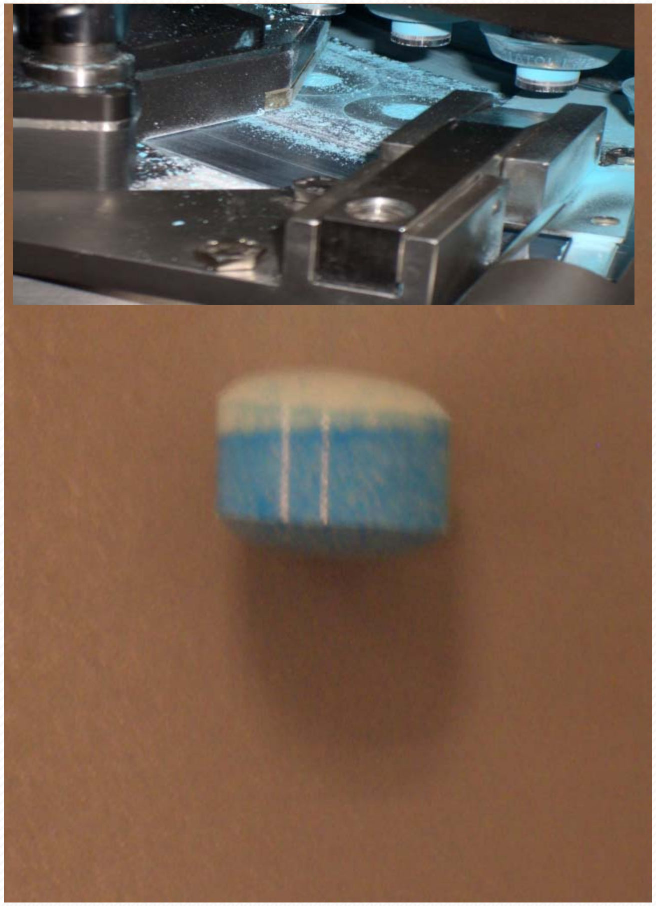
Bilayer tableting: Ejection of the tablet



Ref: Fette America

Bi-Layer challenges

- Centrifugal Force
- Granulation Loss
- Poor Yields
- Tablet Waste
- Cross Contamination of Layers
- Capping
- Lamination
- Weight Variation
- Final Layer Weight



Ref: Fette America

Bilayer Considerations

- Major differences from monolayer
  - Layer Adhesion
    - Low adhesion results in delamination
    - Factor of formulations and compression parameters
    - Coating adds strength and protects from delamination on stability but also creates a lot of stress on tablets during processing
    - Need additional sorting step to ensure all tablets are whole

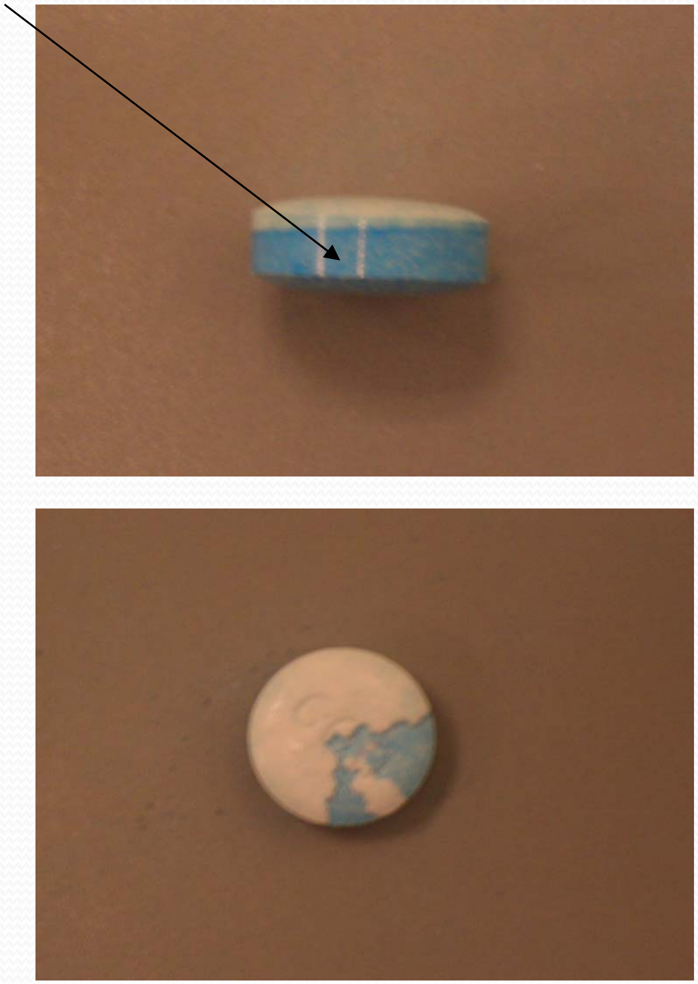
Layer Adhesion

- Most Bi-Layer products are formulated to adhere at several different force ranges. Problems arise when the first layer de-laminates or separates (caps) from the final layer. In these cases it is often necessary to use little to no force on the first layer of the press. On many presses the ability to control tablet weight on the first layer diminishes as the force becomes less measurable.

Ref: Fette America

Centrifugal Force

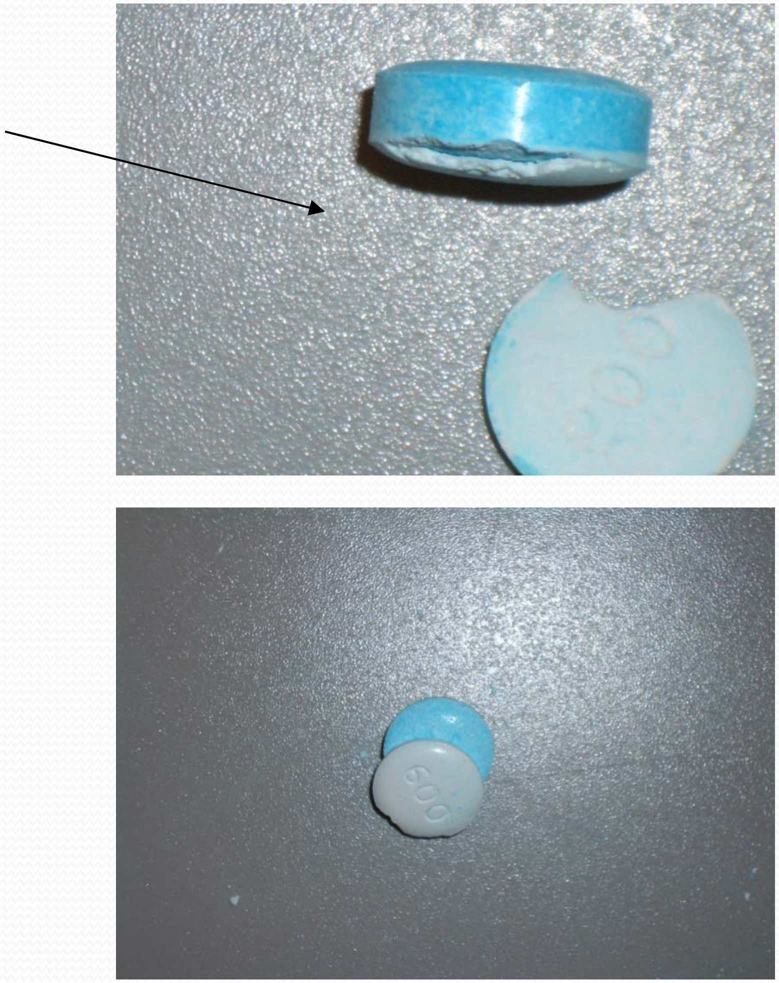
- First layer weight and press speed can cause slinging affect.
- Problem is more pronounced with large tablets.
- Tablets may have weak edge and poor friability
- Feeder and tail over-adjustments may help.
- To eliminate, the press speed should be reduced or the first layer force increased.



Ref: Fette America

Capping Example

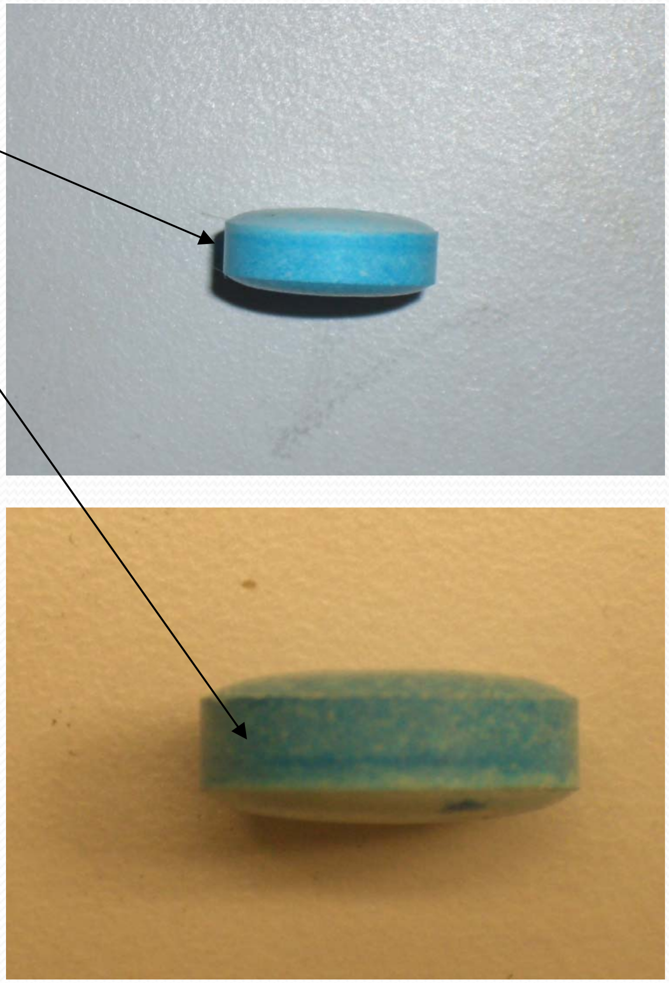
- Note the separation at layer
- In this case capping was caused by over compression of the blue layer
- Second layer weight (white) is extremely light and first layer (blue) compression force is critical factor in bonding



Ref: Fette America

Lamination

- Note the darker blue lines on the side view of the tablet
- When tested on hardness tester tablets capped at these points
- Lamination occurred as a result of over-compression of the first layer



Ref: Fette America

Factors which Affect Layer Bonding

- Weight of first and second layer
- Bonding characteristics of granulations used for each layer
- Tooling tip and die configuration
- Press speed
- Compression force

Ref: Fette America

Bilayer Considerations

- Major differences from monolayer
  - Weight Control
    - First layer weight control not as accurate (low force = low sensitivity)
    - Second layer determined by difference (requires accurate sampling)
    - Second layer more sensitive to poor flow
    - Second layer weight control affected by first layer variability
    - Generally more sensitive to speed than monolayer
    - Un-similar weight ratios can be challenging for meeting assay
  - Contamination of layers

	500	100
0.95	475	95
1.05	525	105
difference	50	10

Bilayer Considerations

- Major differences from monolayer
  - Compression
    - Dealing with 2 formulations = each of which affect the whole
    - Transmission of force not equal throughout tablet – buffered by layers, layers react differently to force
    - Small changes in formulation can have larger impact than monolayers
    - Changes in tooling have larger affect
    - Hardness measurements reflect hardest layer

Compaction Simulation

One must characterize the physico-mechanical properties of the materials in order to have a better understanding of compaction behavior of a given material!

