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

Module 3: Formulation & Process Development Guidelines

IMPACT OF EXCIPIENT FUNCTIONALITY ON PRODUCT QUALITTY AND PERFORMANCE

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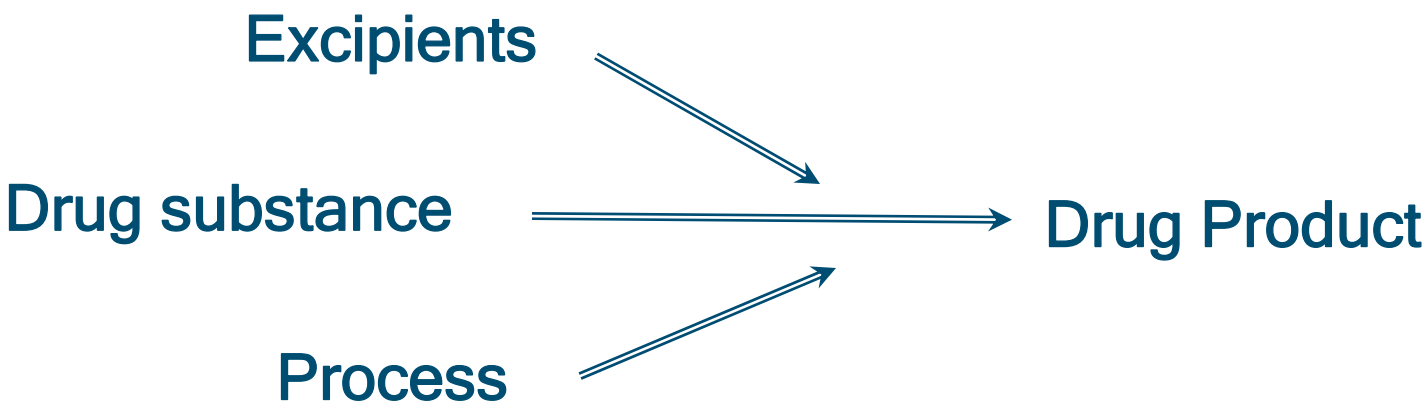
OUTLINE

- Introduction and Background
- Excipient Variability and Impact on Functionality
- Excipient Functionality and Impact on Dosage Forms Performance

DRUG PRODUCT DEVELOPMENT GOALS

Formulation Components and Process



EXCIPIENT DEFINITION

Any component, other than the active substance(s), intentionally added to the formulation of a dosage form to:

- Enable Processing and Manufacture
- Enhance Stability
- Increase Patient Acceptability
- Provide Product Identification
- Control Drug Release Rate(s)
- Enhance Bioavailability
- Provide Taste Masking and Palatability Enhancement

CLASSIFICATION OF EXCIPIENTS

- Fillers (Diluents)
- Disintegrants
- Glidants
- Sweeteners
- Flavors
- Antioxidants
- Chelating Agents
- Binders
- Lubricants
- Colors
- Film Formers
- Preservatives
- Buffers
- Release Modifiers

CHARACTERIZATION OF EXCIPIENTS

- Bulk material properties
  - Density (Bulk/Tapped)
  - Flow
  - Shear
  - Compressibility (compaction indices, dynamic studies of powder compaction)
- Particulate material properties
  - Particle size
  - Particle shape
  - True density

THE EVOLUTION OF EXCIPIENTS

- 1960's
  - Less Focus on Excipients
  - Limited Acceptable Excipients
    (e.g. Corn Starch, Talc, Sucrose and Lactose)
  - No Distinct Role in Product Performance
- Currently
  - Significant Interest in Excipients
  - New Excipients Introduced
    - Disintegrants
    - Release Modifiers (Polymers)
    - Direct Compression Carriers
  - Focus on functionality
  - Focus on Bioequivalence Issue

BULK DRUGS vs. EXCIPIENTS CHARACTERIZATION

- Bulk Drugs
  - Full Characterization of Physicochemical Properties
    - Potency and Degradation Profiles
    - Polymorphism
    - Crystal Habit

- Excipients
  - Inadequate Physicochemical Characterization
    - Different Compendial Methodology of Chemical Tests (USP, BP, JP and EP, etc.)
    - Limited Physical Testing
    - Limited Functional Testing

IMPACT OF EXCIPIENT VARIABILITY

- Product Manufacture and Processing
- Product Uniformity
  - Content Uniformity
  - Viscosity
  - Tablet Hardness
- Product Performance
  - Disintegration & Dissolution
  - Bioavailability
- Stability Issues
  - Product Shelf-Life
  - Aging Effects

SOURCE OF EXCIPIENT VARIABILITY

- Lot-to-lot Variability from the Same Manufacturer
- Different Production Sites for One Manufacturer
- Different Manufacturers
- Shipping and Storage Conditions; Aging Effects

BENEFITS OF USING WELL-CHARACTERIZED EXCIPIENTS

- The formulation process would be more predictable, and performance would be more reproducible because:
  - Raw materials complying with stringent but meaningful specifications would behave in a more predictable manner
  - Formulations could be more suitable for automation requiring much less operator intervention
  - Lot-to-lot variability in the final product would be minimized, and failure of batches could potentially be eliminated

EXCIPIENT FUNCTIONALITY

Definition

An attribute of excipient that can alter the product quality and performance of either the drug substance and/or the drug product

Impact of Excipient Functionality on Product Performance

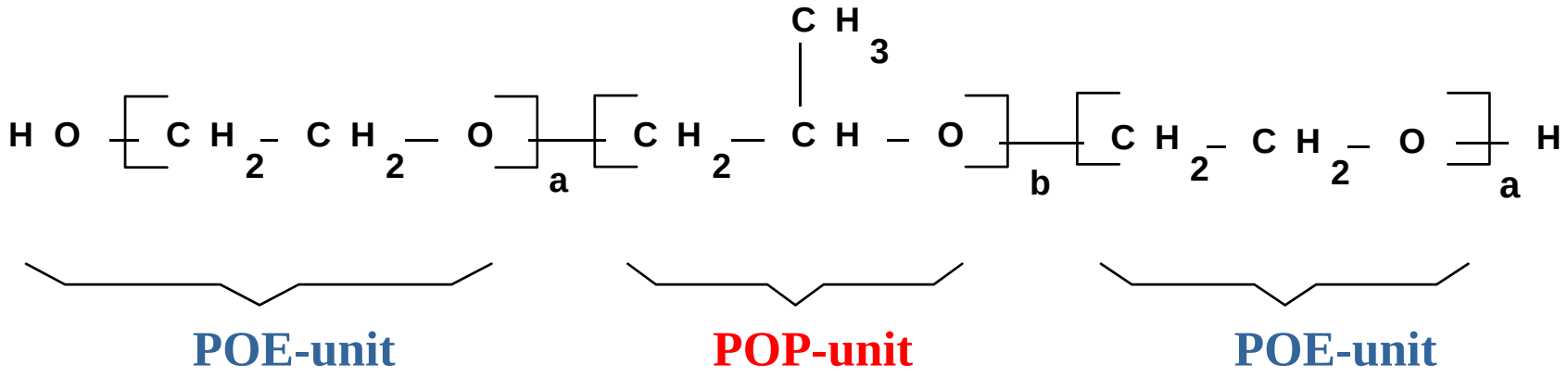
- Bioavailability
- Stability
- Manufacturability

IMPACT ON DISSOLUTION AND BIOAVAILABILITY

Poloxamers are block-copolymers consisting of Polyoxyethylene-(POE-) and Polyoxypropylene-(POP-) units

Chemical nature of poloxamers

Chemical composition:



Poloxamer 188	**a = ca. 79**	**b = ca. 28**	**Lutrol F 68**
Poloxamer 407	**a = ca. 98**	**b = ca. 57**	**Lutrol F 127**

Pharmacopoeial name	trade name

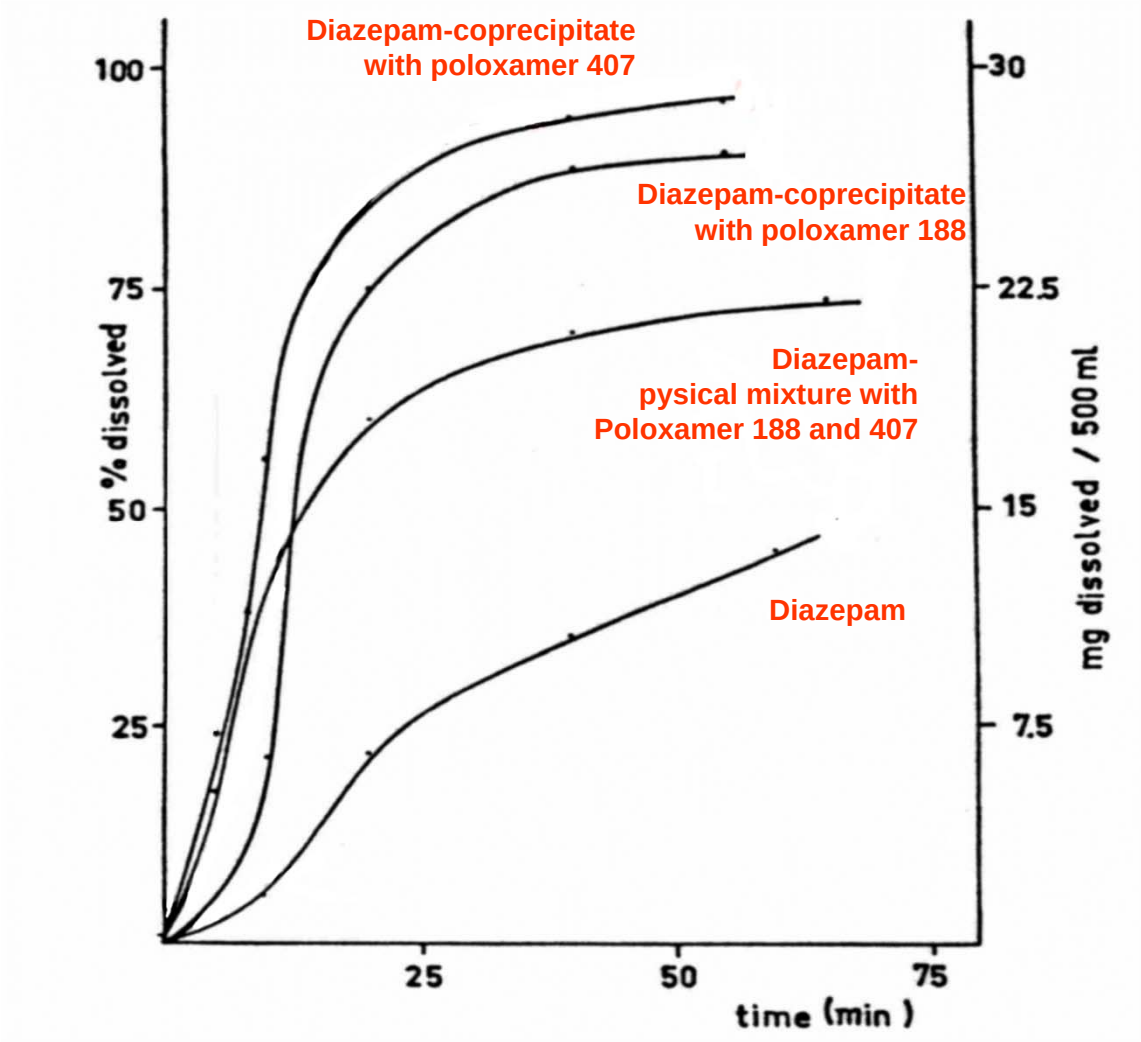
Lutrol F68 - function in solid dosage forms

- dispersing and wetting agent
- excipient to improve solubility, dissolution, absorption and bioavailability of drugs with low solubility in solid oral dosage forms, melt-granulated and spray-granulated formulations

  tabletting lubricant
- plasticizer for tablet coatings

Improvement of Drug Dissolution Using Lutrol F68

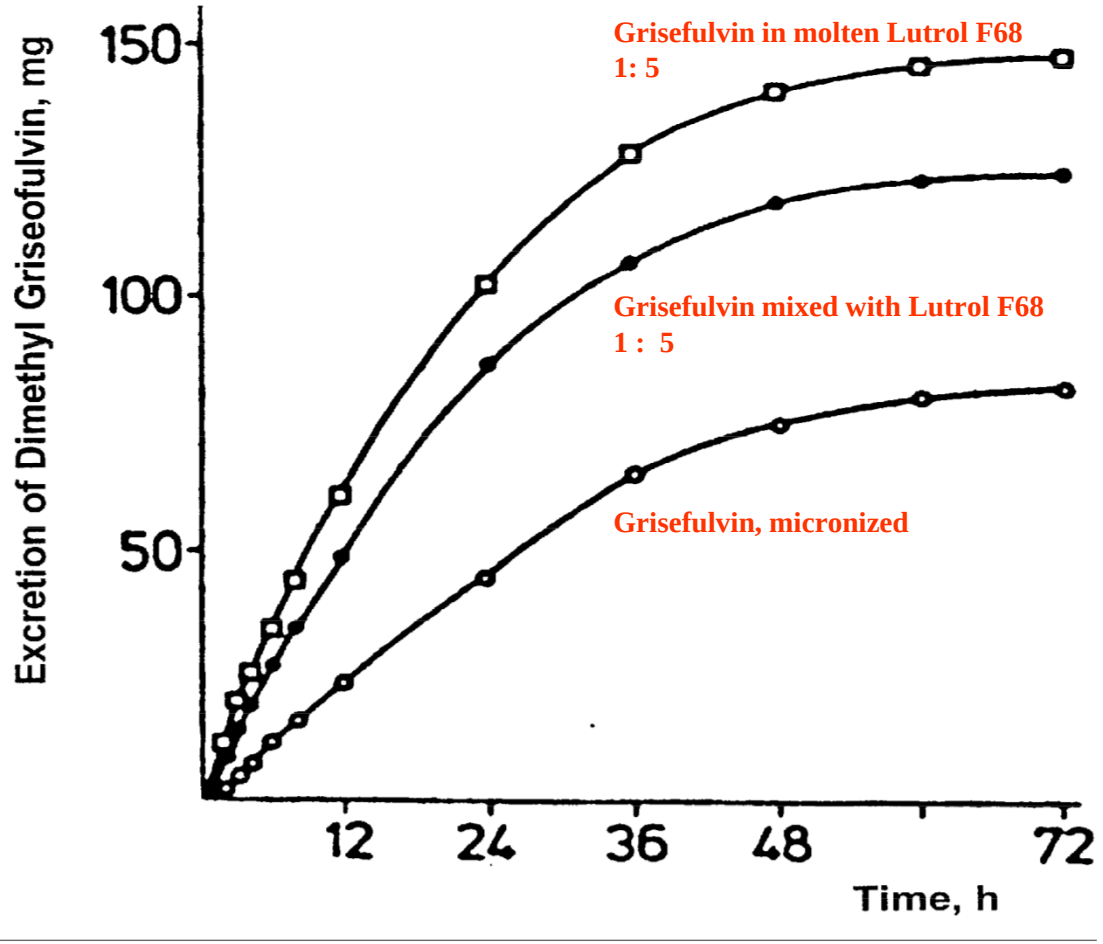
Dissolution profiles of coprecipitates of Diazepam and Lutrol F68 and Lutrol F127