Compaction Simulators

Definition

"A Compaction Simulator is a computer controlled instrumented single station tablet press, capable of mimicking the compaction cycle of any tablet press in real time and recording all important parameters during the cycle."

Celik and Marshall, DDIP, 15(5), 759-800 (1989)

Compaction Simulators

Various Types

ESH Testing Limited (UK)

Hydraulic

STYLCAM Medelpharm (FR)

Mechanical

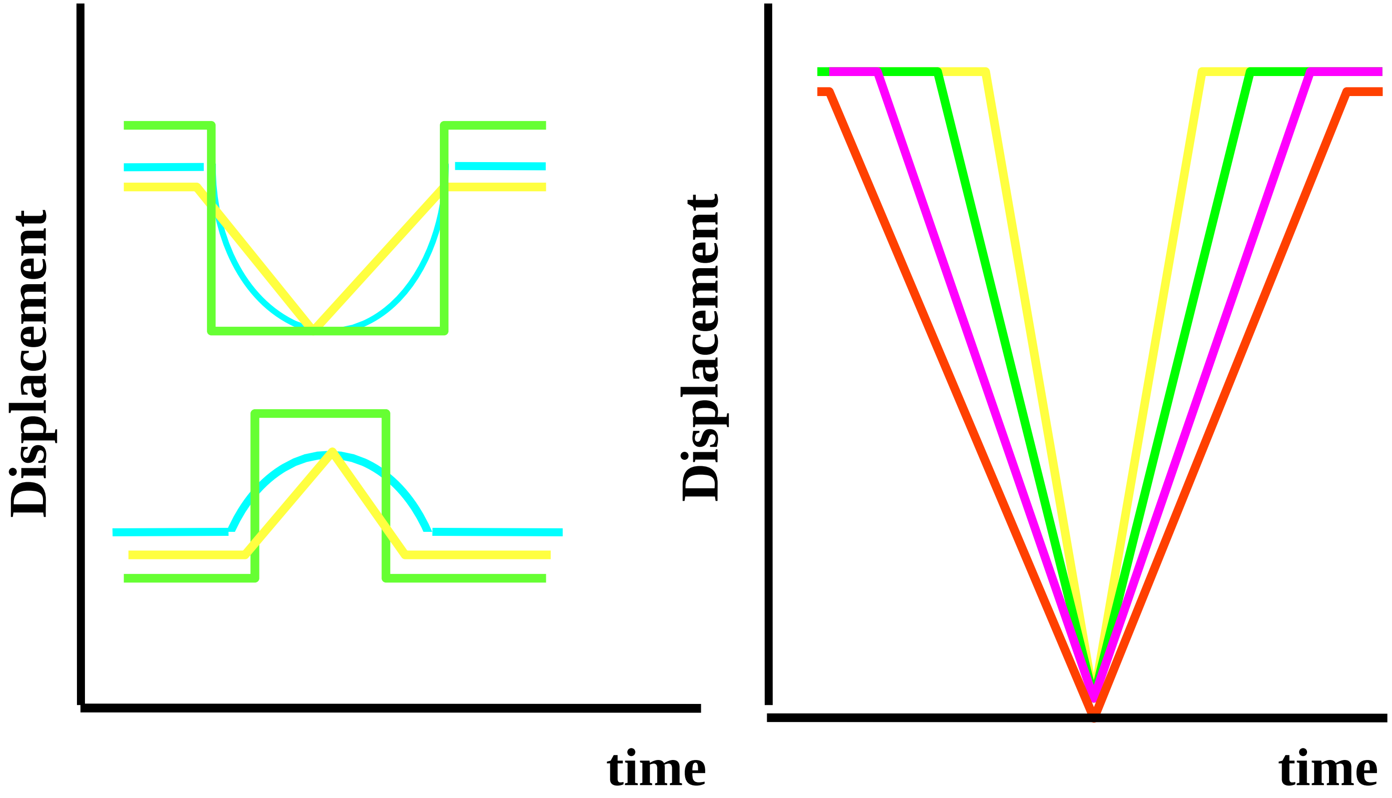
PRESSTER TM (USA)

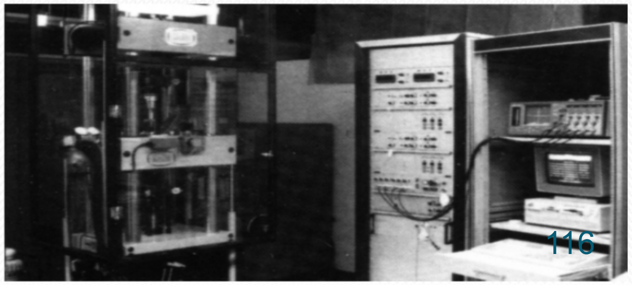
Mechanical

Compaction Simulator

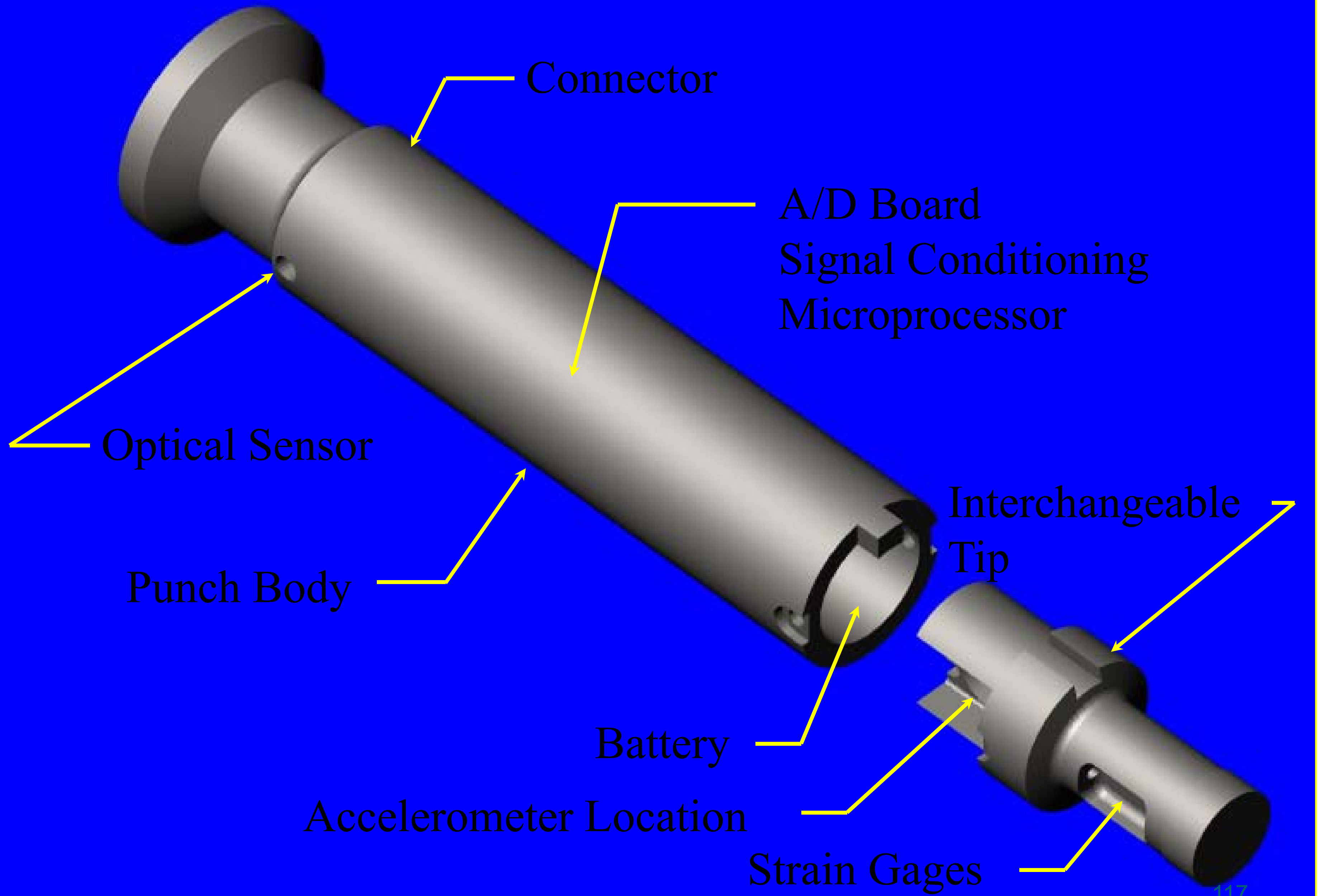
Comparison

Hydraulic Systems:
Stylizes Compaction Profiles

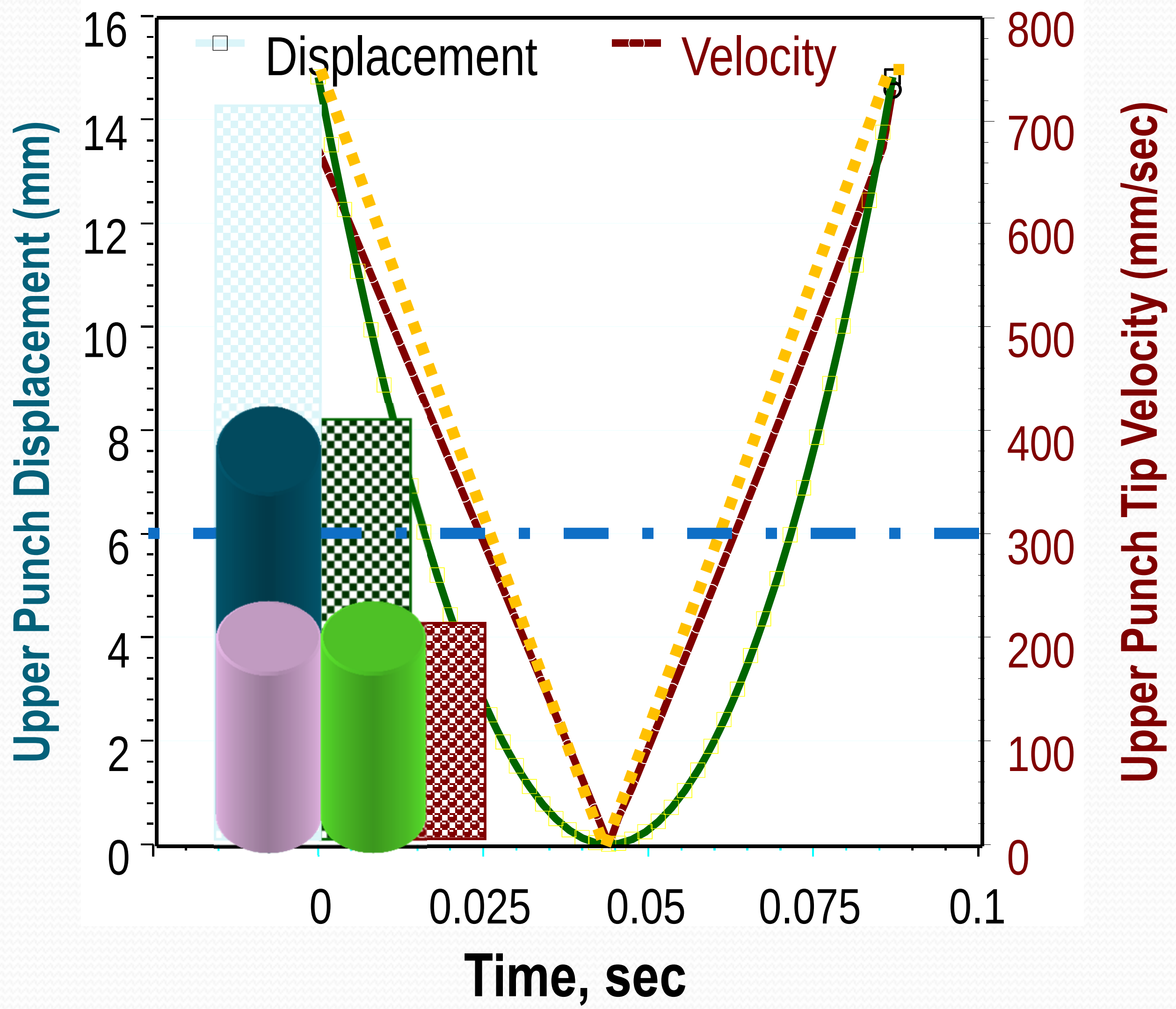




The Punch


Connector
A/D Board
Signal Conditioning
Microprocessor
Optical Sensor
Interchangeable
Tip
Punch Body
Battery
Accelerometer Location
Strain Gages

Sinewave vs Sawtooth



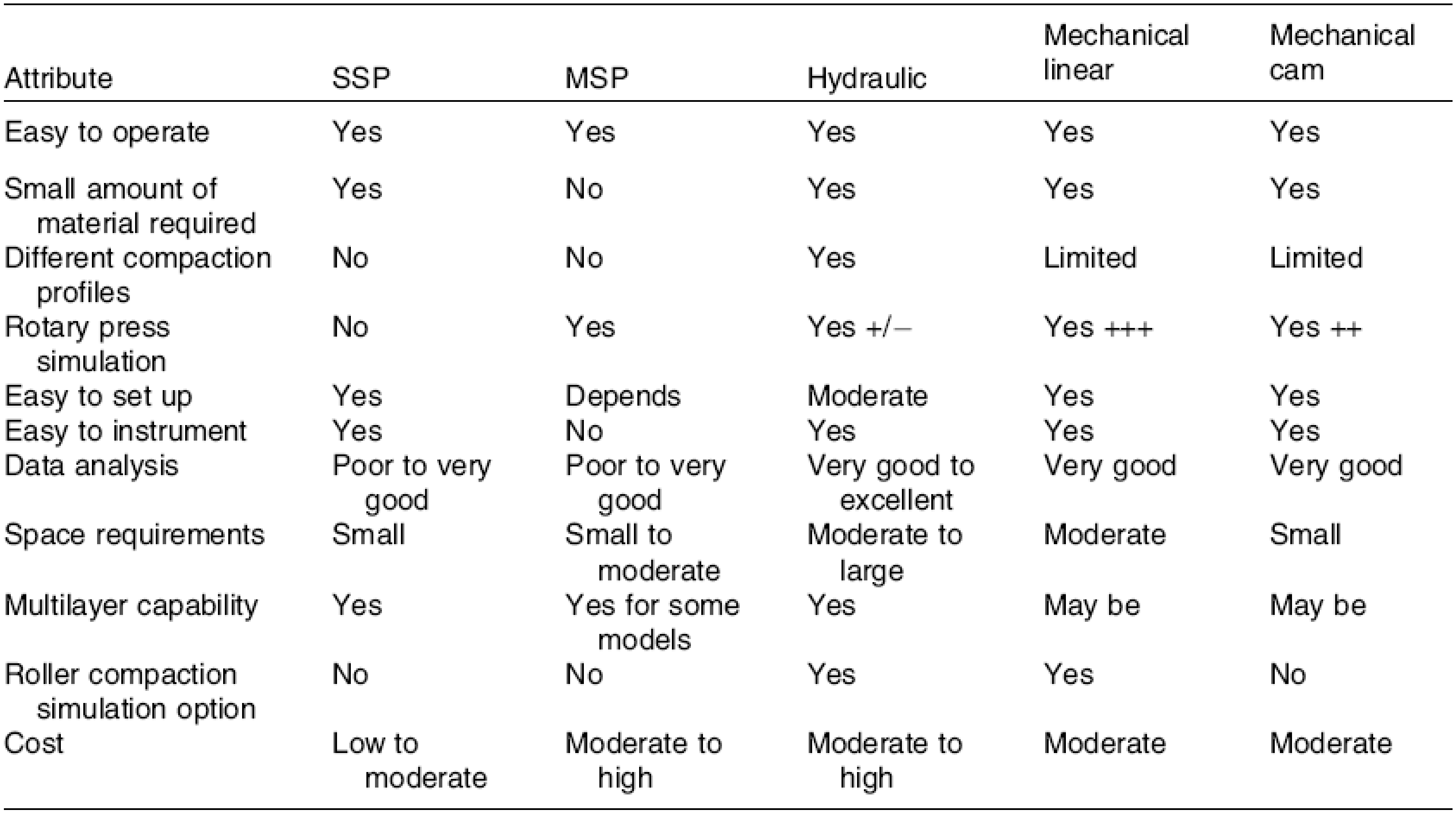
A Simulated Upper Punch Profile for Manesty Beta Press running at 103 rpm
(The Rippie-Danielson method was utilized to obtain the profile)

Why use a compaction simulator vs others?

Advantages of Compaction simulators:

- Compaction simulators can be used to evaluate:
  - The effect of tooling variation
  - Scale up parameters
  - Build up effects such as adhesion problems (much easier with mechanical rotary machine due to number of tablets produced per hour)
  - The effect of process variables (speed, etc.)
  - Basic compaction mechanisms
  - tablet properties (strength, disintegration, dissolution) under identical manufacturing conditions (since the compaction history of each individual tablet is known)
- Milligram quantities of material are required
- Fingerprinting of actives, excipients and formulations is possible

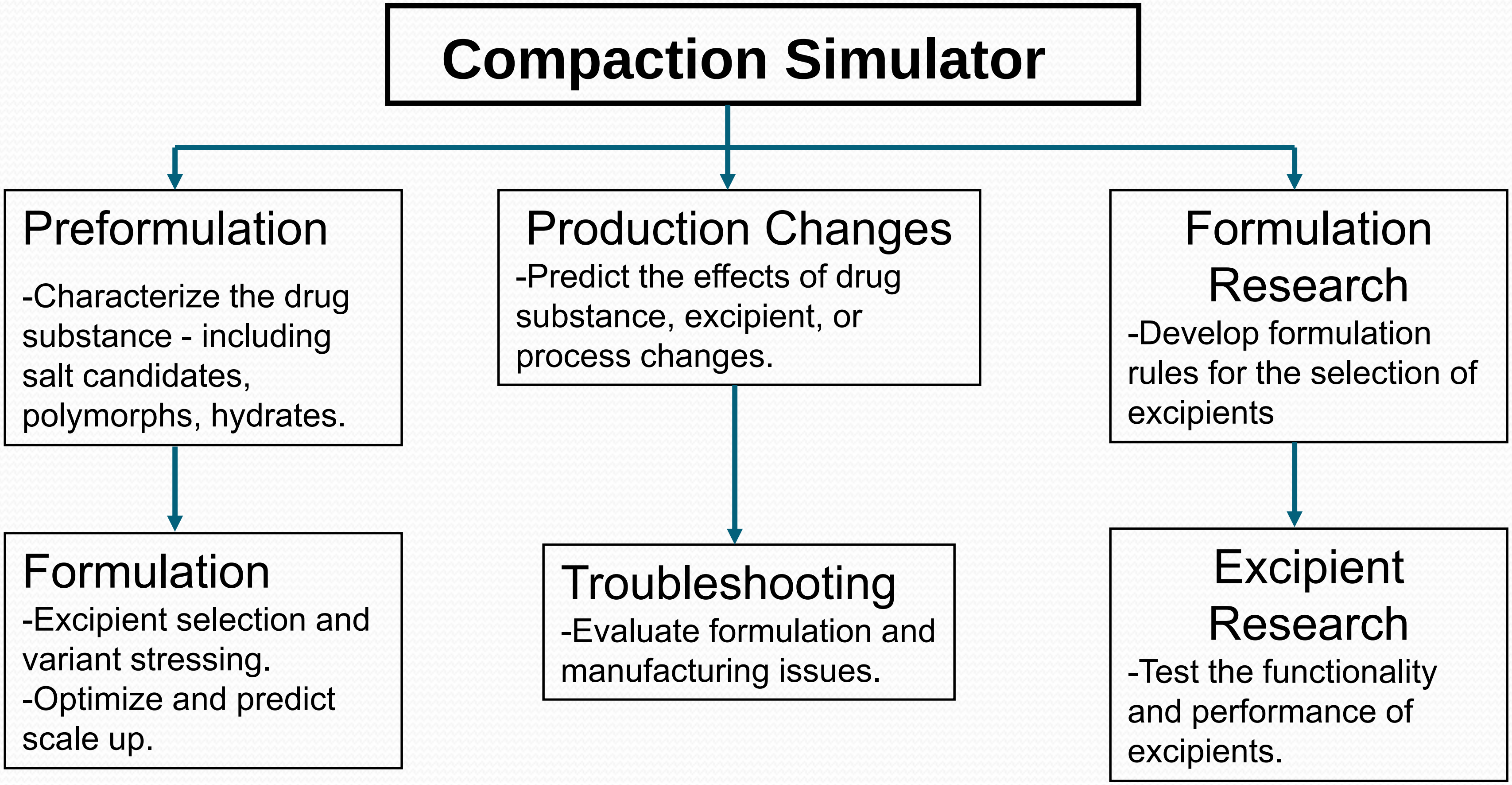
Why use a compaction simulator vs others?



Attribute	SSP	MSP	Hydraulic	Mechanical linear	Mechanical cam
Easy to operate	Yes	Yes	Yes	Yes	Yes
Small amount of material required	Yes	No	Yes	Yes	Yes
Different compaction profiles	No	No	Yes	Limited	Limited
Rotary press simulation	No	Yes	Yes +/−	Yes +++	Yes ++
Easy to set up	Yes	Depends	Moderate	Yes	Yes
Easy to instrument	Yes	No	Yes	Yes	Yes
Data analysis	Poor to very good	Poor to very good	Very good to excellent	Very good	Very good
Space requirements	Small	Small to moderate	Moderate to large	Moderate	Small
Multilayer capability	Yes	Yes for some models	Yes	May be	May be
Roller compaction simulation option	No	No	Yes	Yes	No
Cost	Low to moderate	Moderate to high	Moderate to high	Moderate	Moderate

Compaction Simulator

Broad Based Applications



Compaction Simulator

Preformulation

-Characterize the drug substance - including salt candidates, polymorphs, hydrates.

Formulation

-Excipient selection and variant stressing.

-Optimize and predict scale up.

Production Changes

-Predict the effects of drug substance, excipient, or process changes.

Troubleshooting

-Evaluate formulation and manufacturing issues.