Improvement of Bioavailability Using Lutrol F68

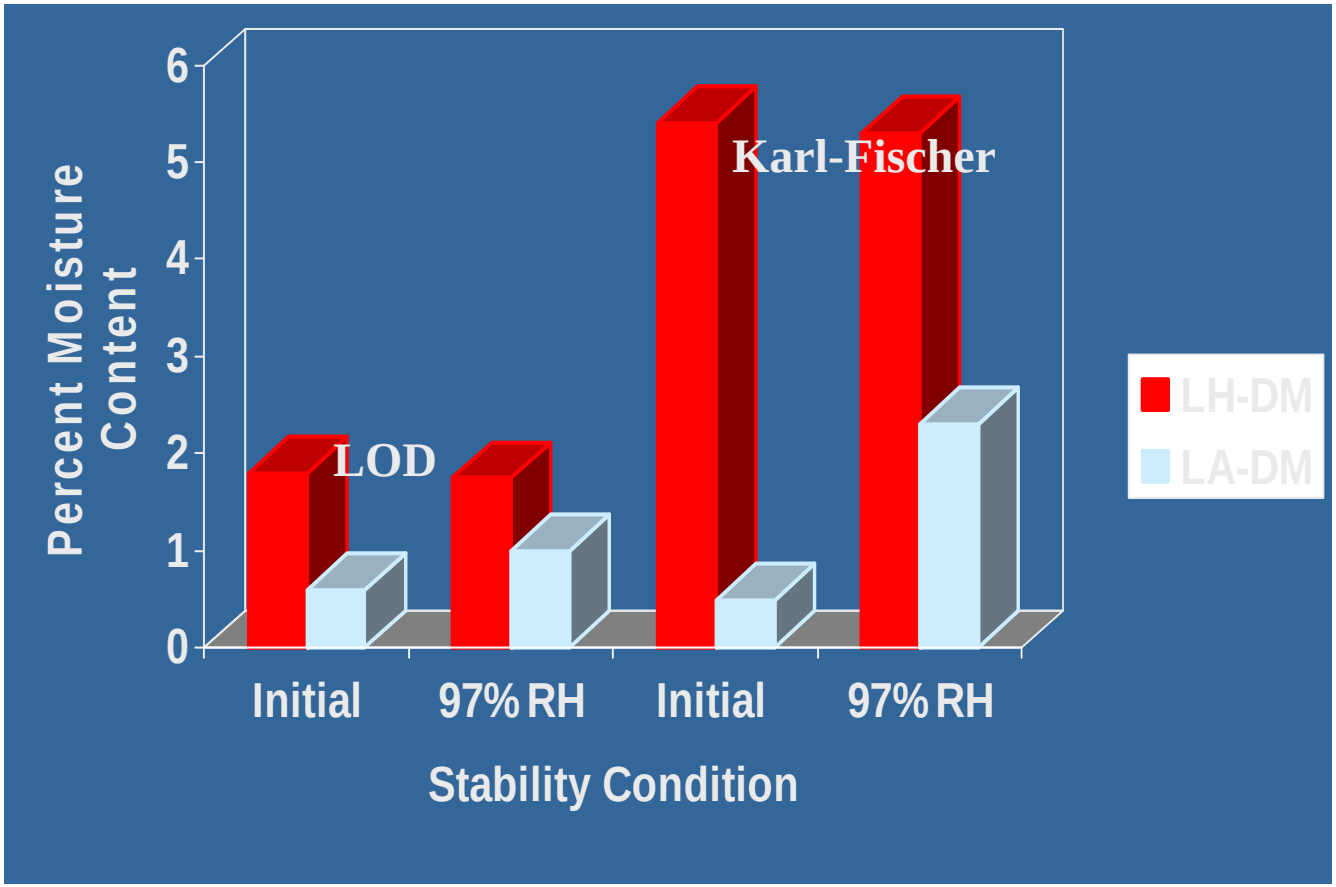
Influence of Lutrol F68 on the bioavailability in humans of orally administered Griseofulvin (250 mg)

Heyer, Frömming, DAZ 123 No. 18, 859, (1983)



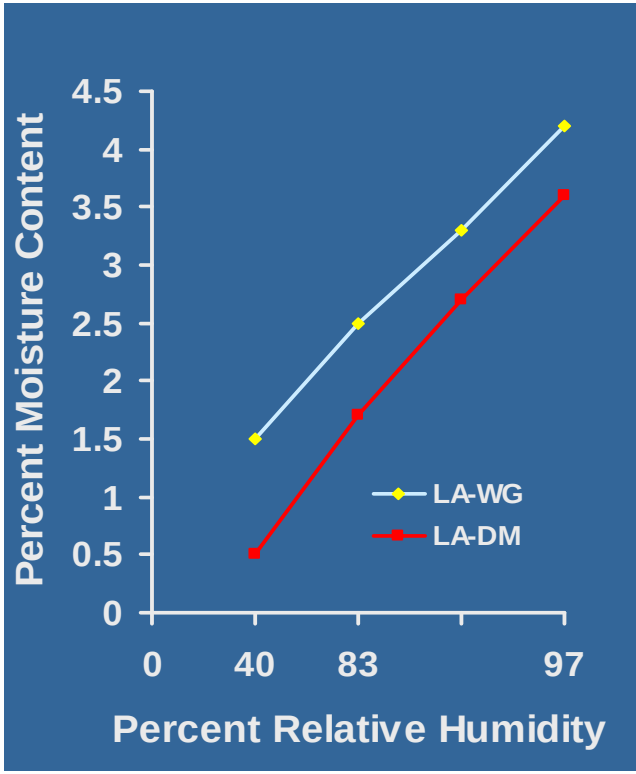
IMPACT ON CHEMICAL STABILITY

MOISTURE UP-TAKE BY LACTOSE HYDROUS AND ANHYDROUS

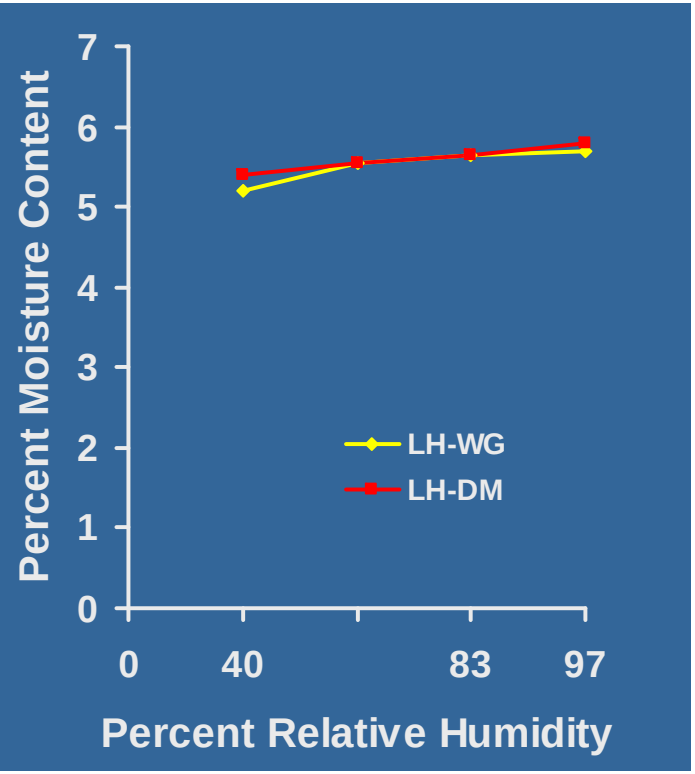


KARL-FISCHER DATA FOR LACTOSE ANHYDROUS/HYDROUS AFTER 30 DAYS STORAGE

Lactose Anhydrous



Lactose Hydrous



STABILITY DATA FOR TWO FORMULATIONS OF A DRUG PRODUCT

Formulation	Storage Conditions	Product A (%	Product B %	Product C %	Total Unidentified Impurities, %	Total Impurities, %	Assay mg/kernel	Assay % of claim
Formulation	Initial	0.26	ND*	0.03	0.03	0.32	4.87	97.4
(Based on lactose anhydrous)	1 Month 40°C/ 75% RH	1.94	ND	0.20	0.81	2.95	4.53	90.6
	1 Month 50°C	1.14	ND	0.05	0.13	1.32	4.72	94.4
Proposed Formulation	Initial	0.01	ND	0.03	0.04	0.08	5.04	100.7
(Based on lactose hydrous)	1 Month 40°C /75% RH	0.04	ND	0.02	0.07	0.13	5.02	100.3
	1 Month 50°C	0.04	ND	0.02	0.06	0.12	4.96	99.2

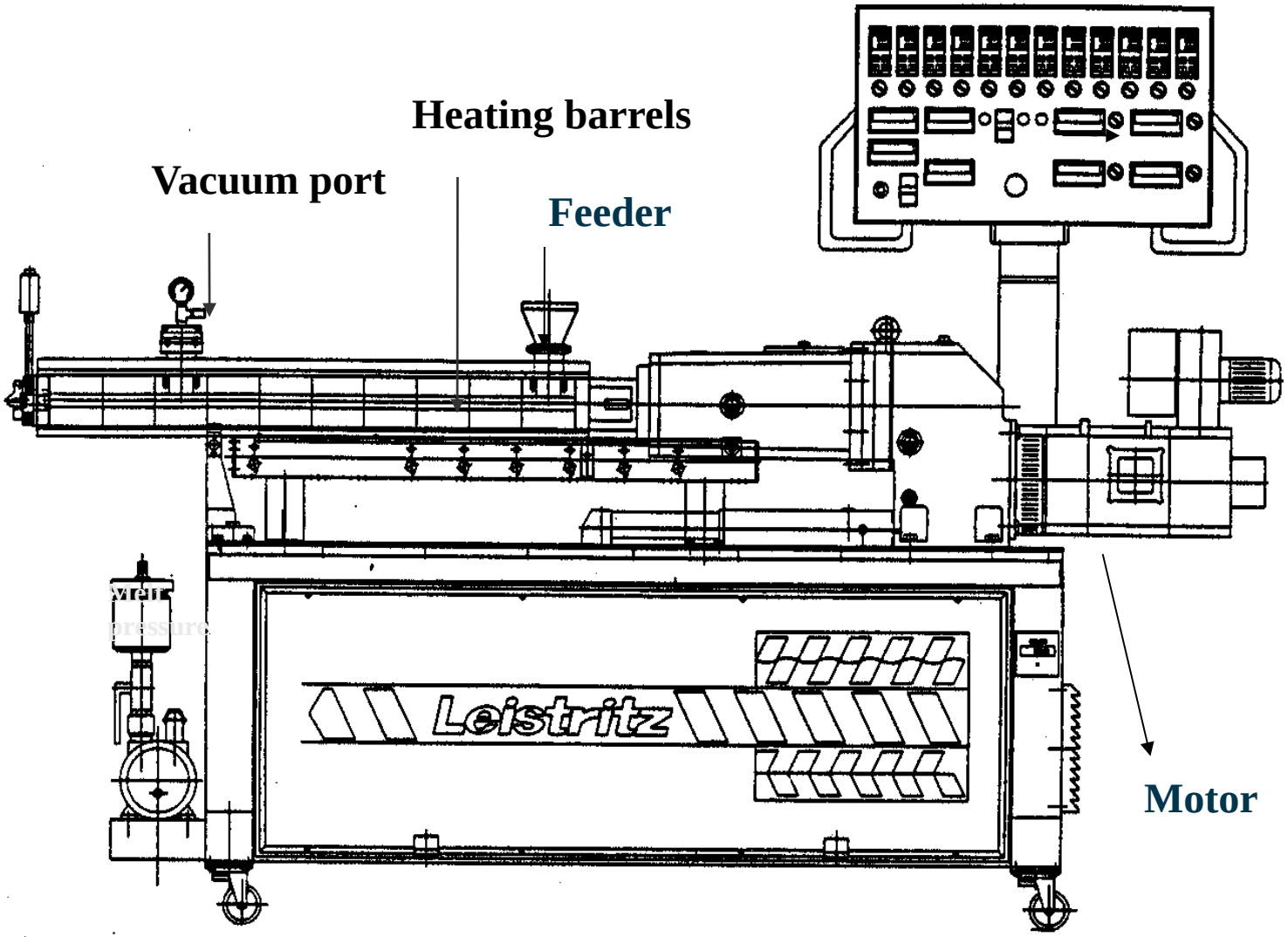
*ND = Not Detected

IMPACT ON PHYSICAL STABILITY

Impact of Polymer Type on Stability of Solid Solution Using Hot Melt Extrusion Process

- Drug: Indomethacin
- Polymer: Eudragit EPO and Povidone K30

HOT-MELT EXTRUDER

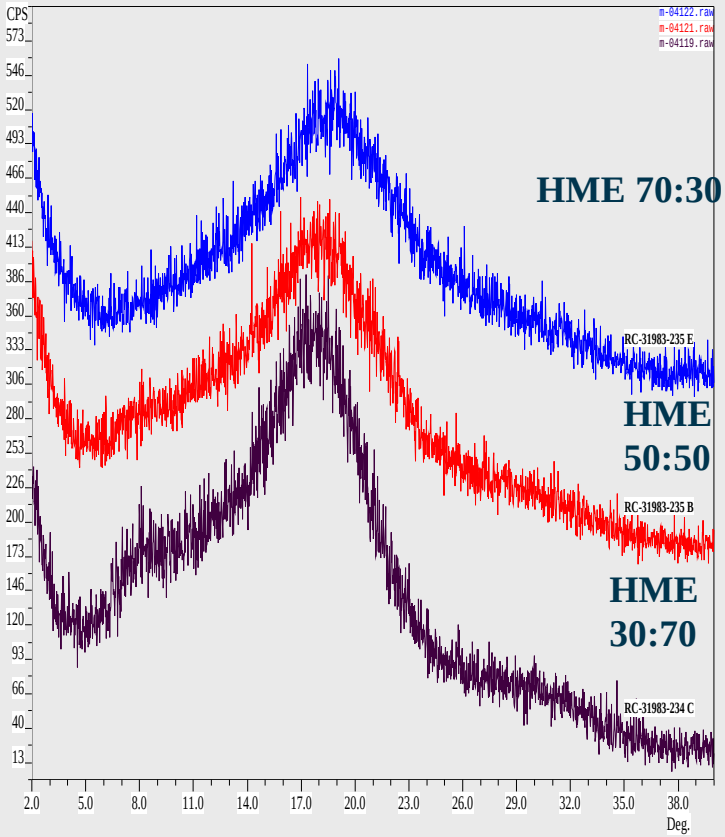


PROCESS PARAMETERS FOR HME

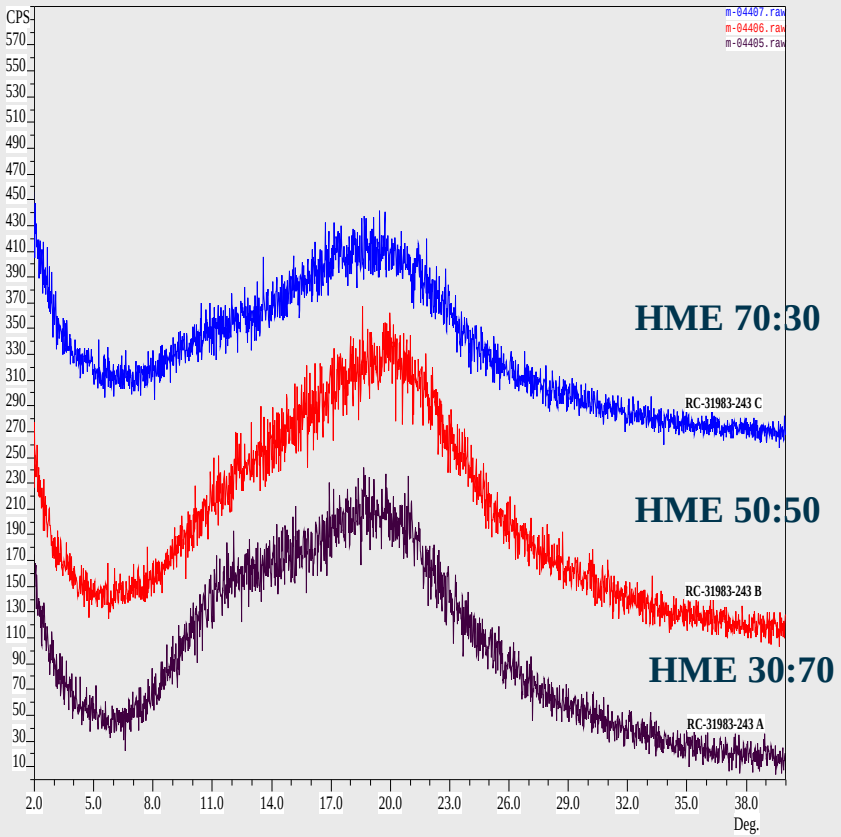
Polymer	Formulations Drug: Polymer	Barrel temperatures Feed – Exit 1- 8 barrel	Feed rate gm/min	Screw speed RPM	Motor load in %	Melt pressure in psi
Eudragit Epo	70:30	80, 110, 115, 120, 120, 120, 125, 125	5-6	45-50	83.3 ± 2.6	14.7 ± 1.8
	50:50				91.6 ± 1.7	85.1 ± 3.1
	30:70				95.3 ± 1.3	146.4 ± 4.6
PVP K30	70:30	100, 125 125, 130, 140, 145, 150, 150	5-6	45-50	33.4 ± 1.5	10.3 ± 1.1
	50:50				38.6 ± 1.7	73.4 ± 5.2
	30:70				83.6 ± 4.2	649.3 ± 6.4