Formulation Research

-Develop formulation rules for the selection of excipients

Excipient Research

-Test the functionality and performance of excipients.

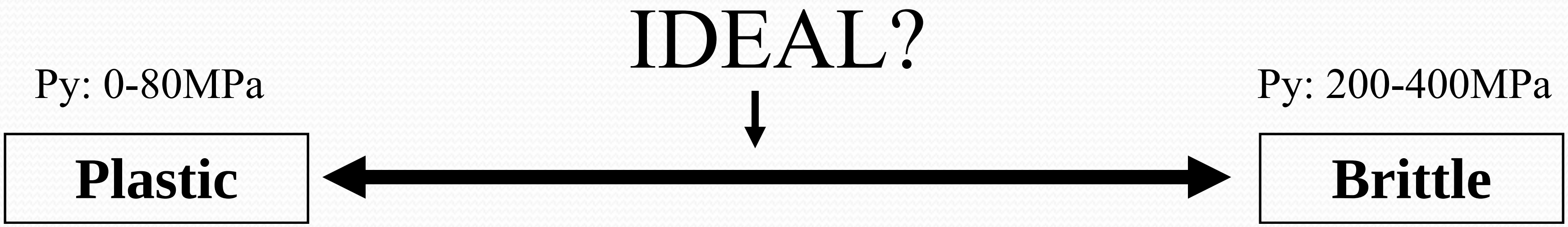
Compaction Simulator

Additional Applications

- PAT/QBD tablet production of various drug loads at manufacturing speeds for analytical model development
- Evaluation of bilayer tablet compaction
- Determine impact of humidity on compaction
- Effect of tooling shape or size, punch coatings, tooling comparisons

Material properties

Selection of diluents according to the mean yield pressure of the drug substance and diluent:



IDEAL?

Py: 0-80MPa

Plastic

Py: 200-400MPa

Brittle

Liable to surface contamination by lubricants.

Capable of bonding at low pressure

Time dependant deformation

Fragmentation reduces the effects of surface contamination.

Bonding occurs at relatively high pressures

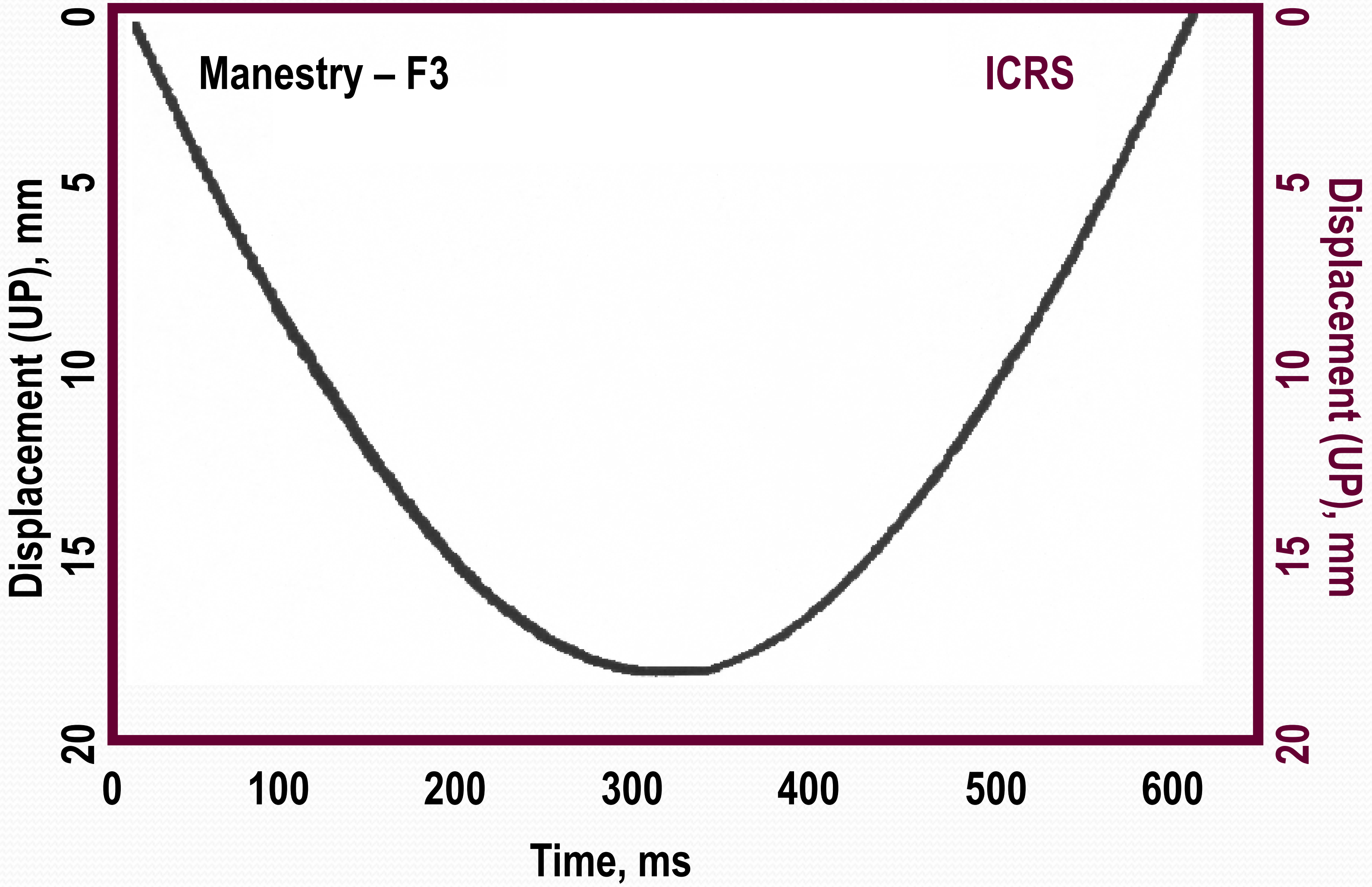
Case studies

Case study 1: Manesty F-3 Press Simulation

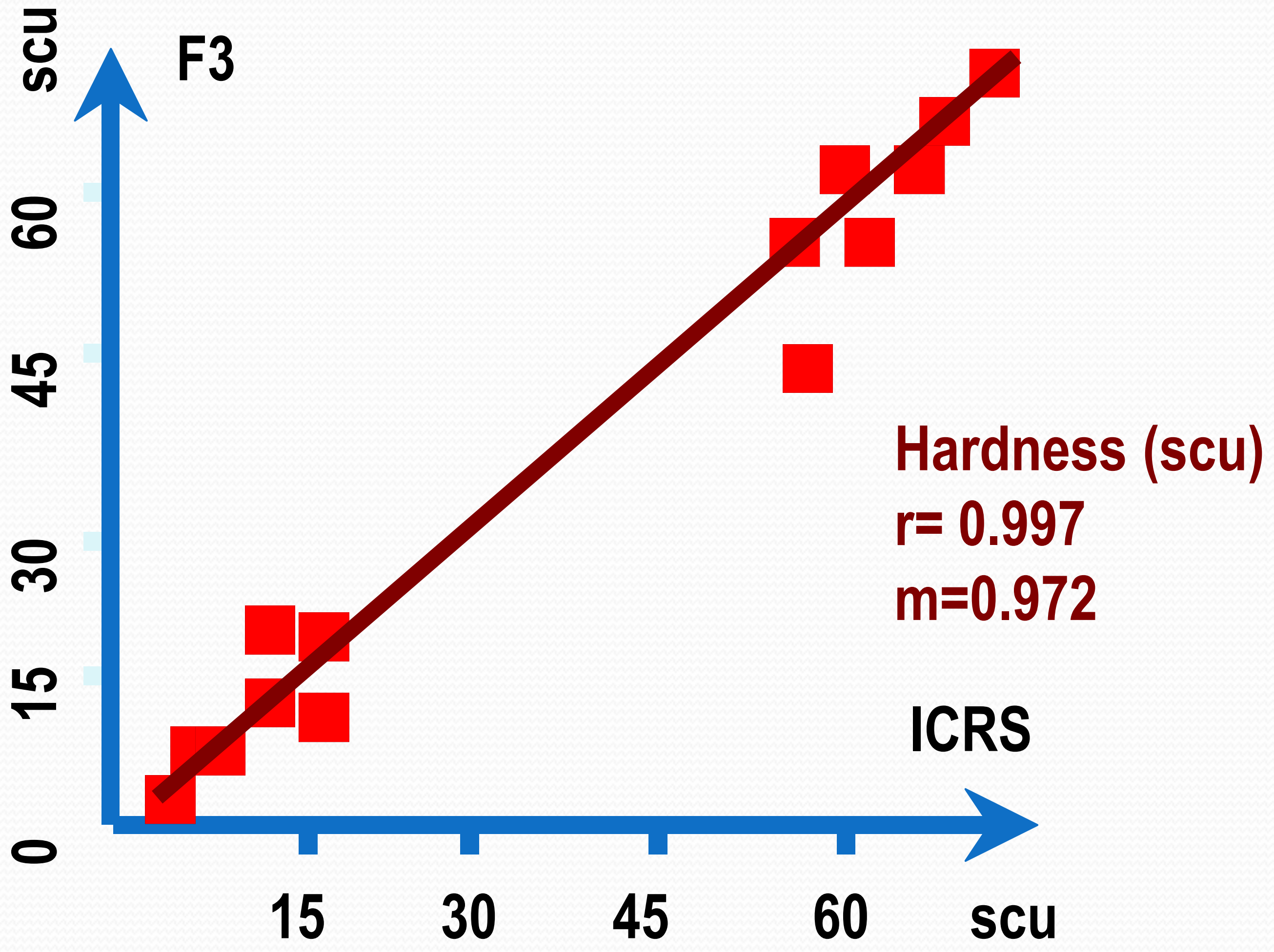
- Materials: microcrystalline cellulose, lactose, pregelatinized starch, dicalcium phosphate dihydrate
- Tooling : 8 mm flat faced, round
- Operation speed : 42 tpm and 89 tpm

SIMULATION
OR
CORRELATION
WHICH ONE IS
MORE IMPORTANT?

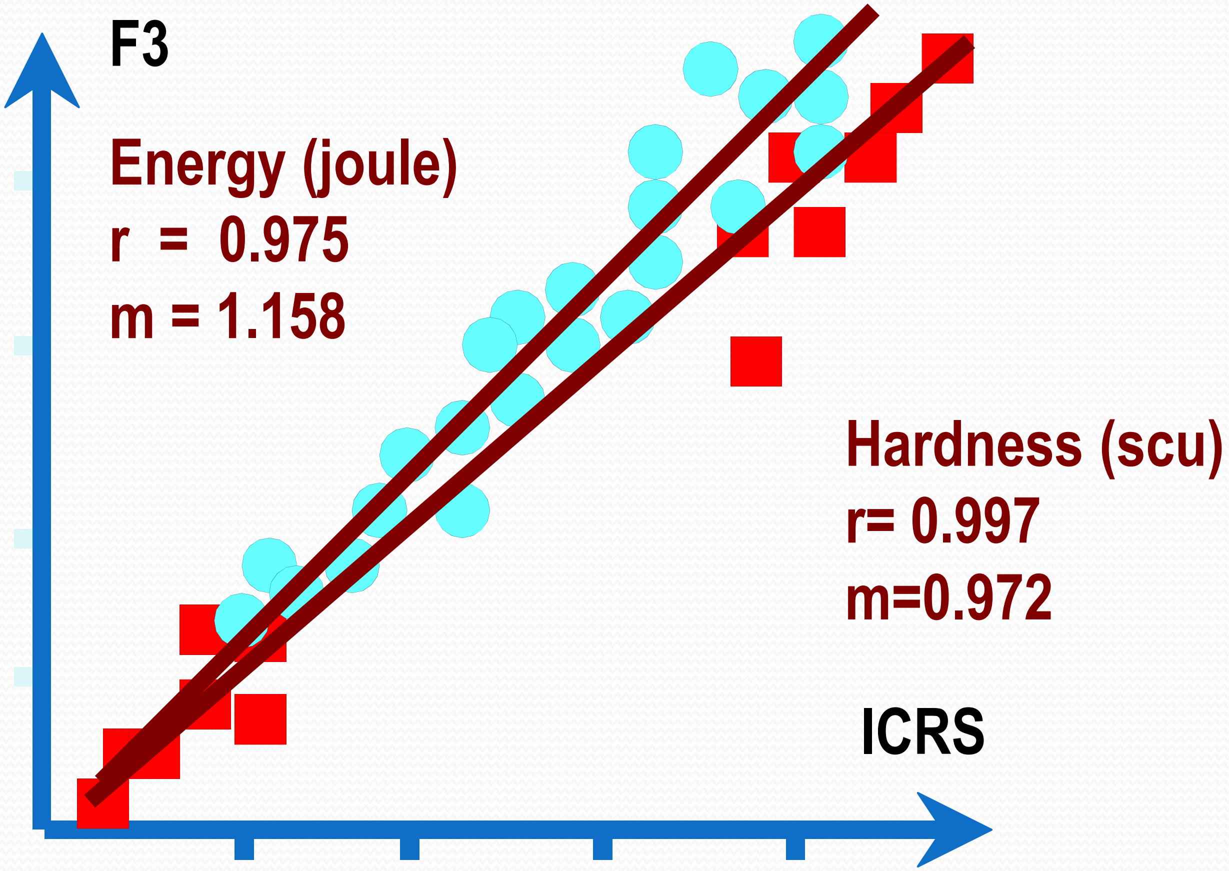
Case study 1: Manesty F-3 Press Simulation



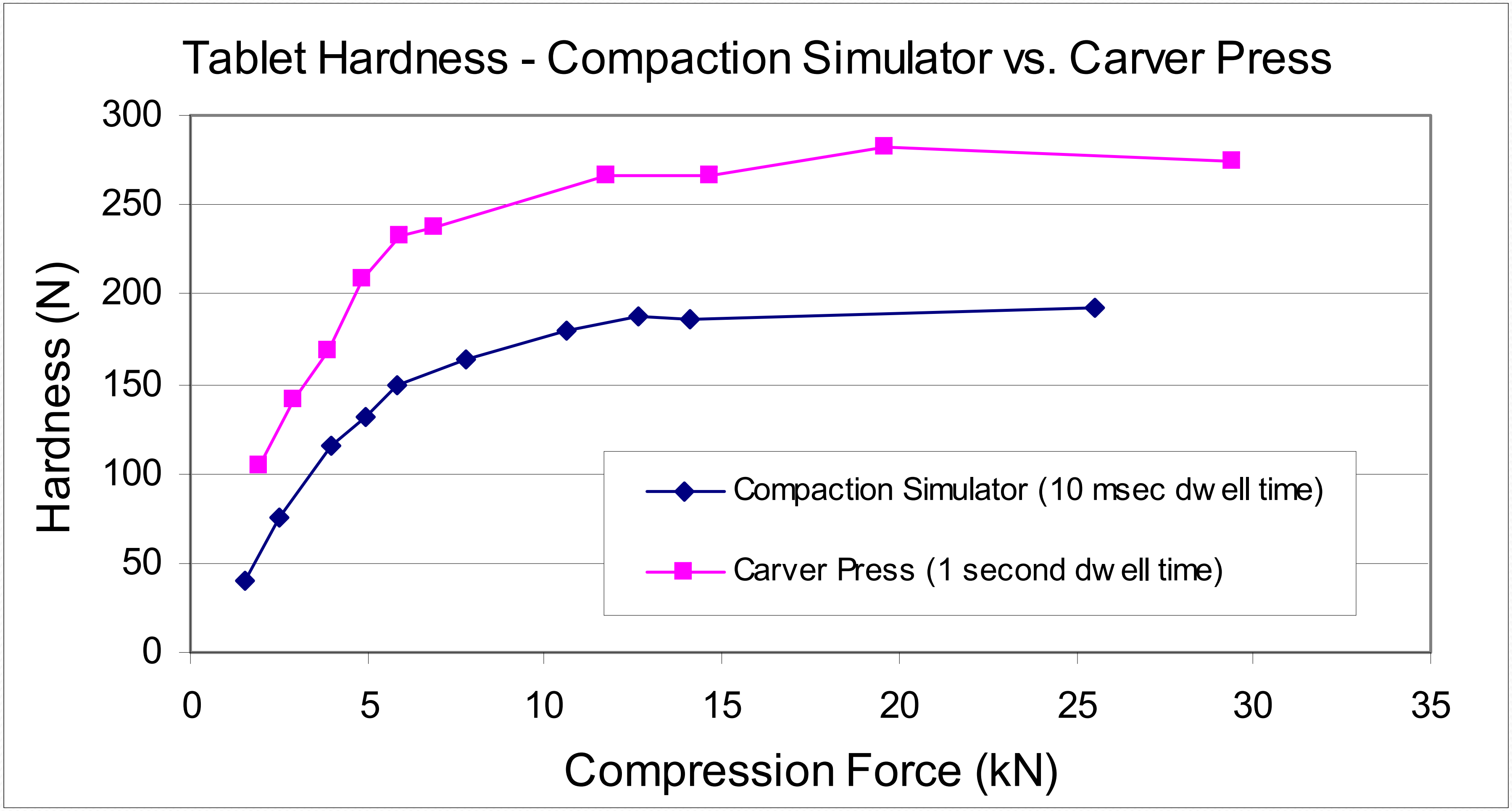
Case study 1: Manesty F-3 Press Simulation



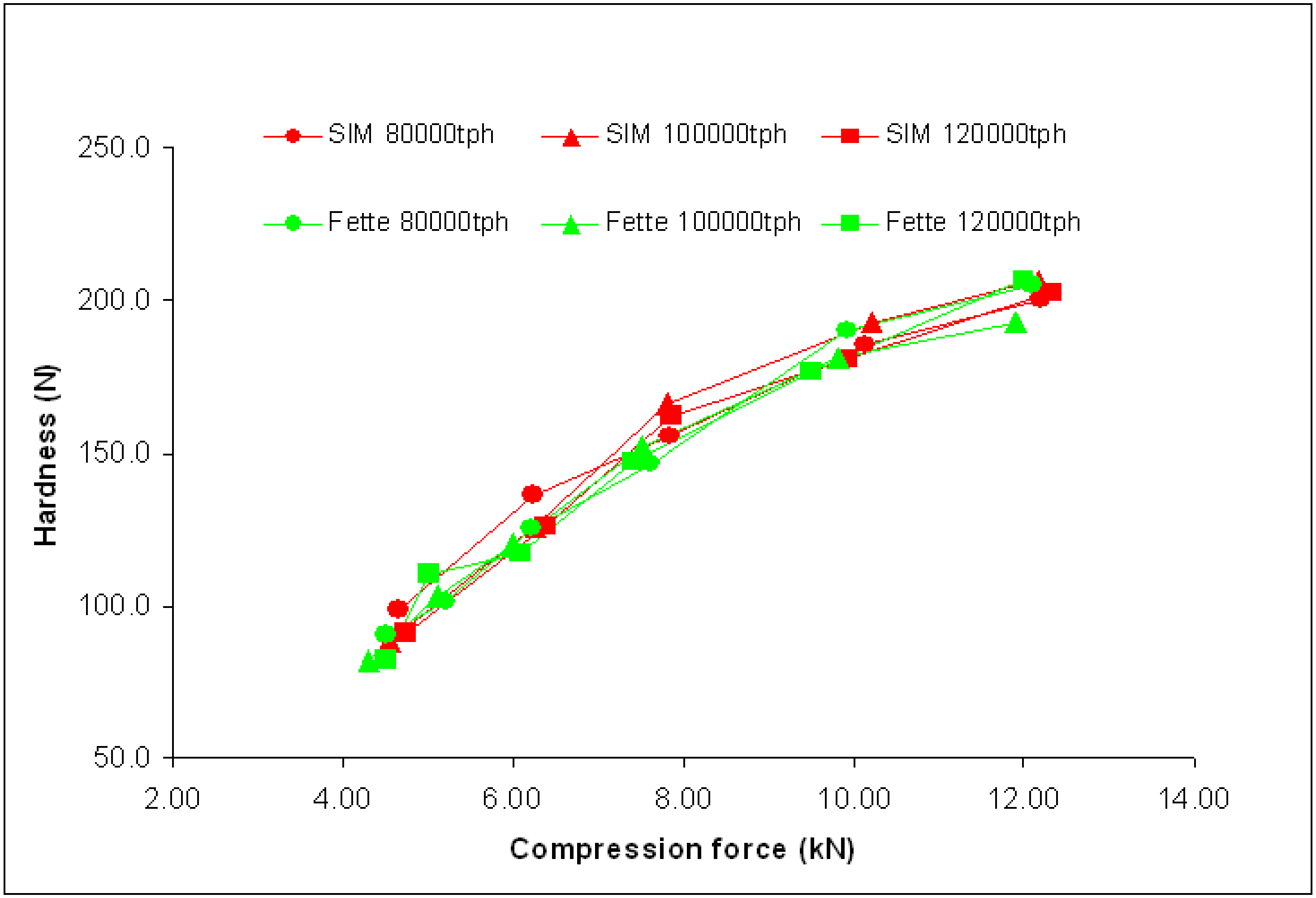
Case study 1: Manesty F-3 Press Simulation