POWDER X-RAY DIFFRACTION

HME of Indomethacin : Eudragit EPO

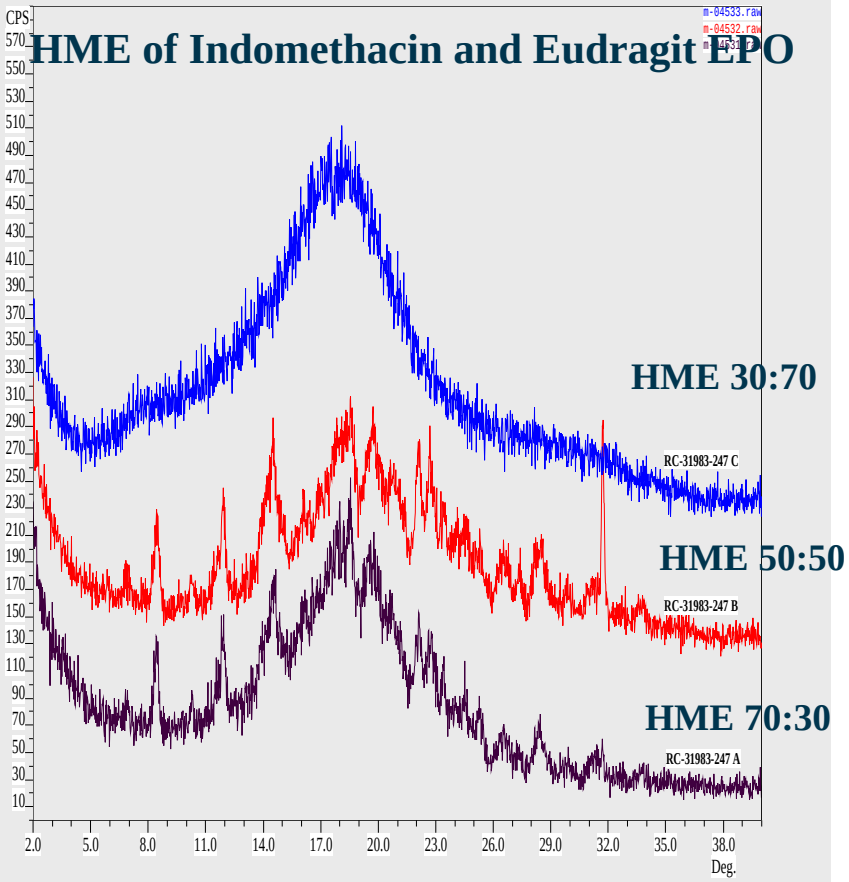


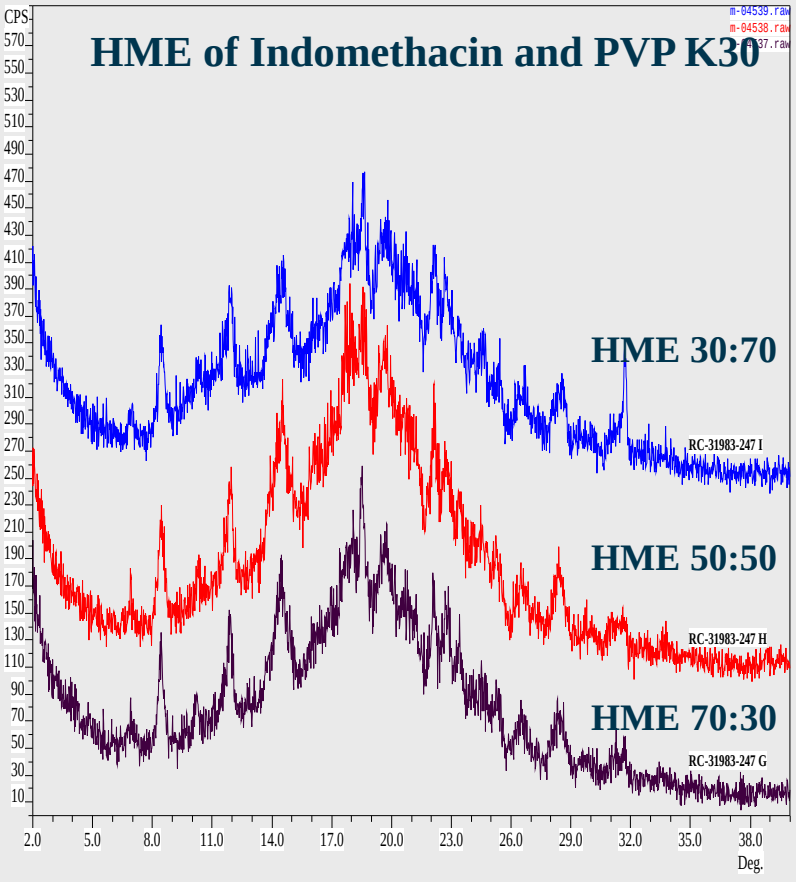
HME of Indomethacin : PVP K30



Indomethacin converts to amorphous form with Eudragit EPO and PVP K30 in all ratios after hot-melt extrusion

POWDER X-RAY DIFFRACTION





In case of hot-melt extrudates with PVP K30, Indomethacin converts back to stable crystalline form when exposed to dissolution medium (SGF)

SOLUBILITY STUDIES

Formulation	Solubility in SGF in mg/ml	
	24 hrs.	72 hrs.
Indomethacin	Can not be detected	0.051
Hot melt extrudate with Eudragit EPO		
HME 70:30	0.20	0.15
HME 50:50	6.52	0.14
HME 30:70	41.42	38.31
Hot melt extrudate with PVP K30		
HME 70:30	0.002	0.02
HME 50:50	0.04	0.05
HME 30:70	0.09	0.12

Summary
Impact of Excipients on Solid Solution Stability

- Eudragit EPO and PVP K30 formed solid solution with Indomethacin
- Hot-melt extrudates with higher concentrations of Eudragit EPO showed improved tendency to stabilize the amorphous form of the drug
- The nature and concentration of polymer played a vital role in stabilizing the amorphous form of the drug

Impact of Excipient Functionality on Manufacturability

- Content uniformity
- Compaction

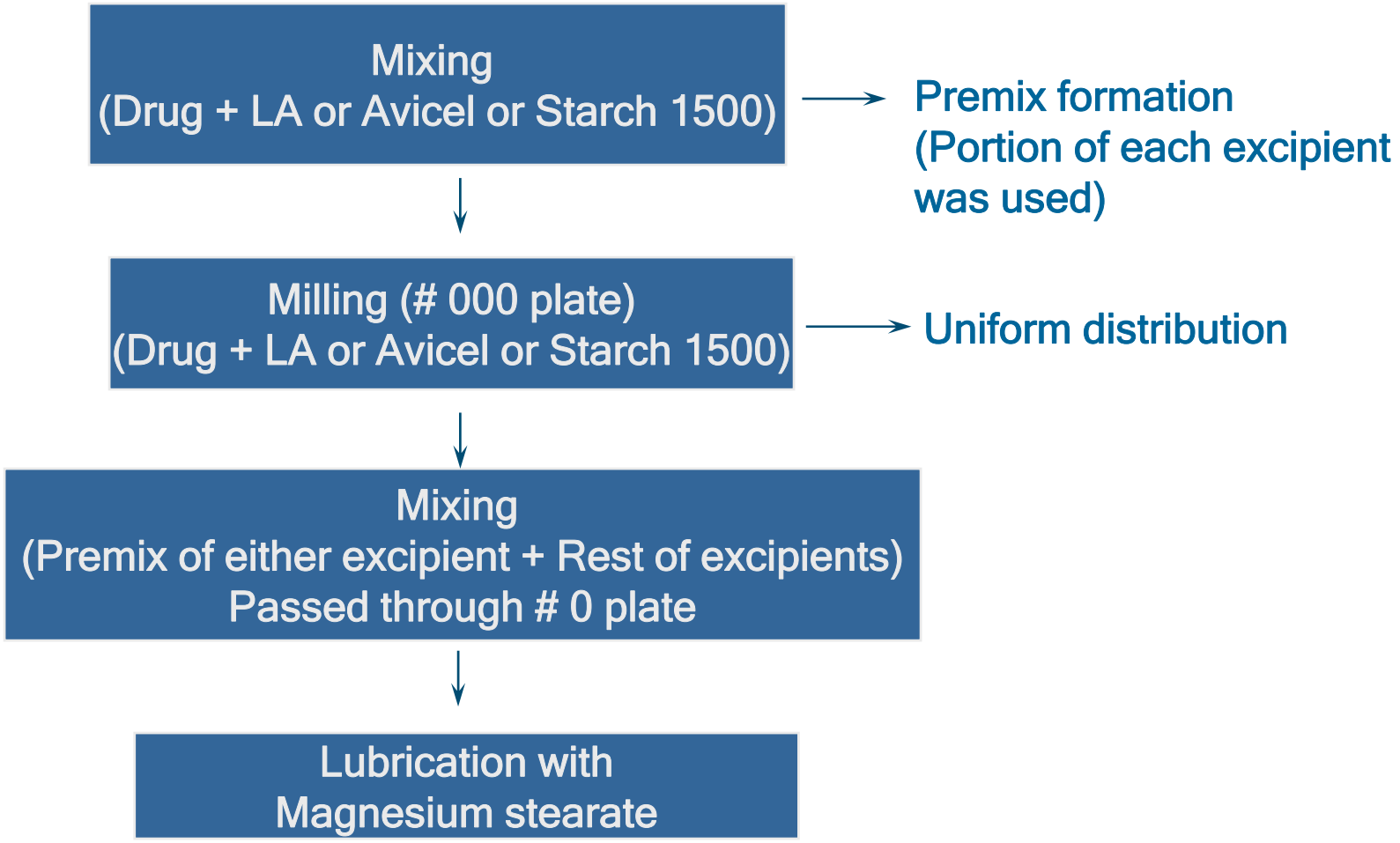
CONTENT UNIFORMITY

Materials

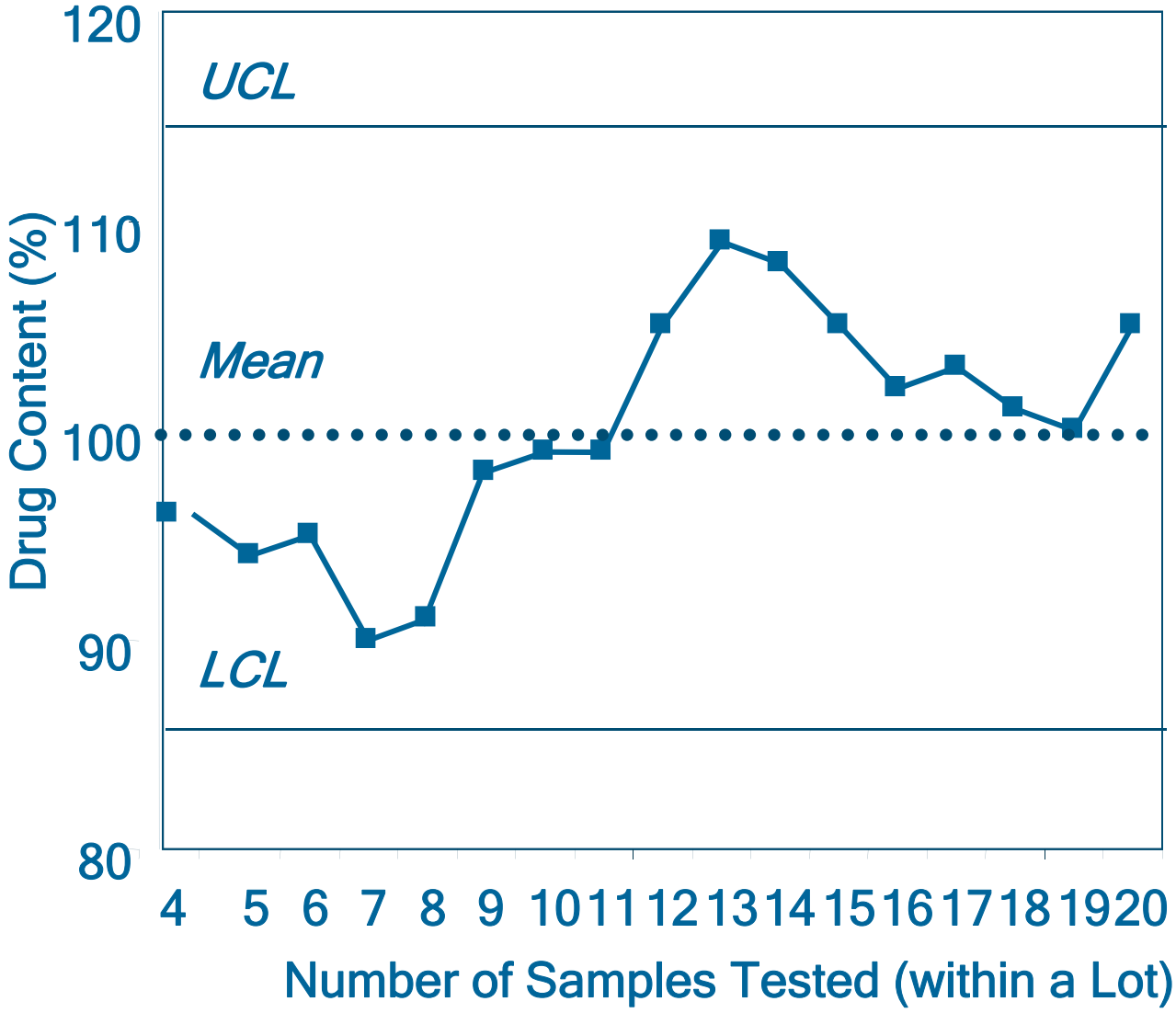
- Model drug: bulk drug substance 50th PCT = 8.9 um
- Lactose anhydrous (LA): as a carrier (Sheffield Products), particle size fraction = 100-150 um
- Starch 1500 (STA): as a disintegrant and a binder (Colorcon Co.), 50th PCT = 52 um
- Microcrystalline cellulose (MCC): directly compressible excipient (Avicel PH102, FMC), 50th PCT = 100 um
- Magnesium stearate: as a lubricant (Mallinckrodt Ltd), 50th PCT = 5 um

Effect of Pharmaceutical Carrier Excipient Properties on Drug Homogeneity and Segregation Tendency of Low Dose Formulations