Case study 2: 200mg MR Tablet 7mm round

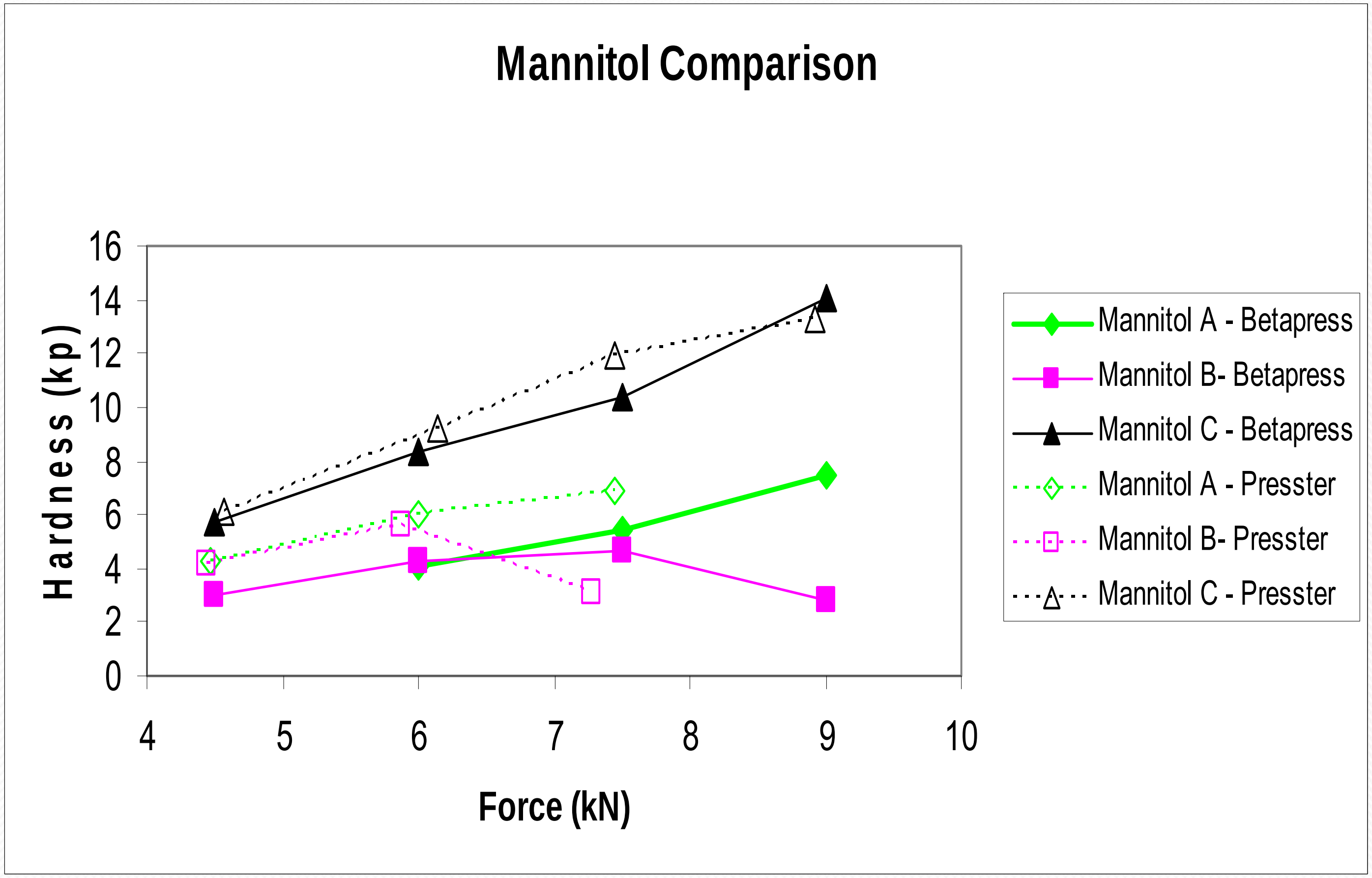


Case study 3: Fette 2090 vs Simulator



Case Study 4: Excipient Evaluation

- Evaluate different mannitols and validate data from compaction simulator



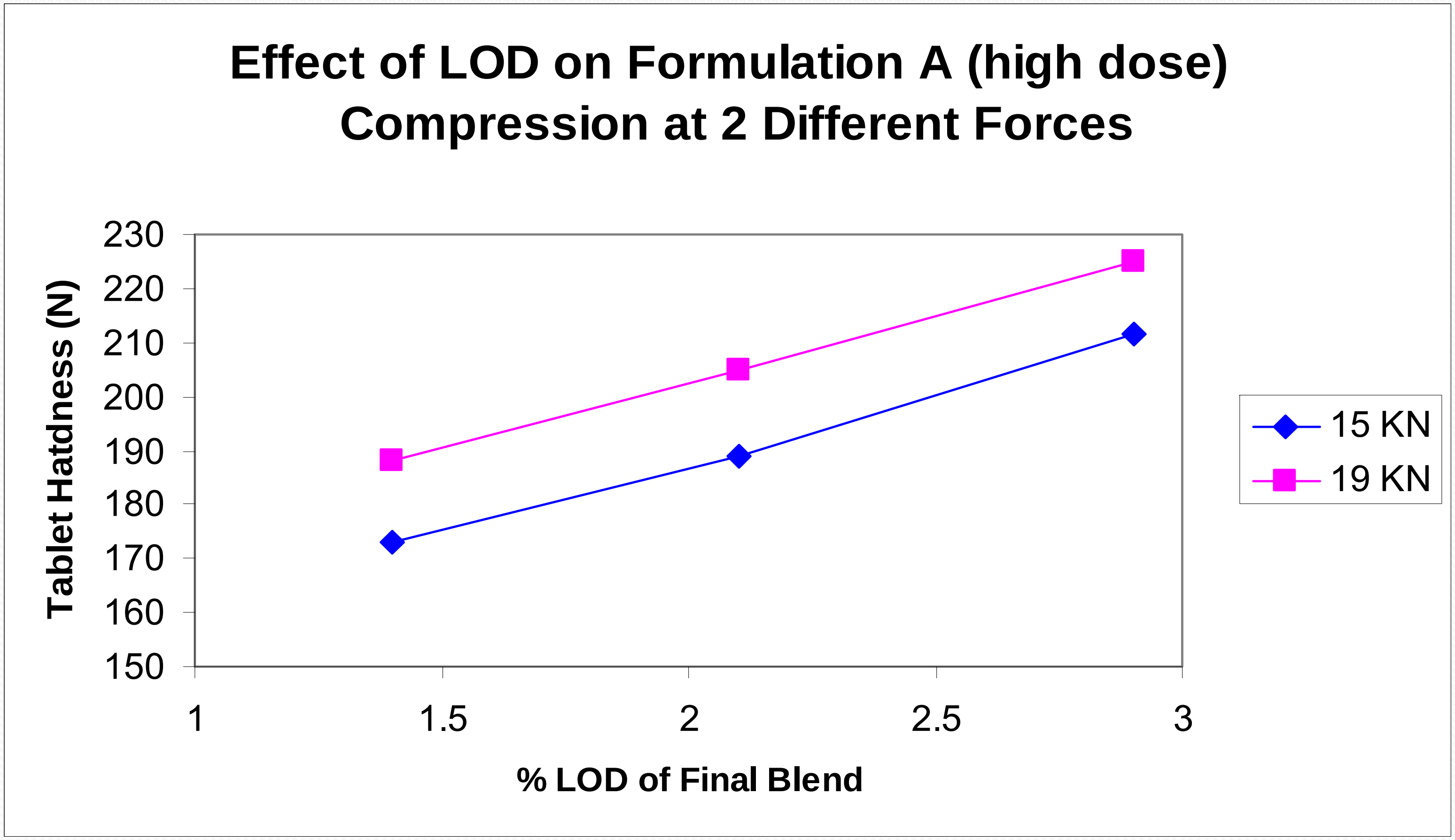
Case Study 4: Excipient Evaluation

Conclusions

A similar rank order of the excipients was found between the Betapress and the simulator. The data from the simulator was useful in allowing excipient selection to move forward with for development.

Case Study 5: Predict impact of changes

- To use the simulator to predict results that would be obtained in production with increased moisture content in final blend.



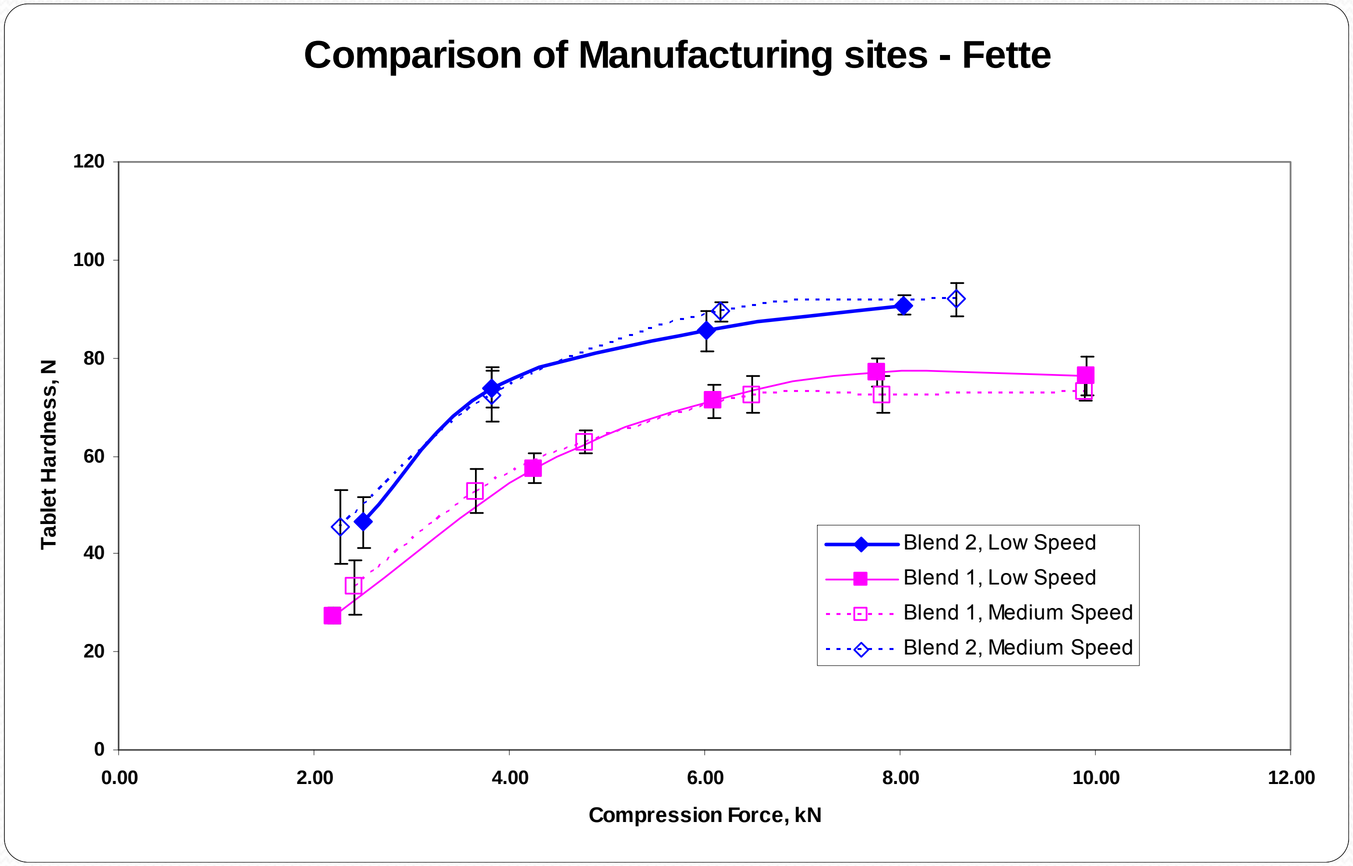
Case Study 5: Predict impact of changes

Conclusions

The simulator successfully predicted the compaction results for production. No issues during manufacturing with the increased LOD%.

Case Study 6: Troubleshooting

- To retrospectively evaluate two final blends to compare differences in results observed between development and production.



Case Study 6: Troubleshooting

Conclusions

The simulator confirmed that there was a difference between the two final blends and could have predicted the differences that were observed in production.