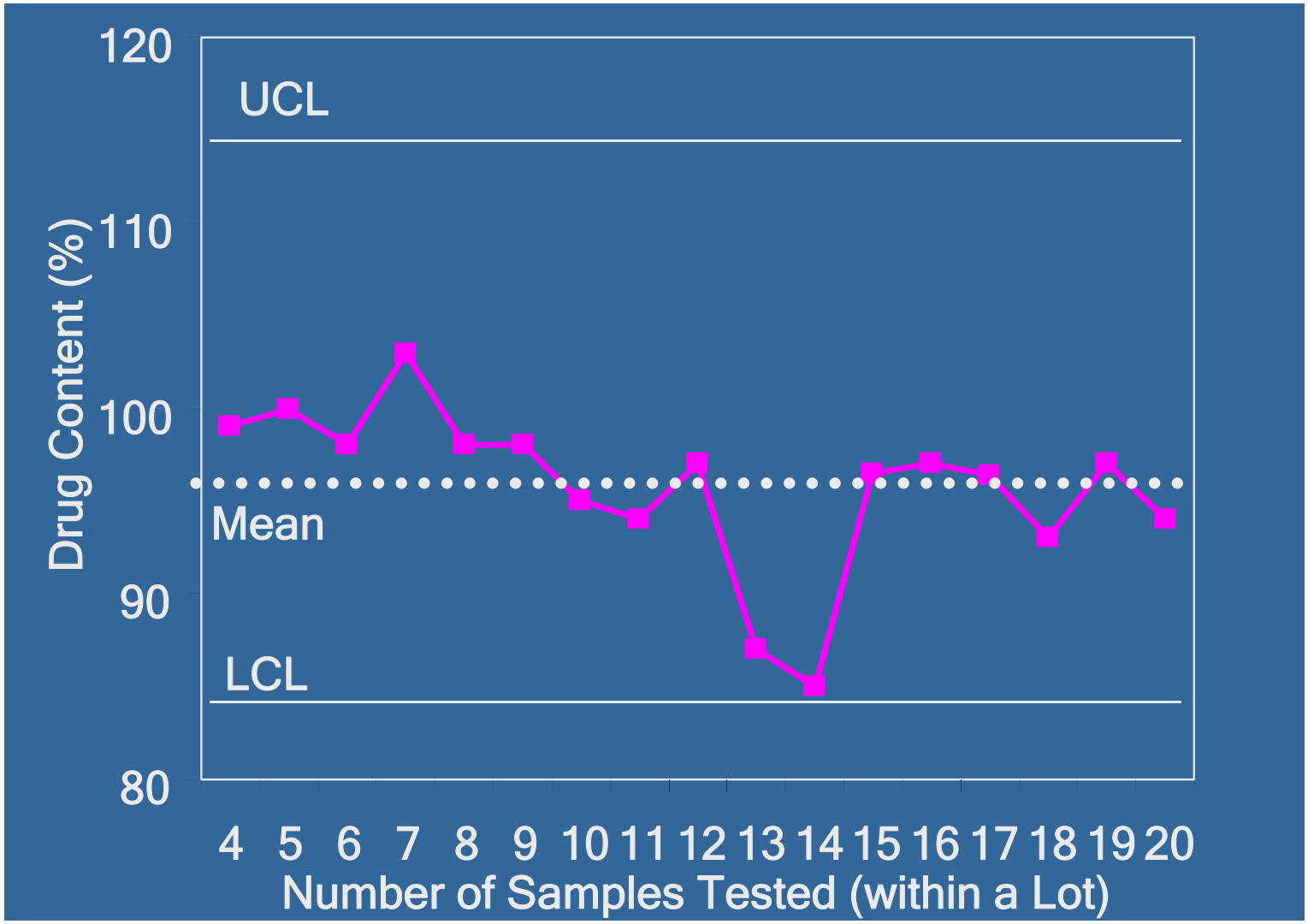
Manufacturing procedure



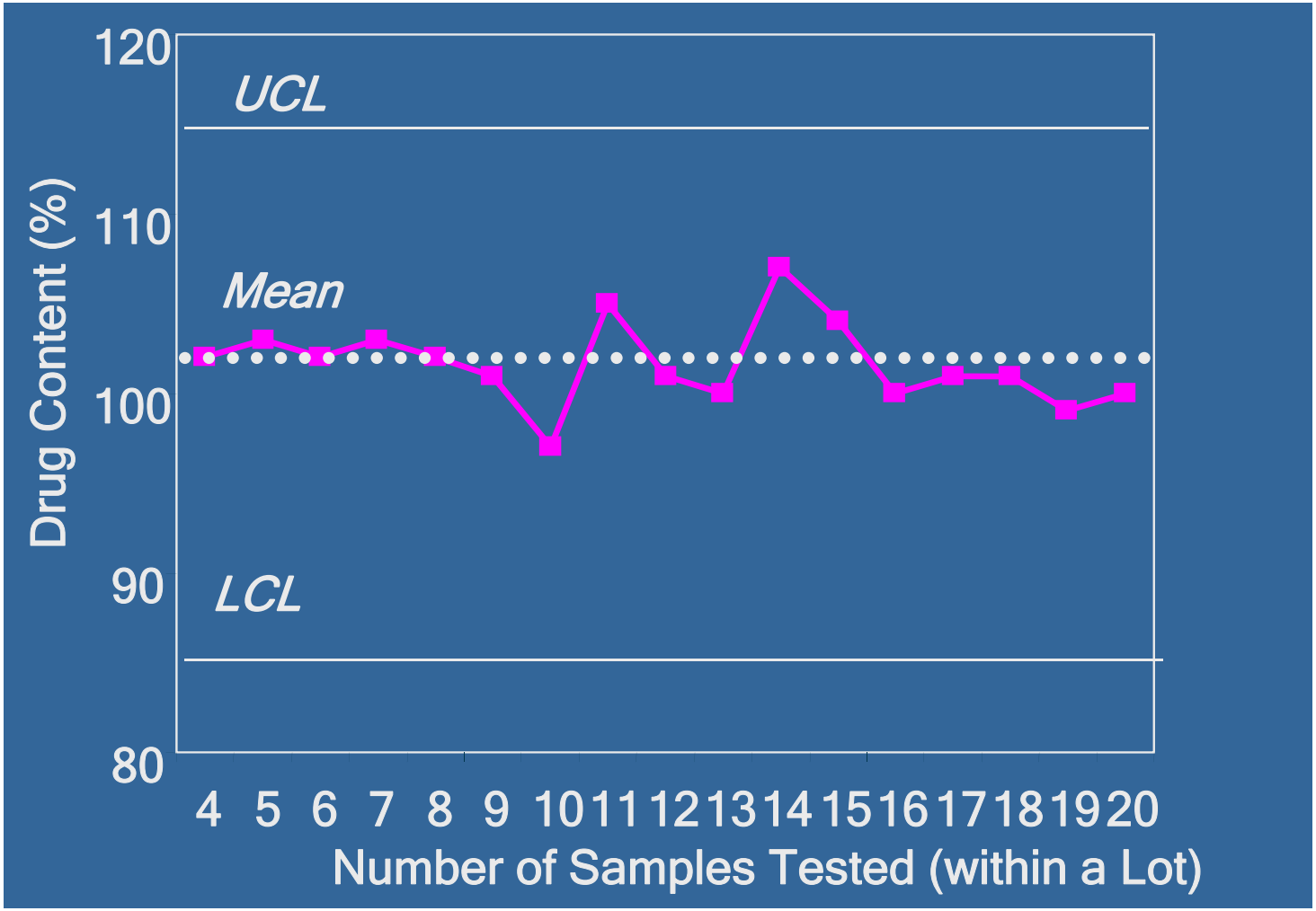
Case Study: Segregation Profile for Formulation Prepared Using Active Premix with Lactose Anhydrous (RSD 5%)



Case Study: Segregation Profile for Formulation Prepared Using Active Premix with Avicel PH102 (RSD = 4%)



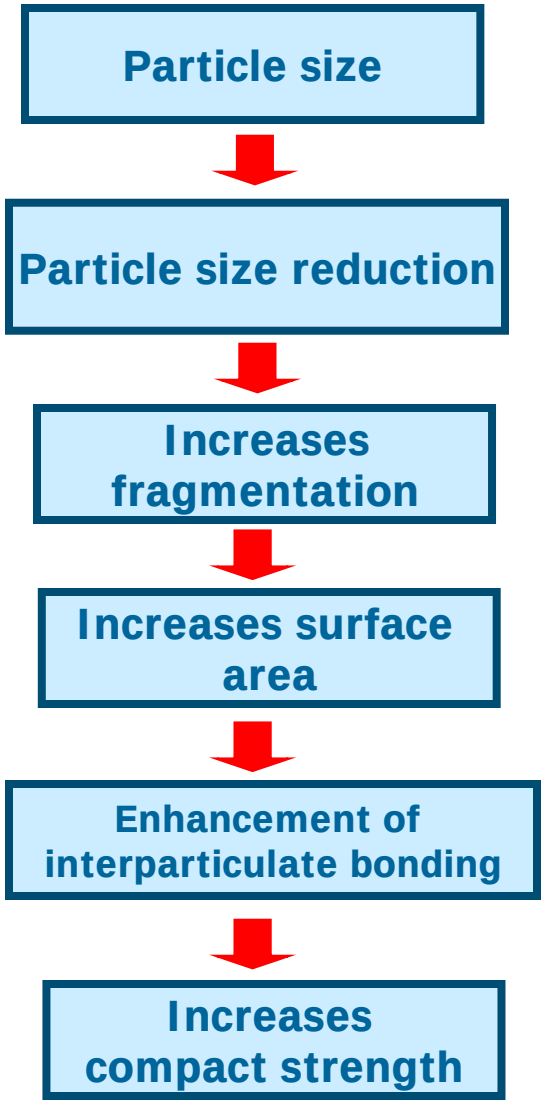
Case Study: Segregation Profile for Formulation Prepared Using Active Premix with Starch 1500 (RSD = 3%)



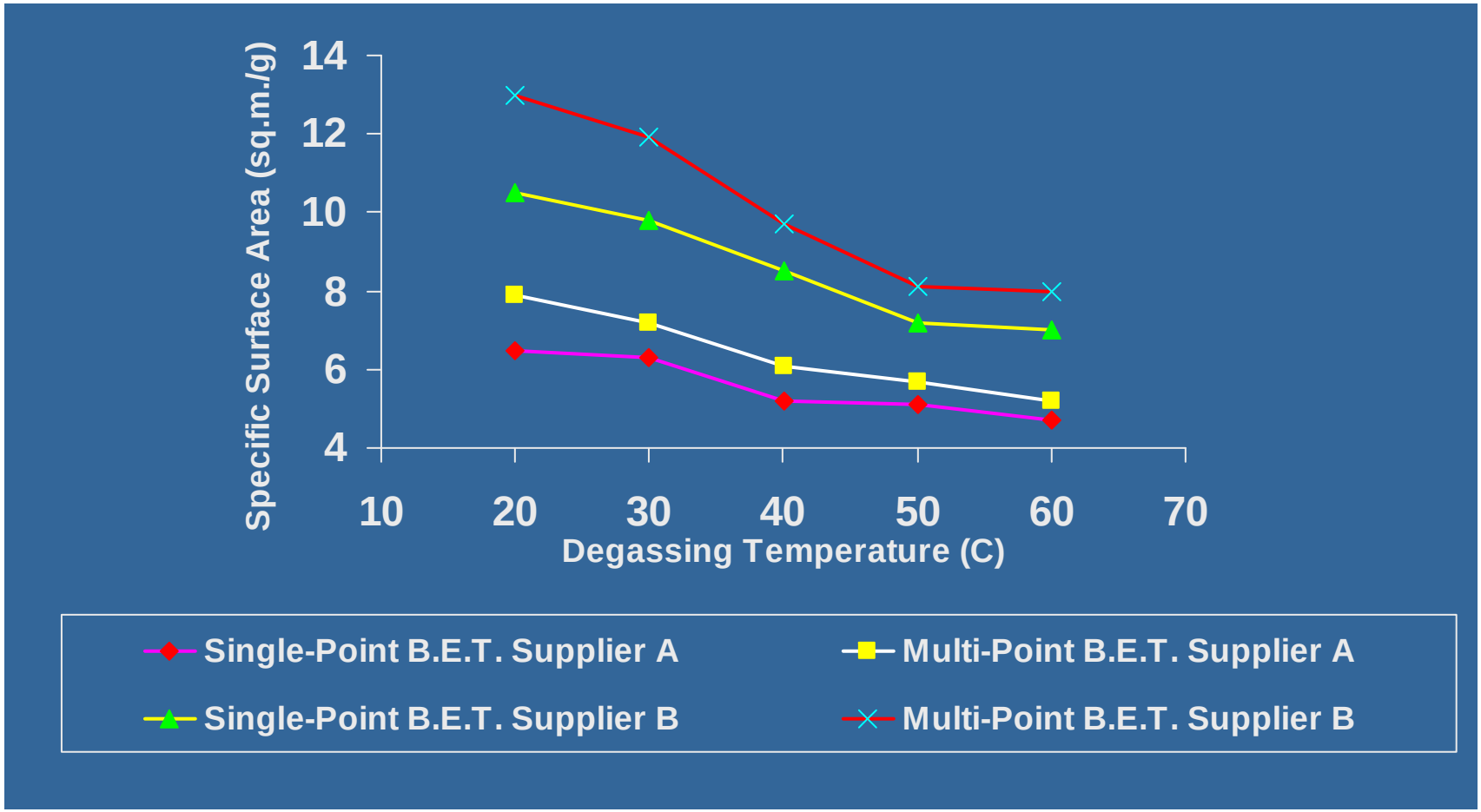
Effect of Particle Size

- Compaction
  - Effect of particle size (surface area)
  - Effect of type of lactose and its particle size
- Effect on surface texture

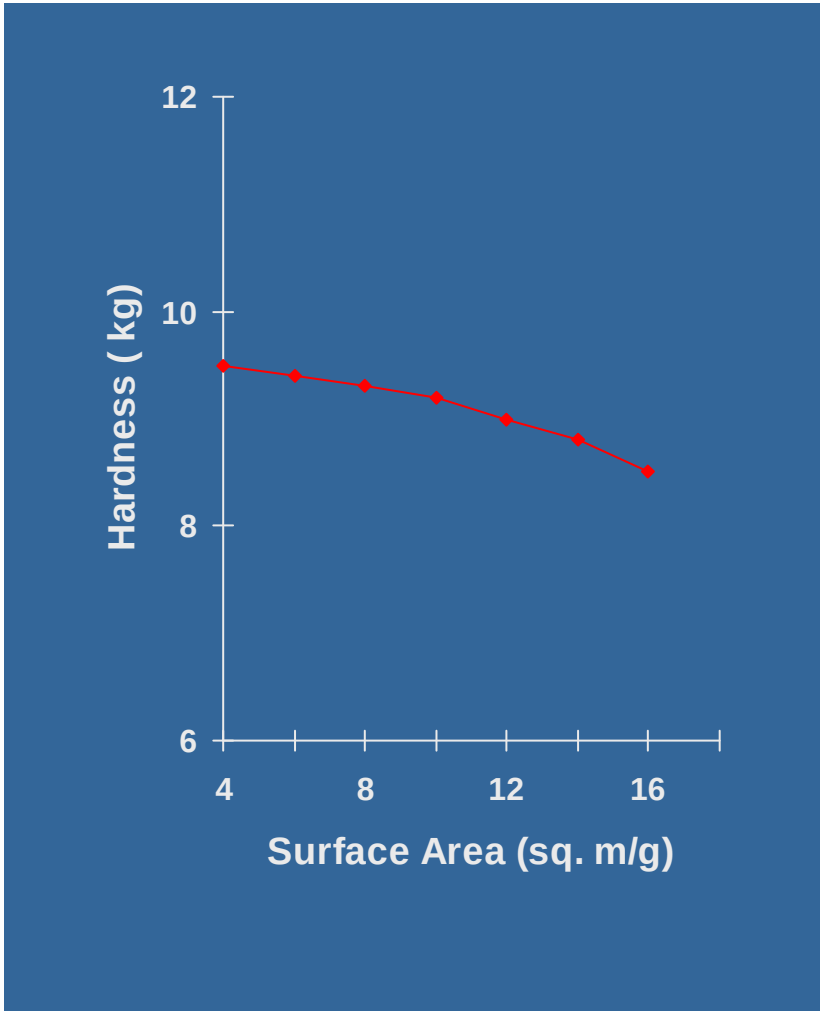
EFFECT OF PARTICLE SIZE ON TABLET STRENGHT



Why Do We Need Universal Methodology ?
B.E.T. Determination of Magnesium Stearate (After Phadke et al)