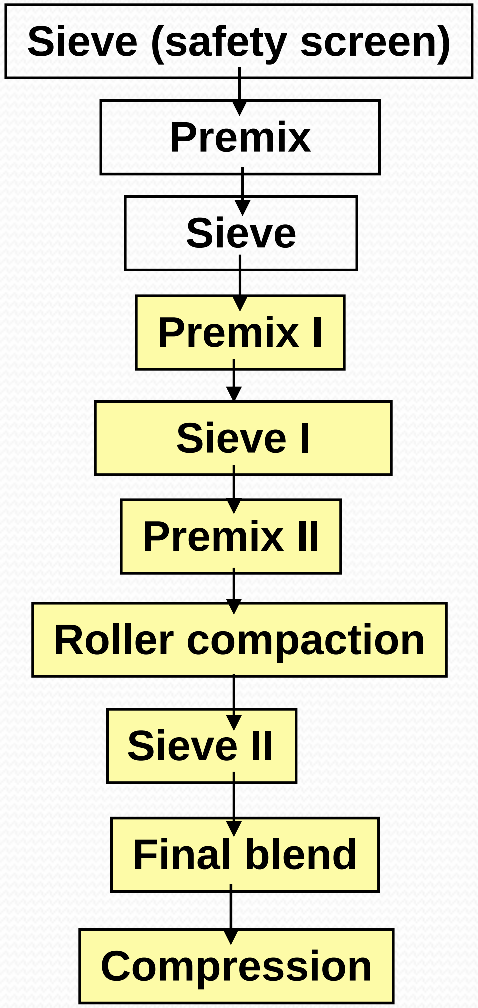
Compaction Simulators Summary

- Uses minimal quantities of material enabling early investigation and faster tablet development
- Can compress drug substance alone
- Early warning of formulation issues
- Predict which excipients should be used
- Predict effects of scaling up and using different presses

Case study 7

Lab scale optimization of a dual component roller compacted tablet formulation

Case study 7: Manufacturing process



Sieve (safety screen)

Premix

Sieve

Premix I

Sieve I

Premix II

Roller compaction

Sieve II

Final blend

Compression

Case study 7: DOE design

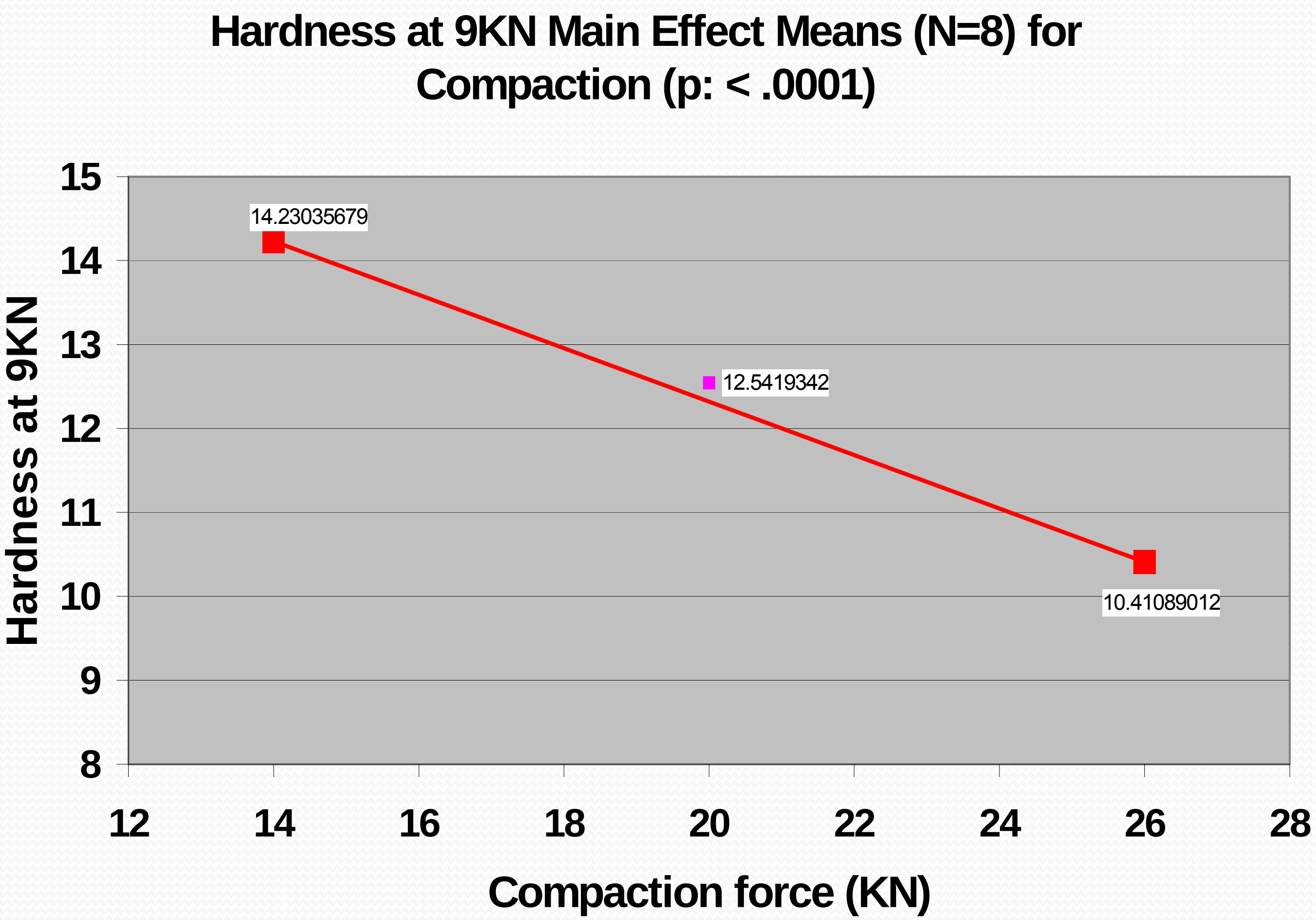
Level	Premix	Sieve	Premix I	Screen I / premix II	Compaction
Low (-1)	0	18	300	0 screen I / 0 premix II	14
Center (0)	300	30	400	18 screen I / 120 premix II	20
High (+1)	300	30	500	18 screen I / 120 premix II	26

- Main responses:
  - Content uniformity of low dose component
  - Dissolution at 30min
  - Tablet friability
  - Tablet hardness at given compression forces
- Twenty batches
  - 16 experiments with 4 center points

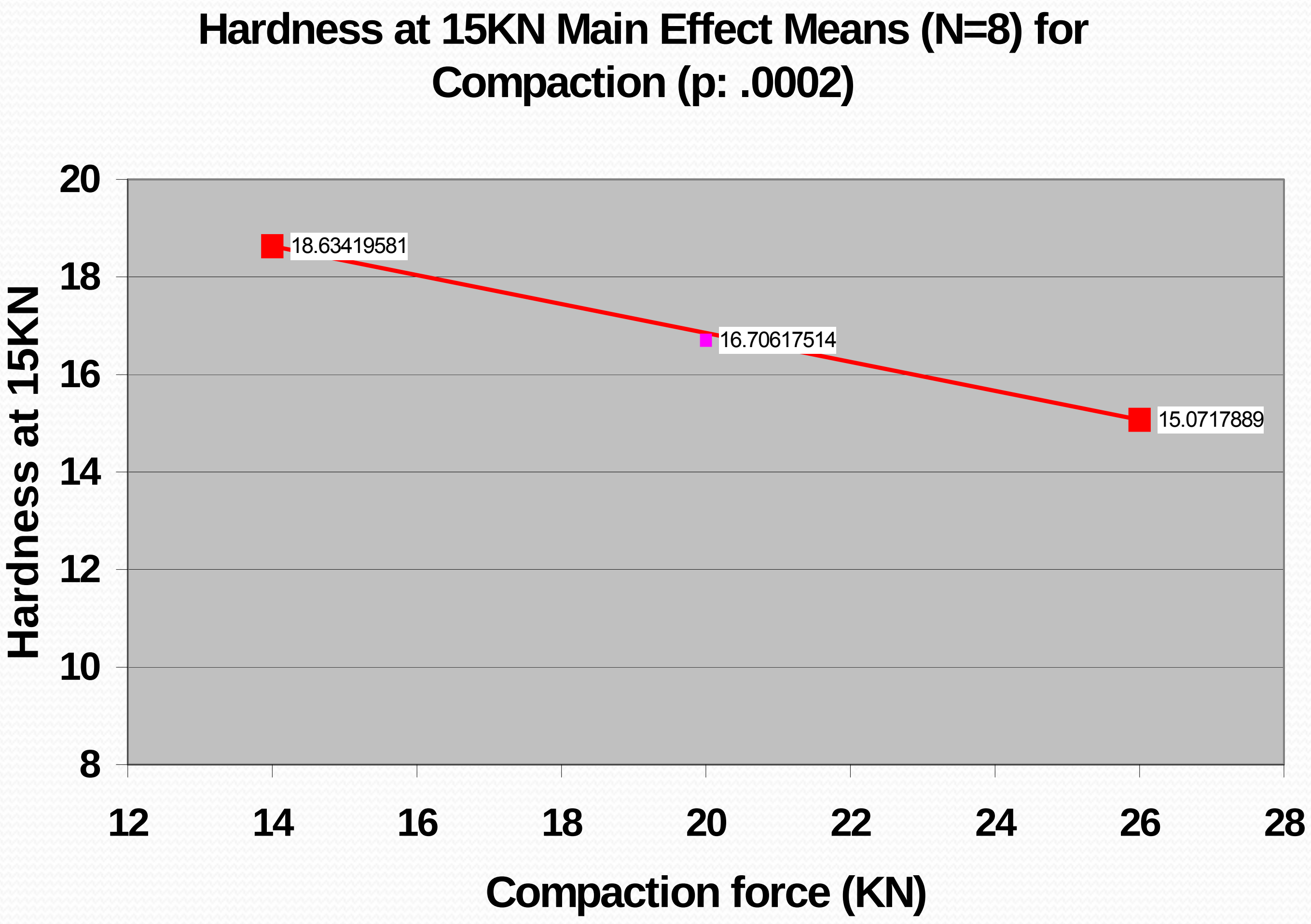
Case study 7

- The content uniformity of both components was satisfactory (RSD% < 2%) and was not affected by any of the DOE variables.
- None of the variables seemed to have significant impact on the dissolution.
- Tablet friability was satisfactory (<0.5%) and was not affected by the DOE variables.
- Compaction force significantly impacted the tablet hardness under given compression forces (both 9 and 15KN compaction force).