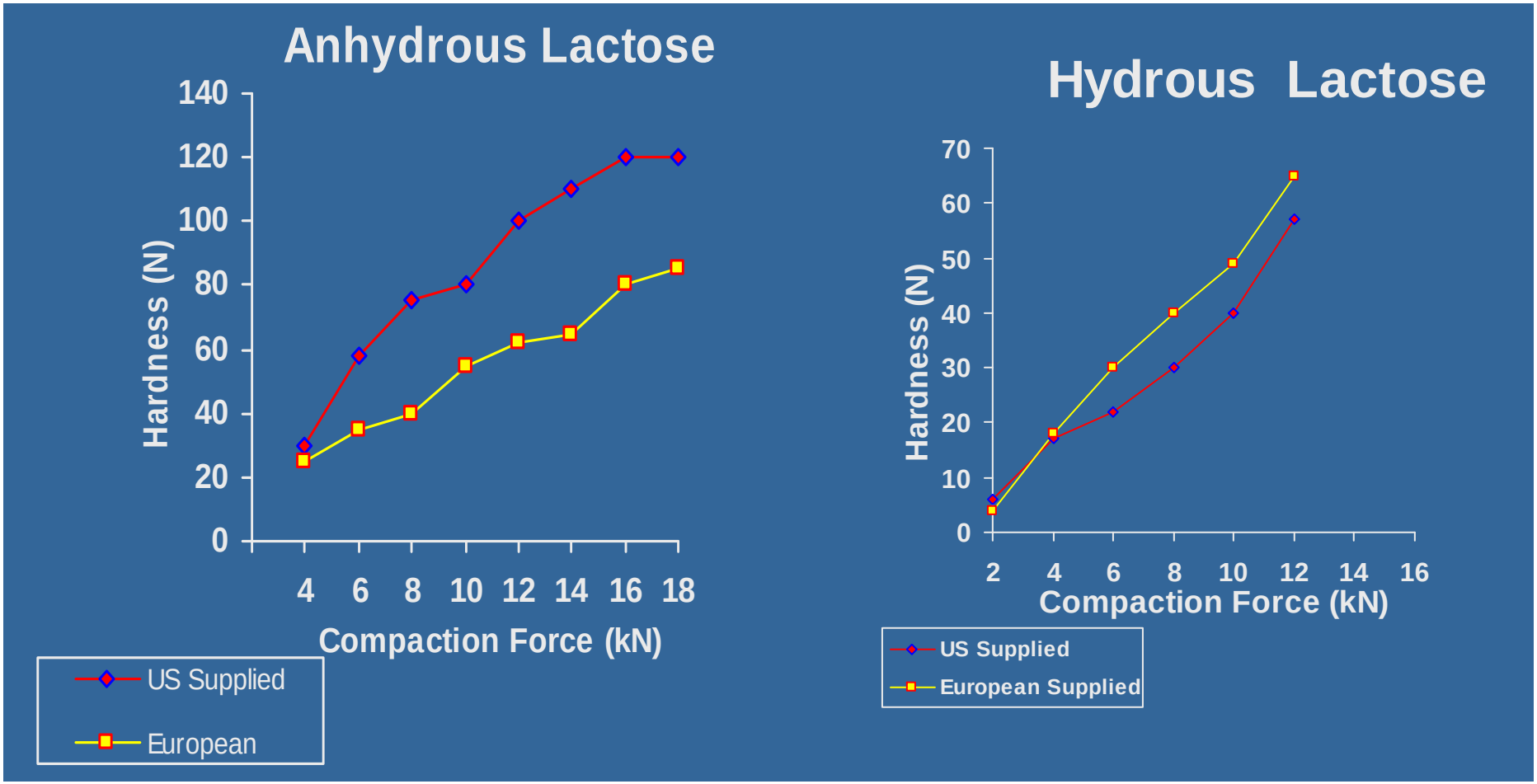


Influence of the Surface Area of 0.5% Magnesium Stearate on Tablet Hardness

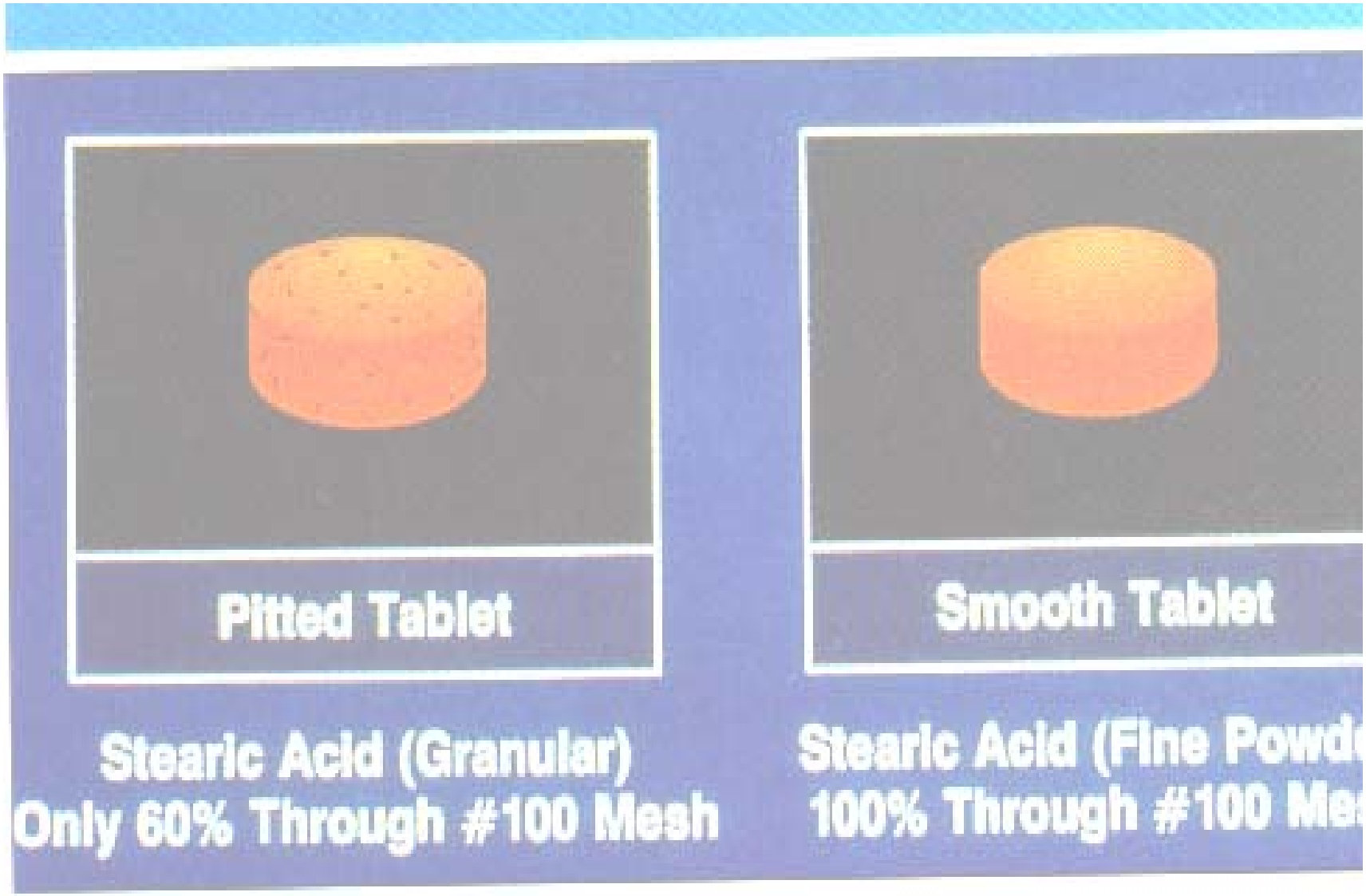


- *Lubricant Properties of Magnesium Stearate*
  - Plates Unfold ("Deck of Cards")
  - *Coat Powder Surfaces*
  - *Reduce Friction at Tablet-Die Wall Interface*
  - *Impede Compaction at High Levels*

COMPACTION FORCE AND HARDNESS PROFILE



EFFECT OF STEARIC ACID PARTICLE SIZE VARIATION ON THE PHYSICAL APPEARANCE OF FILM-COATED TABLETS



FUNCTIONALITY ASSESSMENT

REQUIREMENTS OF A GOOD FUNCTIONALITY TEST

- Meaningful
- Relatively simple
- Use standardized, readily-available equipment

DIFFICULTIES WITH ESTABLISHING A FUNCTIONALITY TEST

- Availability of suitable instruments
- Lack of a suitable methodology for each application
- Lack of agreement between different laboratories
- Unique functionalities are often identified by individual users

CONCLUSIONS

- Excipient functionality plays a significant role in product quality and performance
- Bioavailability, stability and manufacturability could be impacted by functionality of excipients
- Appropriate functionality tests for excipients should be well designed and characterized

Tablet Design - Formulation Development Strategies (SUPAC – PAT)

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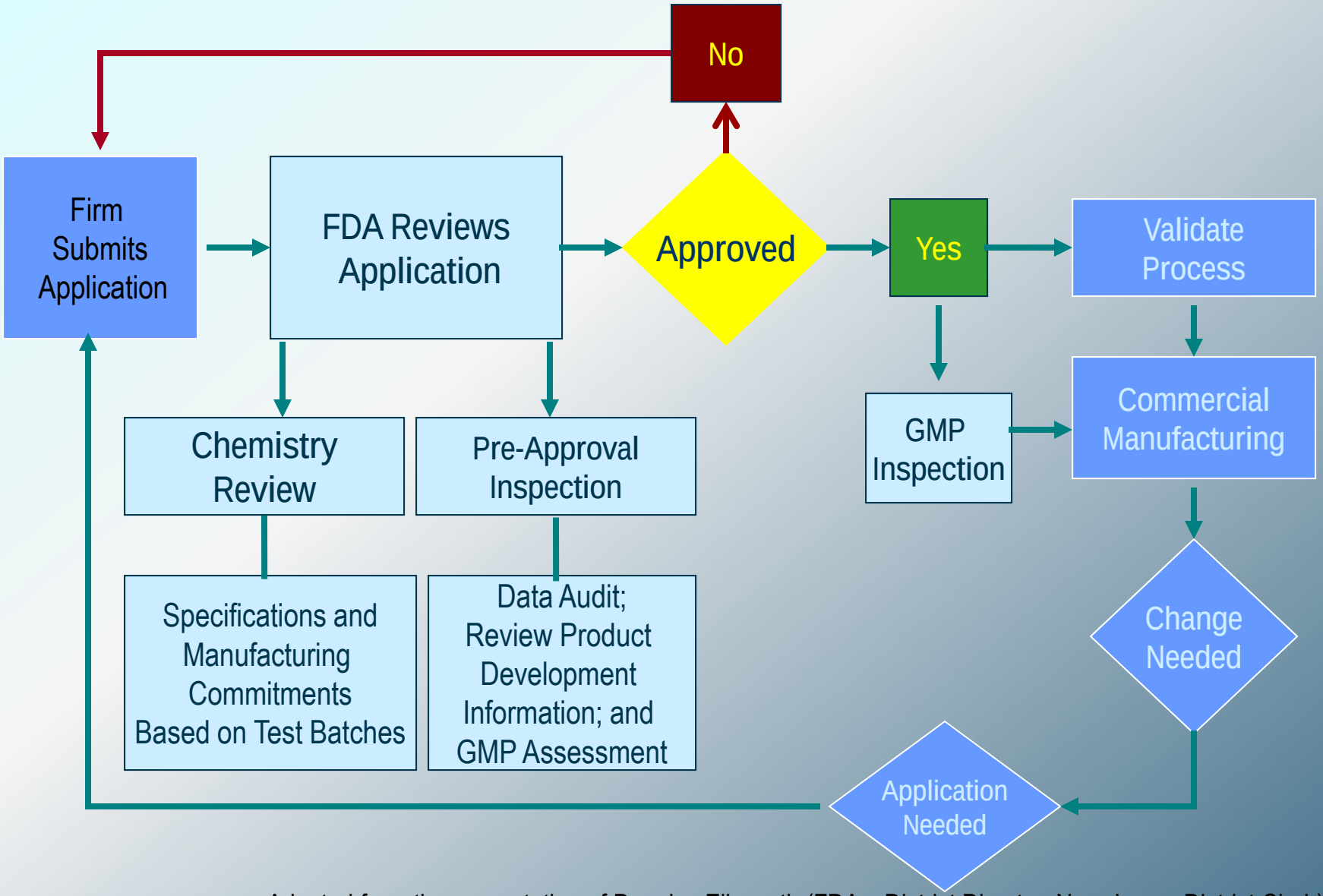
Outline of Presentation:

- A brief overview of
  - Current Regulatory process and SUPAC Guidelines
  - Desired Regulatory Process and PAT
  - QbD and Design Space
- Formulation Development (Strategies)
  - Excipient Selection
  - Case studies
- Process Development (Strategies)
  - Critical Variables
  - New Approaches – Continuous Processing
- Expert Systems
  - Artificial Intelligence Tools
  - Case Studies

Road (map) to a successful Formulation & Process Development

Current Manufacturing Regulatory Process For Drug Quality (Simplified SUPAC Guided Applications)



Adopted from the presentation of Douglas Ellsworth (FDA – District Director, New Jersey District Chair)

SUPAC – IR:
Purpose of Guidance

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the post-approval period, to change:

1) The components or composition;
2) The site of manufacture;
3) The scale-up/scale-down of manufacture; and/or
4) The manufacturing (process and equipment) of an immediate release oral formulation.

The guidance defines:

1) Levels of change;
2) Recommended chemistry, manufacturing, and controls tests for each level of change;
3) In vitro dissolution tests and/or in vivo bioequivalence tests for each level of change;
4) Documentation that should support the change.

SUPAC – IR:
What are the levels of change?

- **Level 1**

  Unlikely to have impact on the product. Filed as an annual report update,normal testing as filed in NDA.

- **Level 2**

  Moderate changes such as technical grade of inert. Filed as CBE or PA,accelerated stability and dissolution profile testing in addition to filed NDA.

- **Level 3**

  Likely to have impact on the product. Filed PA,stability and testing as above in addition a biostudy or IVIV correlation.

SUPAC – IR:
Components and Composition

EXCIPIENT PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT

		Level 1	Level 2	Level 3
Filler		+/- 5%	+/- 10%	<
Disintegrant	Starch	+/- 3%	+/- 6%	<
	Others	+/- 1%	+/- 2%	<
Binder		+/- 0.5%	+/- 1%	
Lubricant	Ca Stearate	+/- 0.25%	+/- 0.5%	<
	Mg Stearate	+/- 0.25%	+/- 0.5%	<
	Others	+/- 1%	+/- 1%	<
Glidant	Talc	+/- 1%	+/- 2%	<
	Others	+/- 0.10%	+/- 0.2%	<
Film Coating		+/- 1%	+/- 2%	<

LEVEL 1: These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. The total additive effect of all excipient changes should not be more than 5%. (Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g. lactose increases 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the Level 1 range).

The components (active and excipients) in the formulation should have numerical targets which represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on previous Level 1 changes in the composition

SUPAC – IR: FAQs (1)

Q:

What is the full definition of a change in 'technical grade" of an excipient? Does this only mean a change in excipient specifications that may impact functionality or does it include a change in supplier even if all applicable specifications remain the same?

A:

Technical grades of excipients differ in their specifications and intended use. Technical grades may differ in: 1) specifications and/or functionality; 2) impurities; and 3) impurity profiles. If a supplier of an excipient changes but its technical grade AND specifications remain the same, the agency should be notified in an annual report.

SUPAC – IR: FAQs (2)

Q:

How does one apply SUPAC-IR to multifunctional excipients, e.g., starch?

A:

SUPAC-IR composition changes are based on being able to define the use or action of the particular excipient in the product. This rationale should be included by the applicants as part of their original applications. Not all multifunctional excipients are listed in the guidance. However, if an excipient was utilized to provide multiple functions such as pregelatinized starch as a filler, starch as a disintegrant, starch paste as a binder, then the most conservative recommended change should be followed (e.g., for an excipient that is a filler, disintegrant and binder, the recommended limit for a Level 2 change is 0.5 percent, see page 7, SUPAC-IR). An applicant may wish to add an explanation of how the change will affect other functions of the excipient in the product. If this information was not included in the original application, the review division should be consulted before filing such a SUPAC change, either through annual report..

SUPAC – IR: FAQs (3)

Q:

What is the reference source for defining the action of an inactive ingredient, for example, lubricant versus glidant? What if the action is defined differently in two sources?

A:

An applicant should be able to justify the choice and the basis for the selection of a particular excipient, i.e., its expected function in the drug product. It may be useful to cite a source. The action may depend on the specific product..

SUPAC – IR: FAQs (4)

Q:

To what category does a change in granulation solvent in a wet granulation process belong?

A:

A change in granulating solvent (e.g., alcohol to water) would alter the composition of the drug product, both qualitatively and quantitatively, even though it may be removed during manufacture of the drug product. Because such a change may have significant impact on formulation quality and performance, it is a level 3 composition change that needs a prior approval supplement.

….. more?...

The Desired State *

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes.

- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance

- An ability to affect continuous improvement and continuous "real time" assurance of quality.

* www.fda.gov/cder/gmp/gmp2004/manufSciWP.pfd

Process Analytical Technology (PAT)

The scientific, risk-based framework outlined in this guidance, *Process Analytical Technology* or PAT, should help manufacturers develop and implement new efficient tools for use during pharmaceutical development, manufacturing, and quality assurance while maintaining or improving the current level of product quality assurance

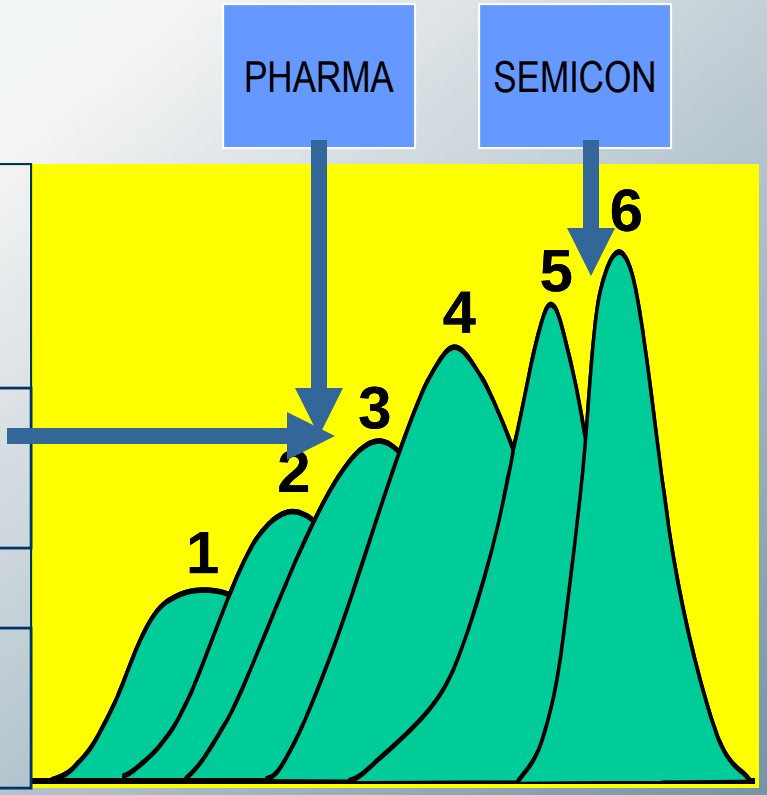
Why PAT Initiative?
Sigma: A Measure of Process Capability

FDA pushes forward the Process Analytical Technology (PAT) Initiative for very good reasons:

- The variability of most pharmaceutical processes needs to be reduced.
- The performance of a process can be described by its Sigma value. Sigma is a measure that focuses on the variation of the process output

Why PAT Initiative?
Sigma: A Measure of Process Capability

SIGMA	DPMO	YIELD	Cost of Quality
0.0	1,000,000	0.0000%	
1.0	691,462	30.8538%	
2.0	308,538	69.1462%	25-35%
3.0	66,807	93.3193%	20-25%
4.0	6,210	99.3790%	12-18%
5.0	233	99.9767%	4-8%
6.0	3.4	99.9997%	1.3%



The performance of the pharmaceutical industry is around 2 Sigma ≤ 4.6 % defectives).

Adapted from Source: Rath & Strong, Lean Sigma Overview

PAT / Quality by Design

Increased understanding of formulations and processes which will allow the development of more robust formulations and processes with larger Design Spaces that will permit more changes without prior notification or approval.

Design Space

Traditional Process:

Limited Knowledge – 3 Batches; Any Change Needs New Data and New Approval)

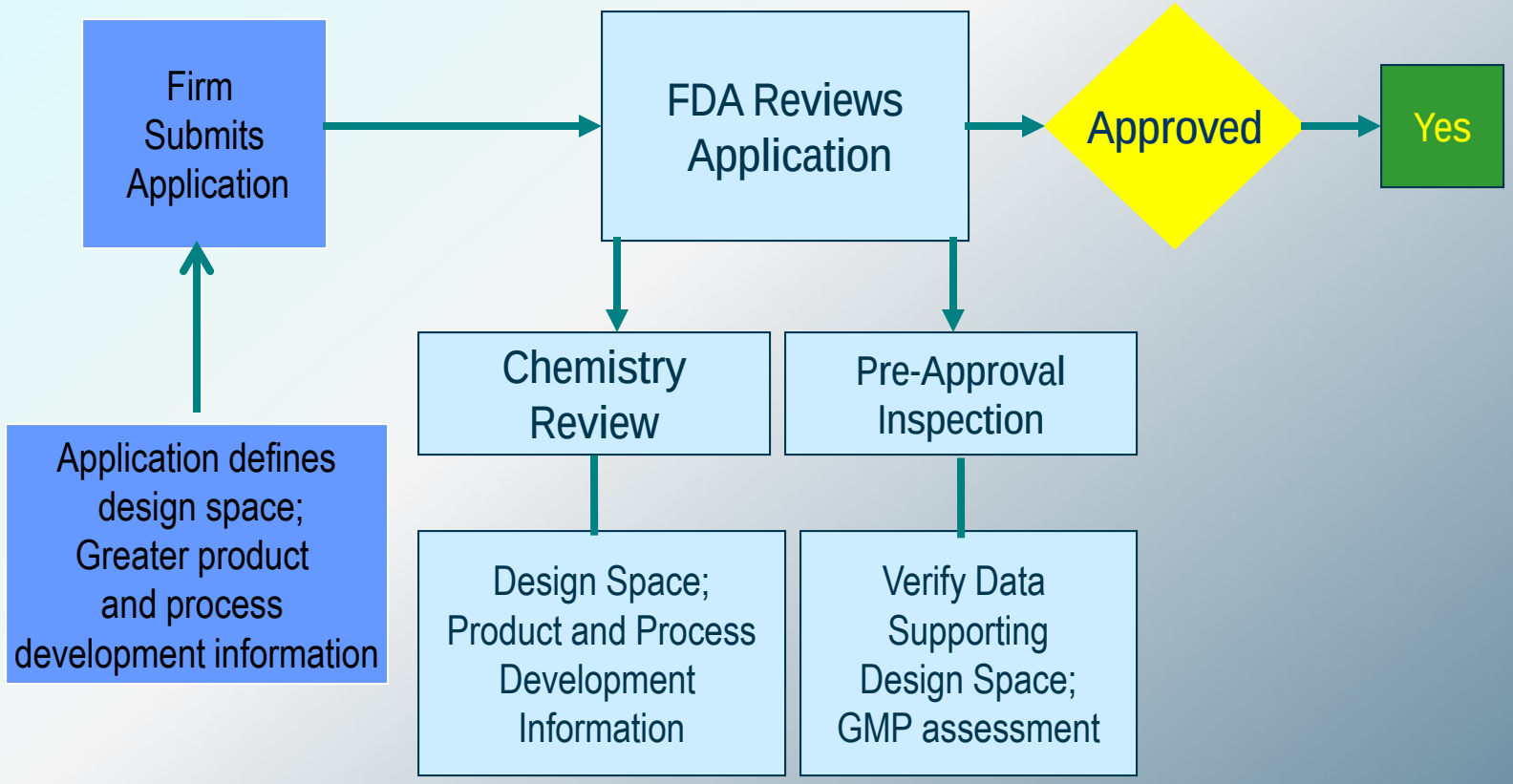
New Paradigm:

Influence of factors explored creating knowledge, Risk analysis of impact of change possible.

Approval to move within defined area post-approval gives flexibility for continuous improvement without need for further approval.

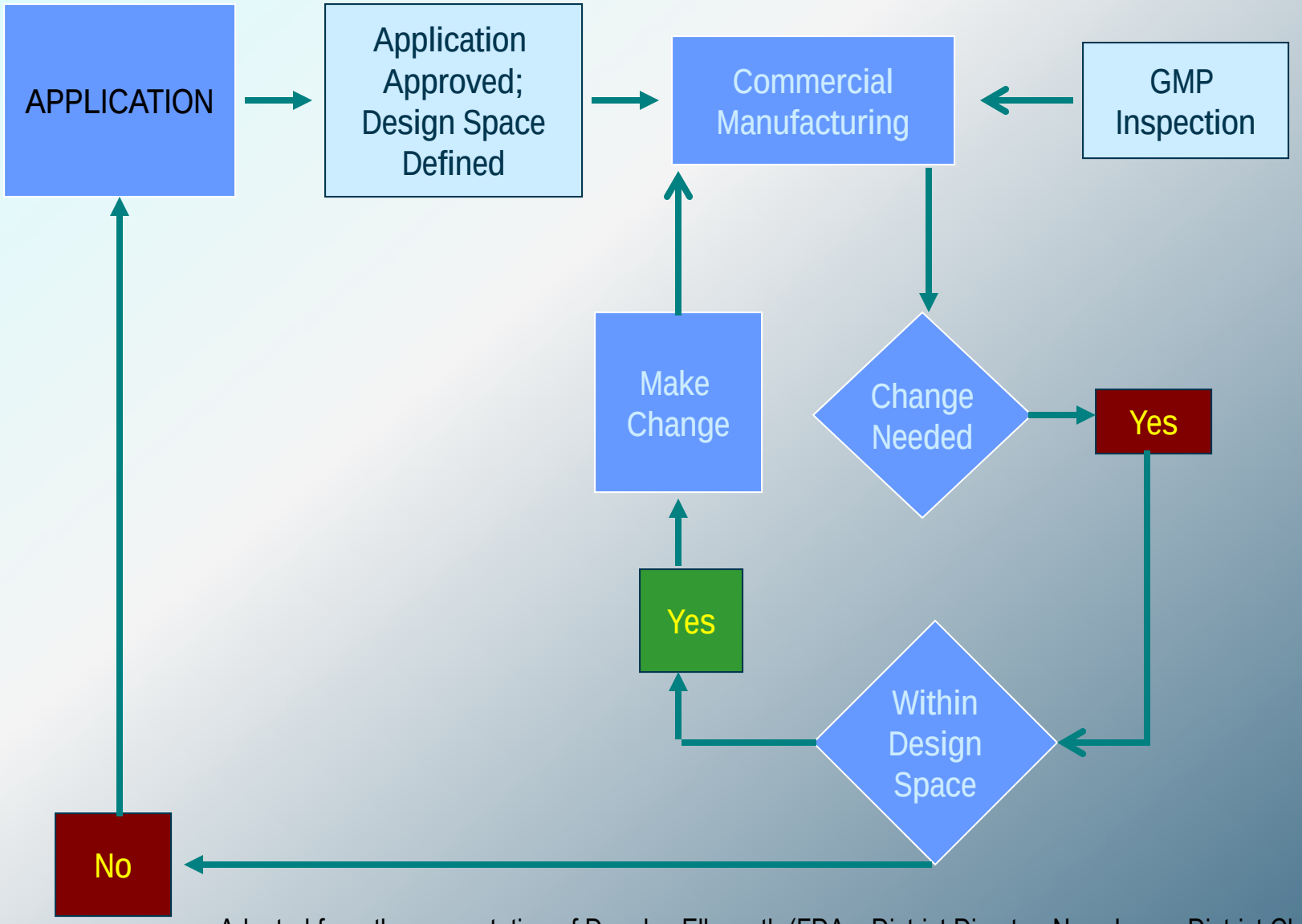
Adopted from the presentation of Douglas Ellsworth (FDA – District Director, New Jersey District Chair)

Future Desired Regulatory Process – Initial Approval (Simplified PAT Guided Applications)



Adopted from the presentation of Douglas Ellsworth (FDA – District Director, New Jersey District Chair)

Future Desired Regulatory Process – Initial Approval (Simplified)



Adopted from the presentation of Douglas Ellsworth (FDA – District Director, New Jersey District Chair)

PAT Framework

Pharmaceutical manufacturing processes often consist of a series of unit operations, each intended to modulate certain properties of the materials being processed.

To ensure acceptable and reproducible modulation, consideration must be given to the quality attributes of incoming materials and their process-ability for each unit operation.

Example:
Incoming material : Pregelatinized starch or dicalcium phosphate dihydrate
Process: Film coating

PAT Framework

- What is it?
- PAT Approach
  - Process Understanding, Risk and Controls
  - Real-Time Release
  - Implementation Strategy and Regulatory Process
- What is Not PAT

What is PAT?

Process Models

Instruments

Data Communications Infrastructure

Manufacturing Execution Systems

Control Models

Analysis tools

Process Equipment Development

"PAT is considered to be a *system* for,

- designing
- analysing, and
- controlling

manufacturing through

- timely measurements of
  - critical quality attributes
  - and performance attributes of
    - raw and in-process materials and
    - processes

with the goal of ensuring final product quality"

SOPs

Raw Materials Data

Regulatory Approval

Mechanistic Models

Real-Time Data Management

Process Control Systems

Adapted from V. Shah, 2007 Rutgers PAT Conference, June 18-20, 2007

What is *NOT* PAT?
(In *Absence* of Process Understanding)

- Use of process analyzers on-line = alternate analytical method (not = PAT)
- Real time monitoring (on-line or at-line measurement) alone will NOT qualify as PAT
- Increase of in-process sample size or automated end product testing are NOT PAT
- Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT
- Automation or Robotics
- Absence of understanding, and no plans for learning or controlling

V. Shah, 2007 Rutgers PAT Conference, June 18-20, 2007

Quality by Design

Increased understanding of formulations and processes which will allow the development of more robust formulations and processes with larger Design Spaces that will permit more changes without prior notification or approval.

What is robust formulation?

Robust Formulation

Robust Formulation is a formulation that is able to accommodate the typical variability seen in:

API

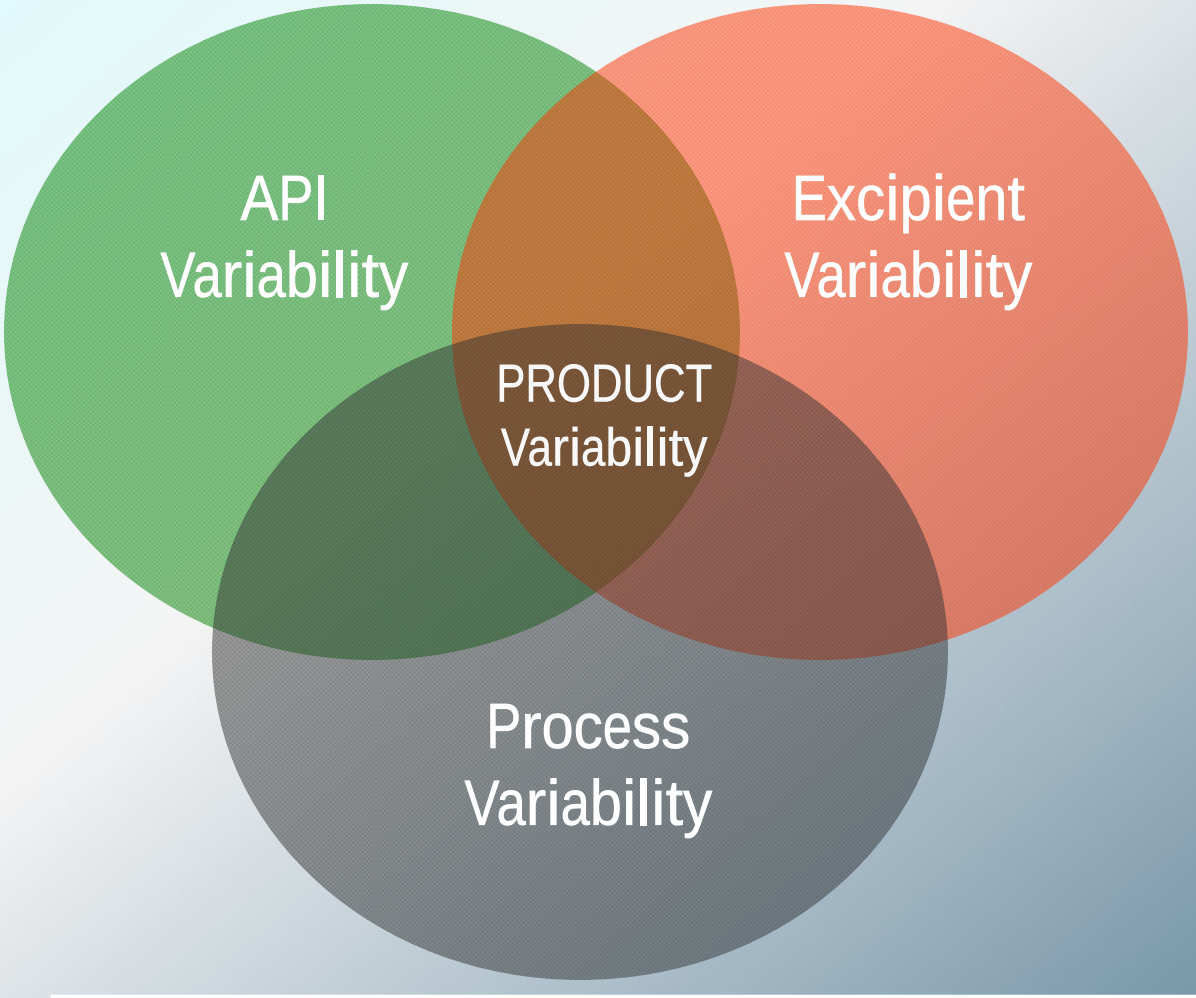
Excipients

Process

without the manufacture, stability or performance of the product being compromised.

So, how do we define variability?