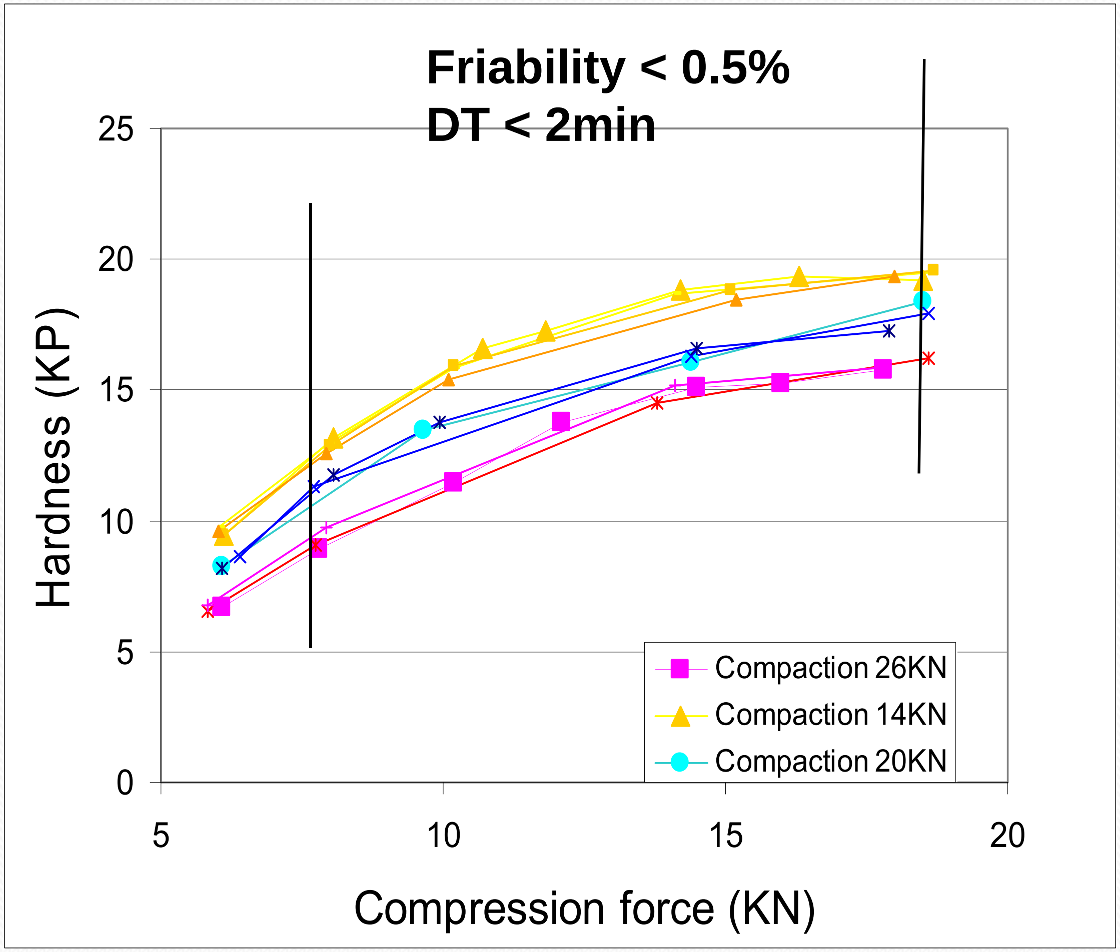
Case study 7


Hardness at 9KN Main Effect Means (N=8) for Compaction (p: < .0001)
Hardness at 9KN
15
14
13
12
11
10
9
8
14.23035679
12.5419342
10.41089012
12
14
16
18
20
22
24
26
28
Compaction force (KN)

Case study 7


Hardness at 15KN Main Effect Means (N=8) for Compaction (p: .0002)
20
18
16
14
12
10
8
Hardness at 15KN
18.63419581
16.70617514
15.0717889
12
14
16
18
20
22
24
26
28
Compaction force (KN)

Case study 7



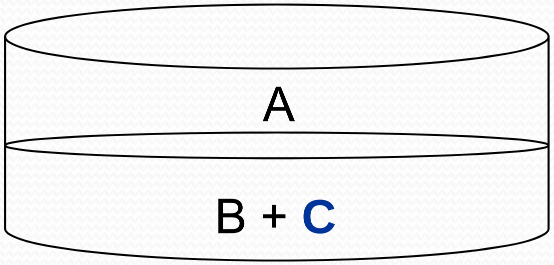
- Compaction force significantly impacted the tablet hardness
- A minimal of 6KP hardness window was observed for every batch regardless of compaction forces.
- All tablets in the window had a friability less than 0.5% and DT less than 2min.

Case study 8

Troubleshooting a CU issue for one component in a triple combo tablet

Case study 8

- **Objective:** To develop a robust triple component bilayer tablet formulation which is independent of compression process parameters



Components B and C are both low dose (<10mg)

- **Challenge**: Low assay observed for component **C**

Case study 8

Formulation	Assay (%)		
	C	B	A
Content uniformity	**89.9**	99.3	99.9
Blend uniformity	98.7	98.9	-

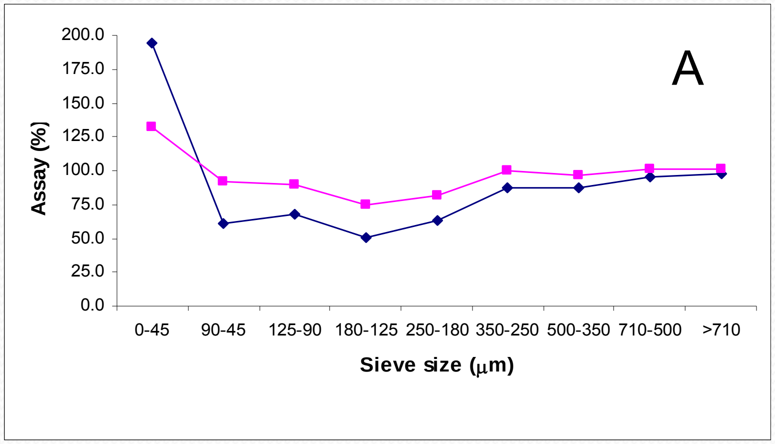
	Bilayer		1st layer		1st layer (split)	
Time point	**Wt.(mg)**	**RSD (%)**	**Wt. (mg)**	**RSD (%)**	**Wt. (mg)**	**RSD (%)**
Start	464.7	0.83	308.7	0.57	309.8	0.83
Middle	459.0	0.70	310.7	0.99	309.4	0.93
End	459.1	0.94	309.3	0.84	309.3	0.84

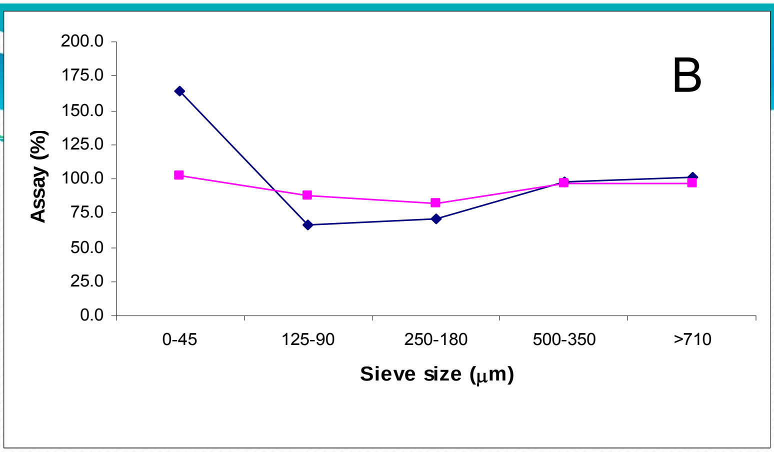
Case study 8

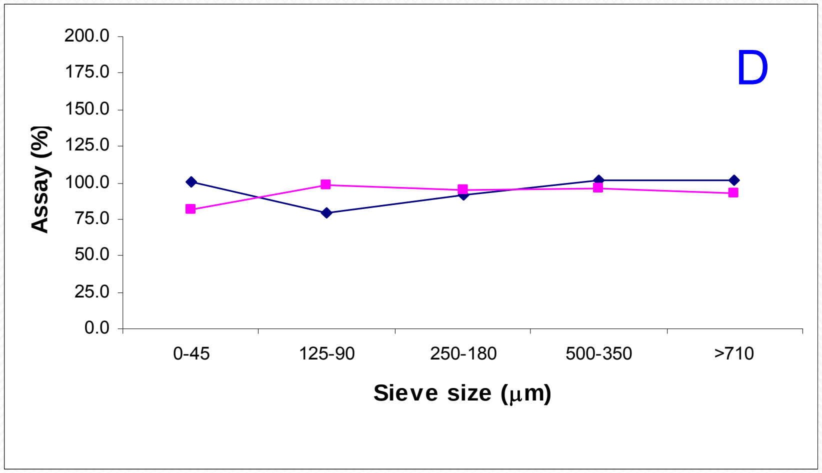
Formulation	Approach	Avicel grade	RC cycle
A	A / B+C	PH102	Once (control)
B	A / B+C	PH102	Twice
C	A / B+C	PH102	Recycling fine
D	A / B+C	PH105	Once
E	A+C / B	PH102	Once

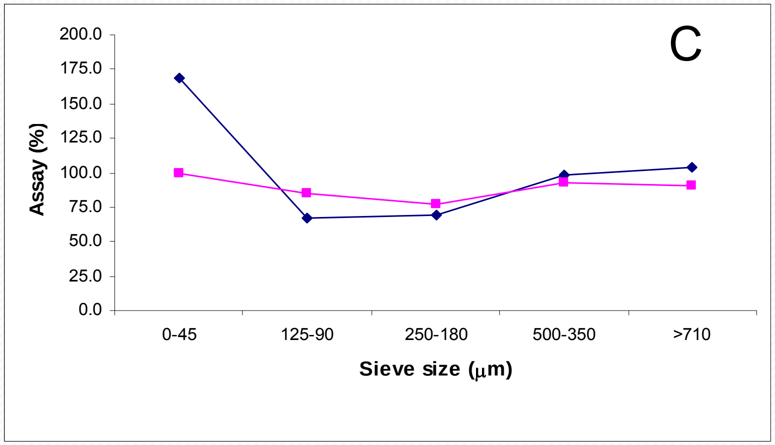
Filler	Mean particle size (µm)	Bulk Density (g/m)
Avicel PH102	90	0.30
Avicel PH105	20	0.25

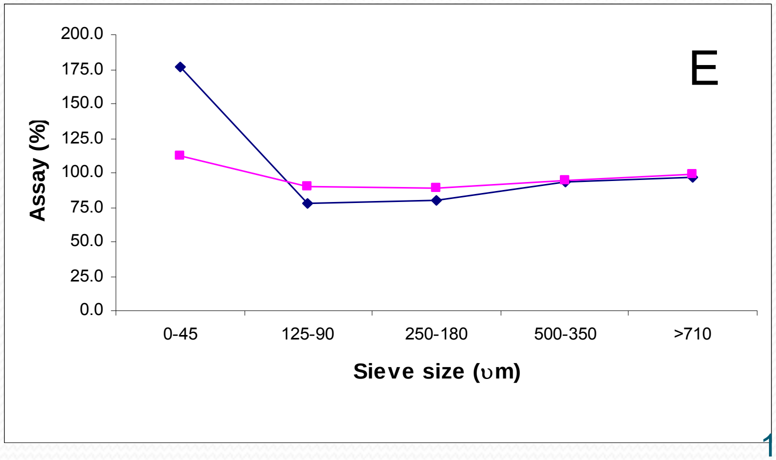
Case study 8











Component B

Component C

Case study 8

Formulation	Assay (%)		
	C	**B**	**A**
A	89.4	97.3	99.5
B	96.3	103.7	98.2
C	94.8	100.1	99.3
D	101.6	100.2	99.5
E	98.5	101.6	99.0

Acknowledgements

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- Ping Li
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- Simon Bateman
- Sudha Vippagunta
- Fette America

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Thank you for your attention!