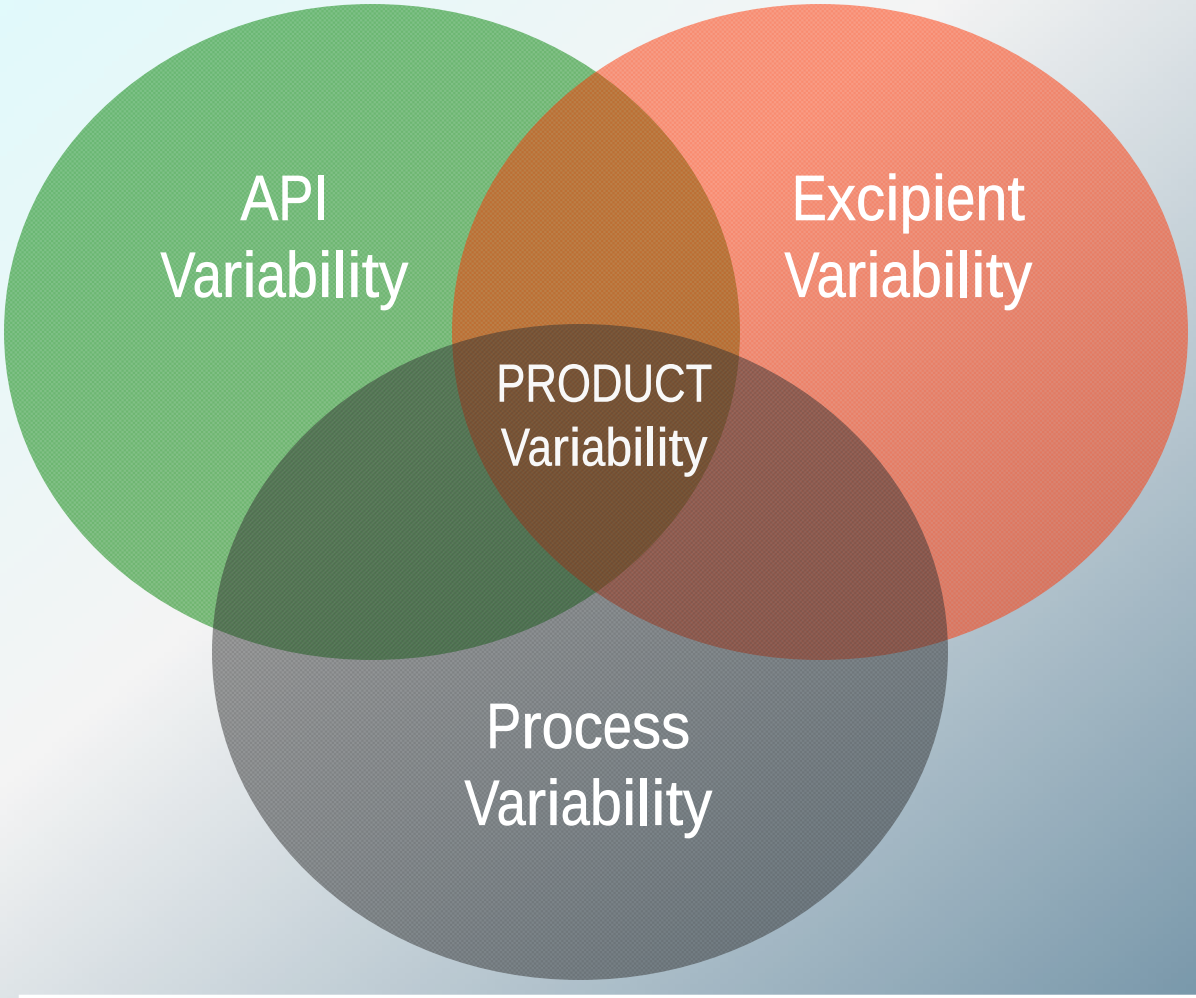
Defining Product Variability:



$$\sigma^2_{Product} = \sigma^2_{API} + \sigma^2_{Excipient} + \sigma^2_{Process} \quad \sigma^2$$

Adopted from the presentation of Chris Moreton, Pharaceutical Excipients, San Diego, CA, Jan 2007

Understanding/Defining Product Variability



$$\sigma^2_{Product} = \sigma^2_{API} + \sigma^2_{Excipient} + \sigma^2_{Process} + \sigma^2_{Interactions}$$

Adopted from the presentation of Chris Moreton, Pharaceutical Excipients, San Diego, CA, Jan 2007

Interactions in Product Manufacture

Powder	–	Powder
Powder	–	Liquid
Powder	–	Equipment
Liquid	–	Equipment
Powder	–	Operator
Liquid	–	Operator
Equipment	–	Operator

Product Variability: Its Sources

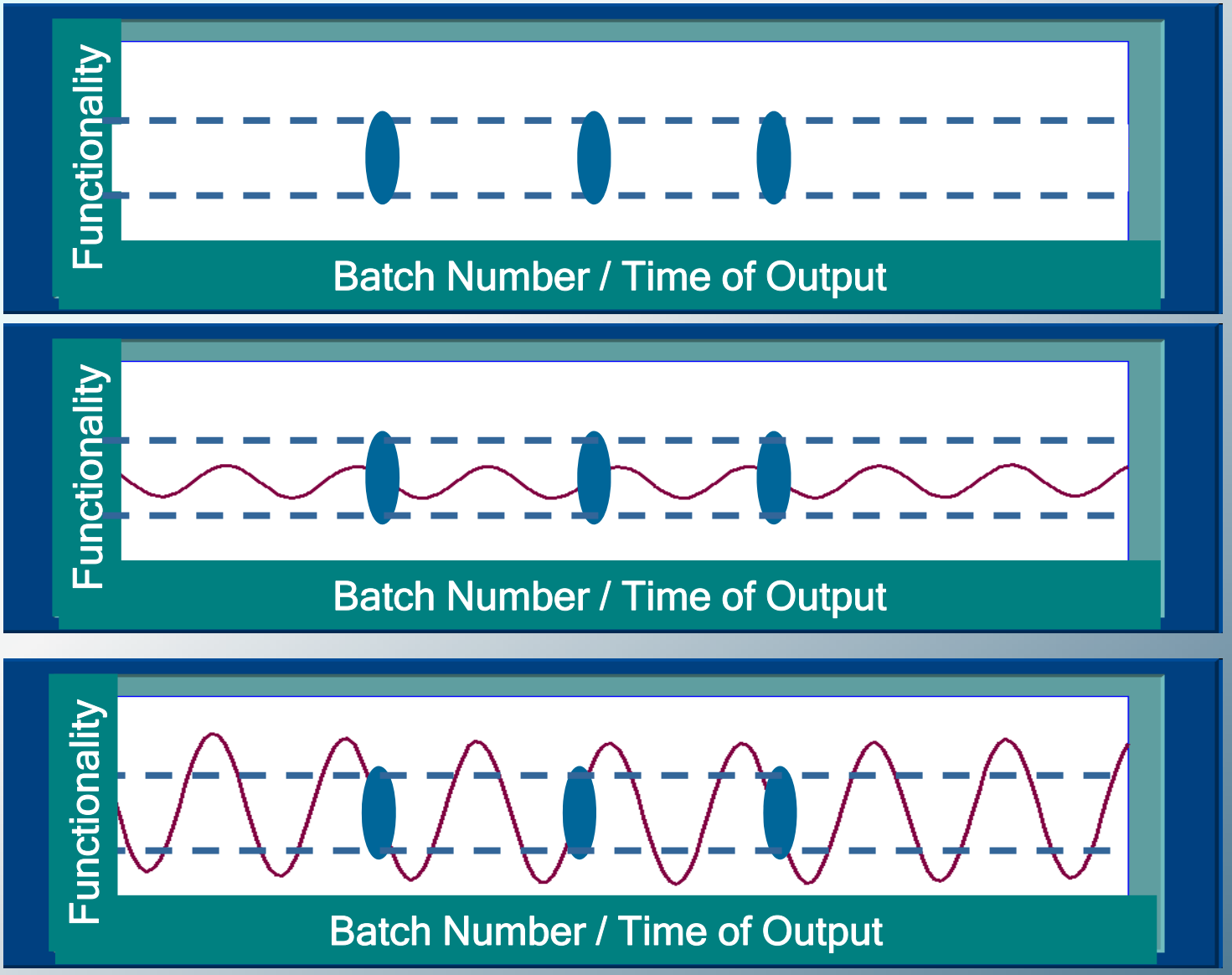
- Control of raw materials
- Batch versus Semi-Continuous, Continuous Process
- Variability in raw materials
  - Conditions during growing season
  - Conditions at harvest
  - Variations in growing season year upon year
- Changes in raw material due to
  - Drought
  - Flood
  - War
  - Accident
- Weather at the time of production
  - Hot or cold
  - Dry or humidity
- Lack of consistency in materials and process conditions
- Lack of determination of the process end-point
- Lack of understanding of the interaction between the three components
- Misinterpretation and utilization of functionality
- Etc.

Preventing / Reducing Product Variability

- Robust Formulations and processes
- Tight controls on equipment and process
- Tighter specifications for materials
  - API and excipients
    - Custom grades
    - Batch Selection
    - etc.

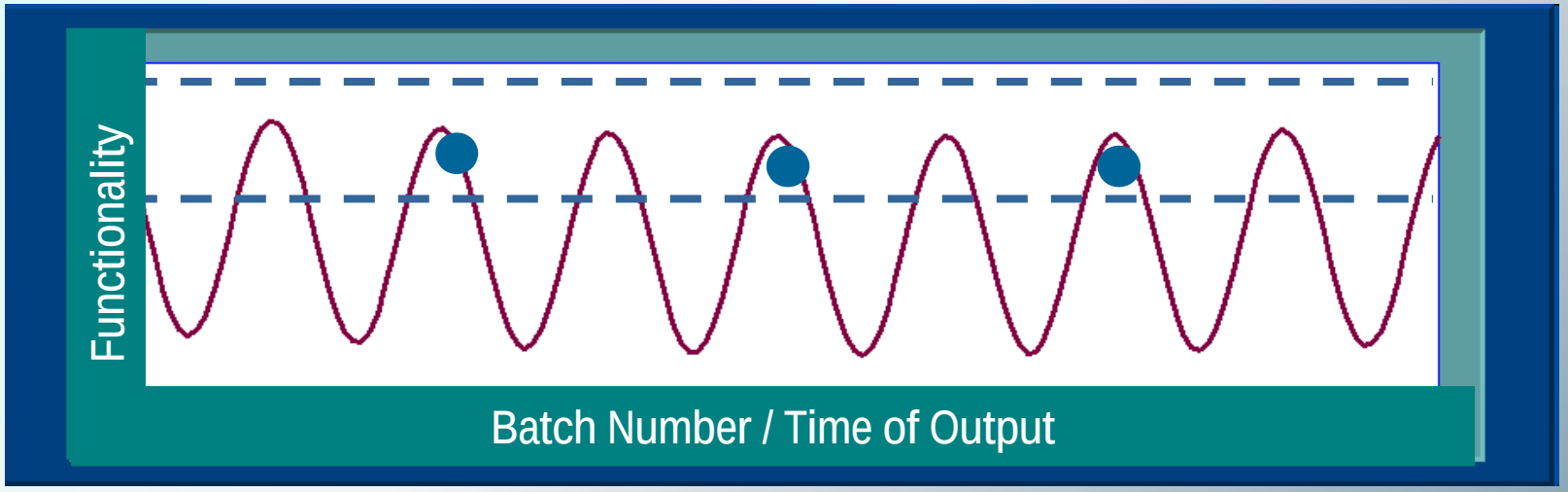
YES, BUT HOW ABOUT INHERENT VARIABILITY?

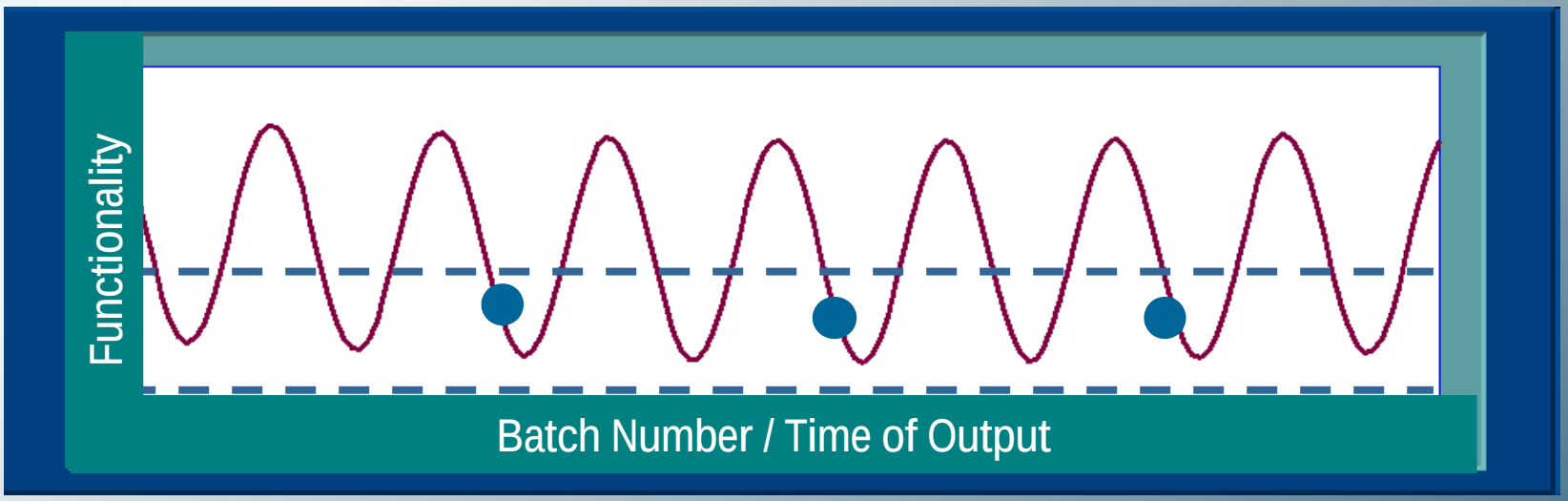
How About the Inherent Variability?



Adopted from the presentation of Chris Moreton, Pharaceutical Excipients, San Diego, CA, Jan 2007

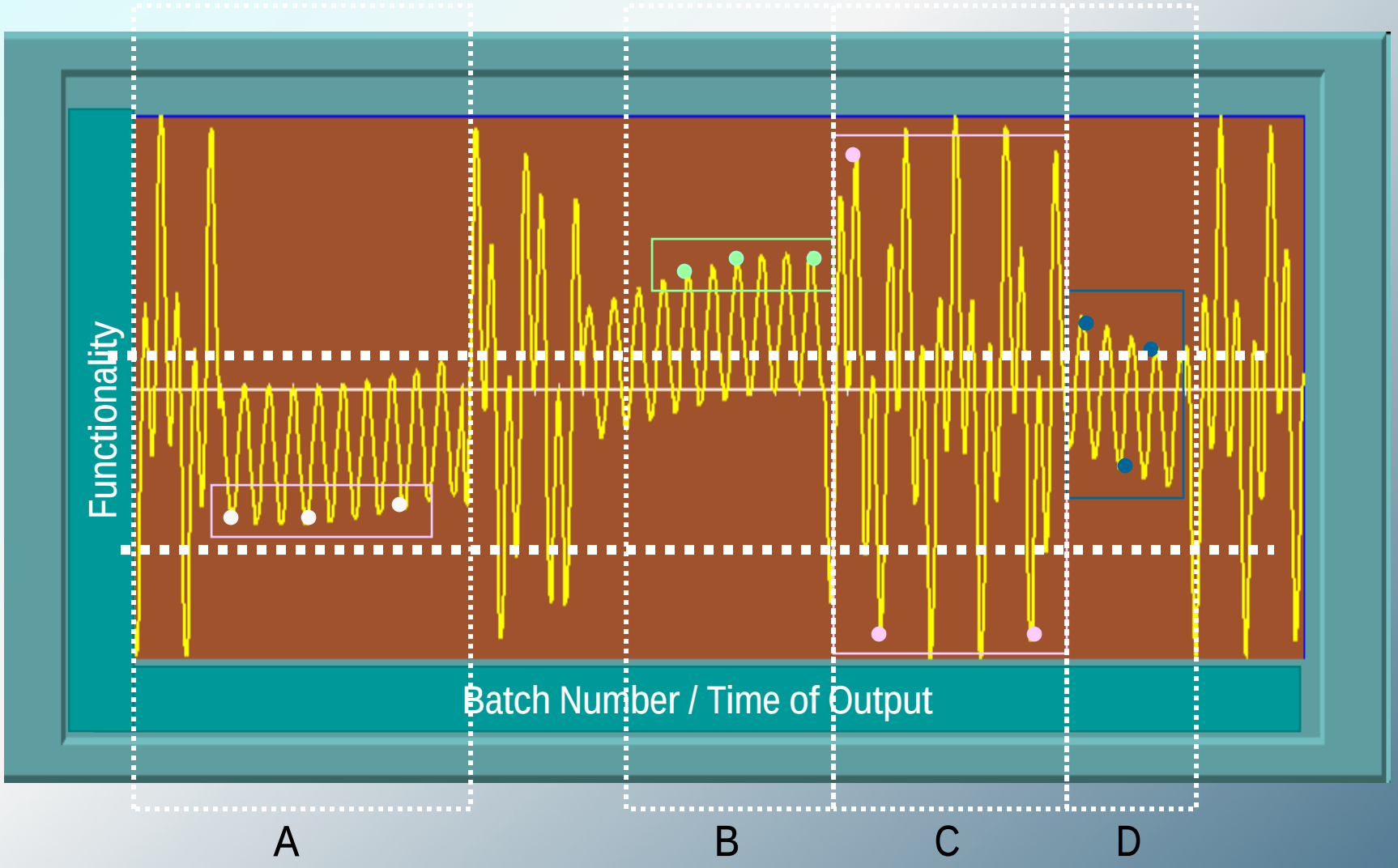
Inherent Variability Considerations





Adopted from the presentation of Chris Moreton, Pharaceutical Excipients, San Diego, CA, Jan 2007

Inherent Variability Considerations



Adopted from the presentation of Chris Moreton, Pharaceutical Excipients, San Diego, CA, Jan 2007

EXCIPIENT SELECTION

Critical Issues

Physico-Mechanical Properties

- Micromeritics
  - Particle Size
  - Particle Shape
  - Surface Area
  - Porosity
  - Density
    - True
    - Bulk and Tap
    - Particle
- Flowability
- Moisture Content
- Solubility
- Compaction Behavior
- Other Physico-Mechanical Properties

Potential Impact of Excipients on Formulation/Processing Attributes

Excipient Characteristics	Product Property Effect							
	Flow	Blending	Wetting	Drying	Mechanical	Content Uniformity	Disinteg/ Dissolution	Stability
Particle Size Distribution	X	X	X	X	X		X	X
Particle Shape	X				X		X	
True Density				X	X			
Bulk Density	X		X		X	X	X	
Tapped Density	X		X		X	X	X	
Pore Size Distribution			X	X			X	
Surface Area	X	X	X	X	X		X	X
Surface Energy	X	X	X		X	X	X	
Flow	X				X	X	X	
Cohesiveness	X	X						
Internal Friction	X				X			
Wall Friction	X				X			
Crystal Structure			X		X	X	X	X
Degree of Crystalinity					X	X	X	X
Hydration State					X		X	X
Elastic Modulus					X			
Compactability					X			
Brittleness					X			
Static Charge	X	X						
Hygroscopicity	X			X				X

Utilization of Preformulation Databases:

- research articles
- product literature
- Handbook of Pharmaceutical Excipients
- create your own database

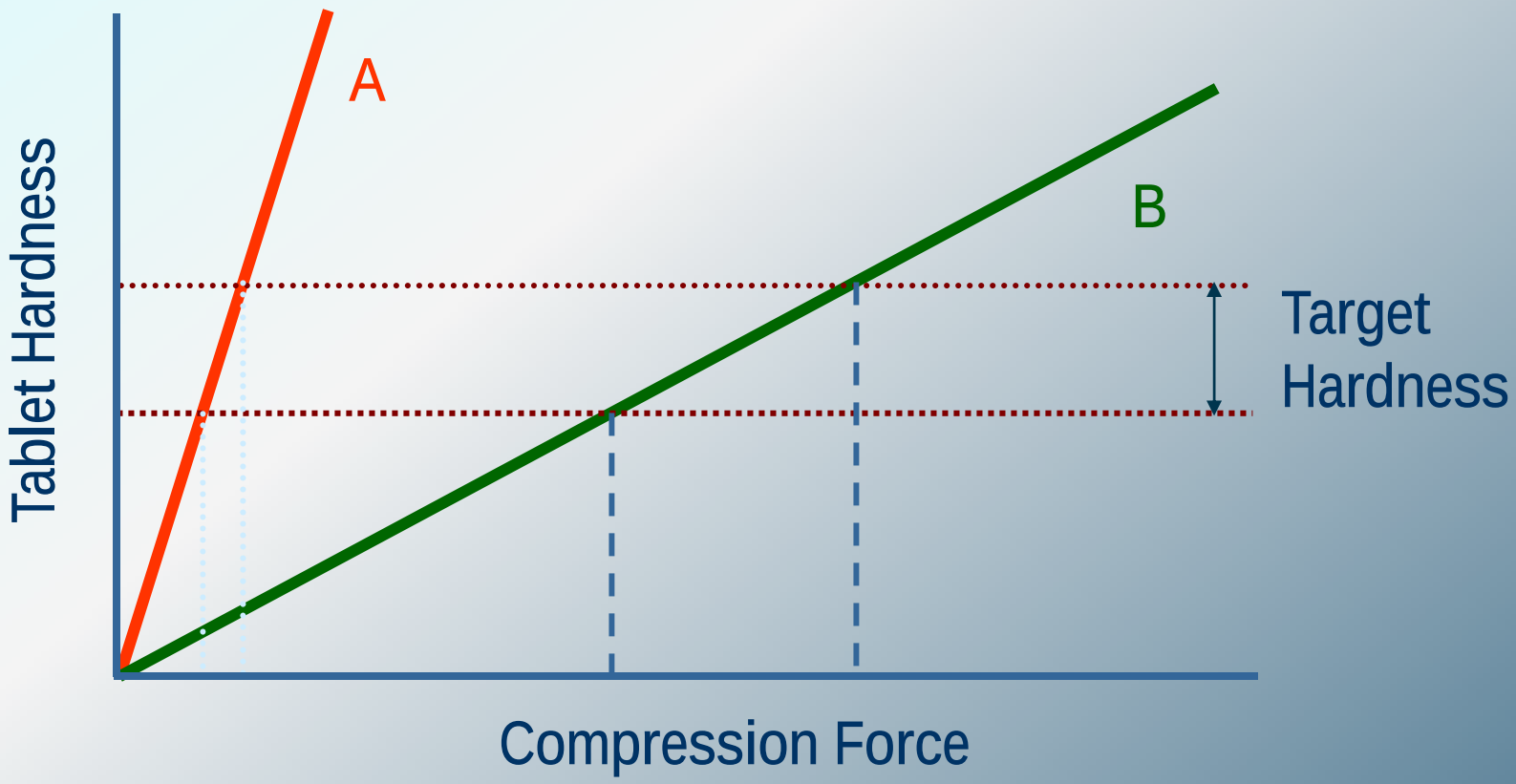
Literature based databases: Disadvantages

- incomplete database
- various methods applied to the same test
- lab-to-lab variations (equipment/personnel)
- data not in electronic form

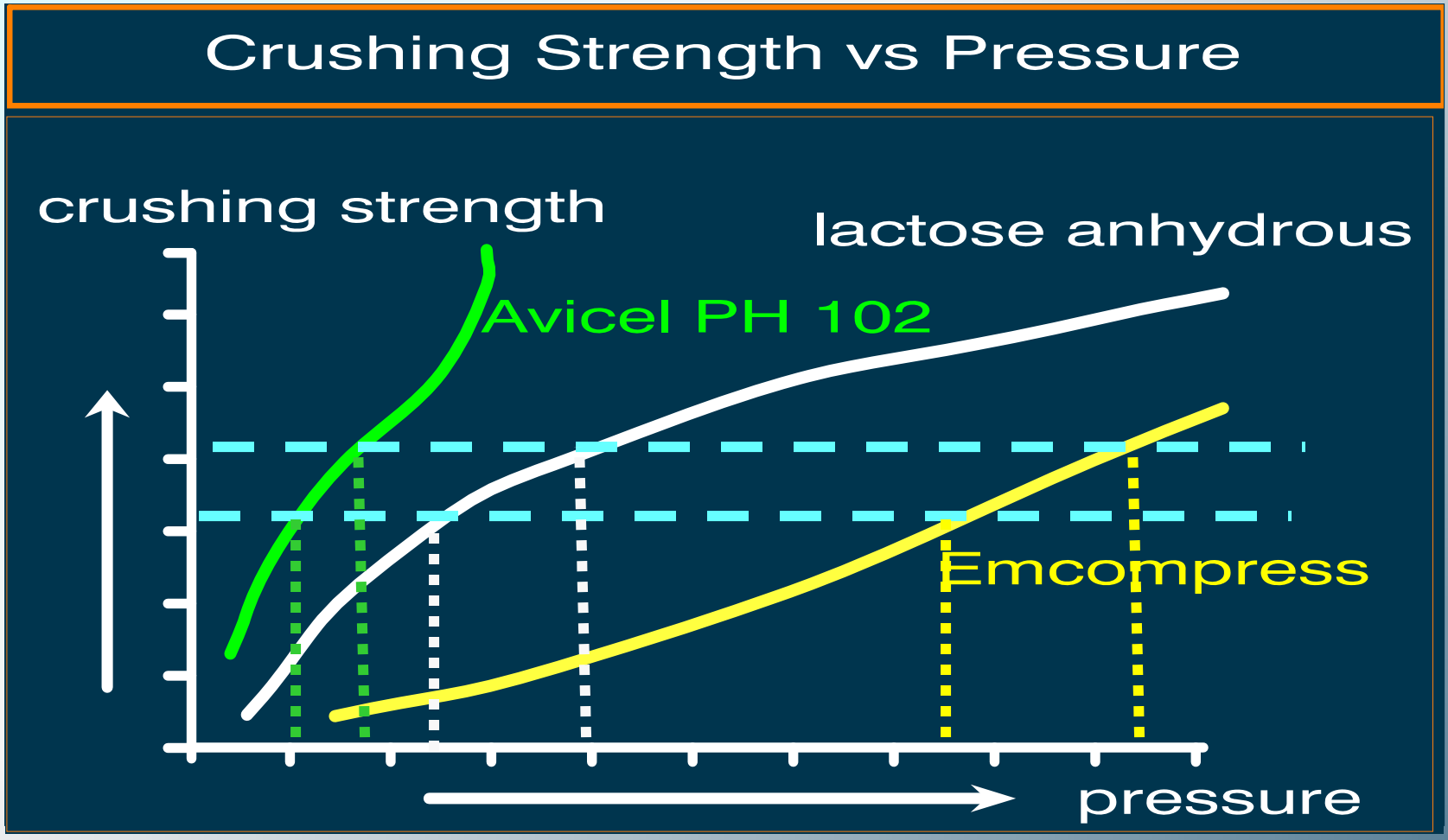
Attention:
Utilization of Handbook of Pharmaceutical Excipients

- Compression Characteristics (7)
- Density
  - True (5)
  - Bulk and Tap Density (6)
- Flowability (1)
- Moisture Content (31)
- Particle Size Distribution (10)
- Solubility (8)

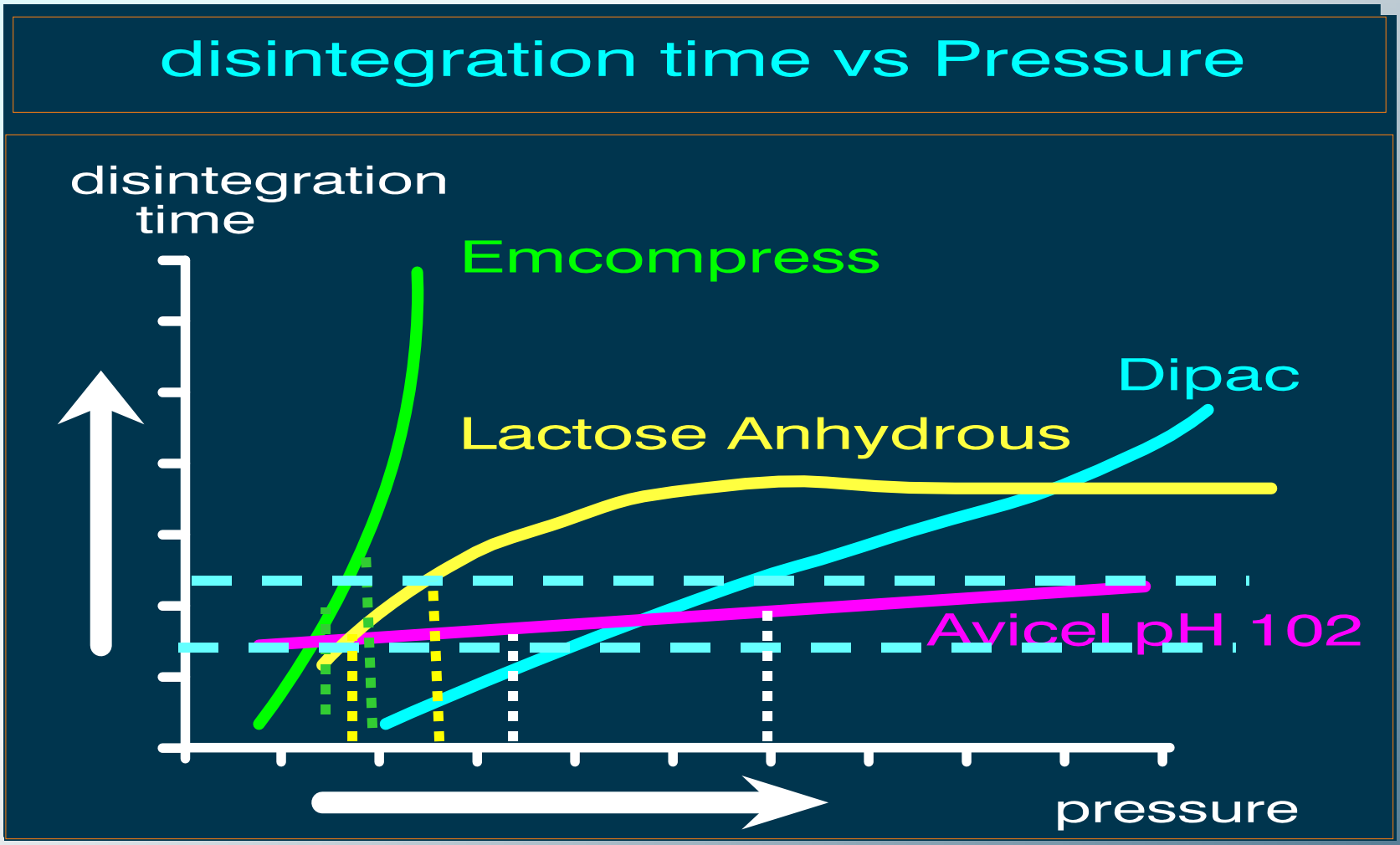
EXCIPIENT SELECTION
Determine the target range of a process parameter properly!



EXCIPIENT SELECTION
Diluents/Filler: Which one is the best excipient?



EXCIPIENT SELECTION
Diluents/Filler: Which one is the best excipient?



EXCIPIENT SELECTION

CASE STUDY

Microcrystalline Cellulose

- Miscellaneous Properties
- Batch-To-Batch Variations
- Grade-To-Grade Variations
- Plant-To-Plant Variations
- Supplier-To-Supplier Variations

Microcrystalline Cellulose
Important Properties

- requires no/little lubrication (when used in high concentrations)
- sensitive to lubrication with magnesium stearate (in proportion to blending times)
- entraps micronized poorly soluble drugs and decrease of rate of dissolution (when microcrystalline cellulose is used at a concentration of >50%)
- control the movement of the water through the powder mass and modifies the rheological properties of the other ingredients conferring a degree of plasticity allowing the mass to be extruded (- granulation by spheronization)

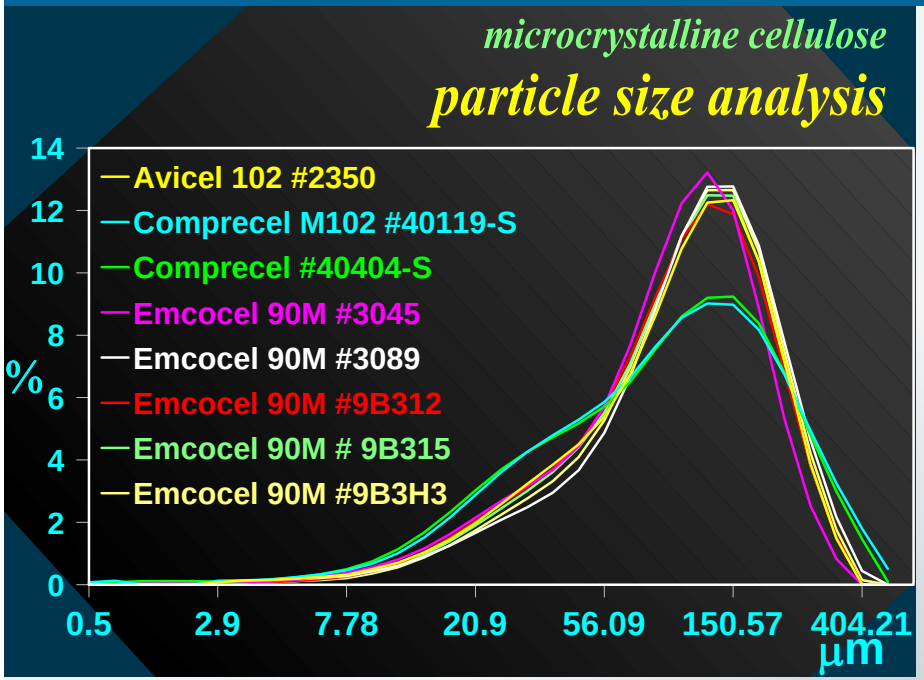
Microcrystalline Cellulose
Important Properties

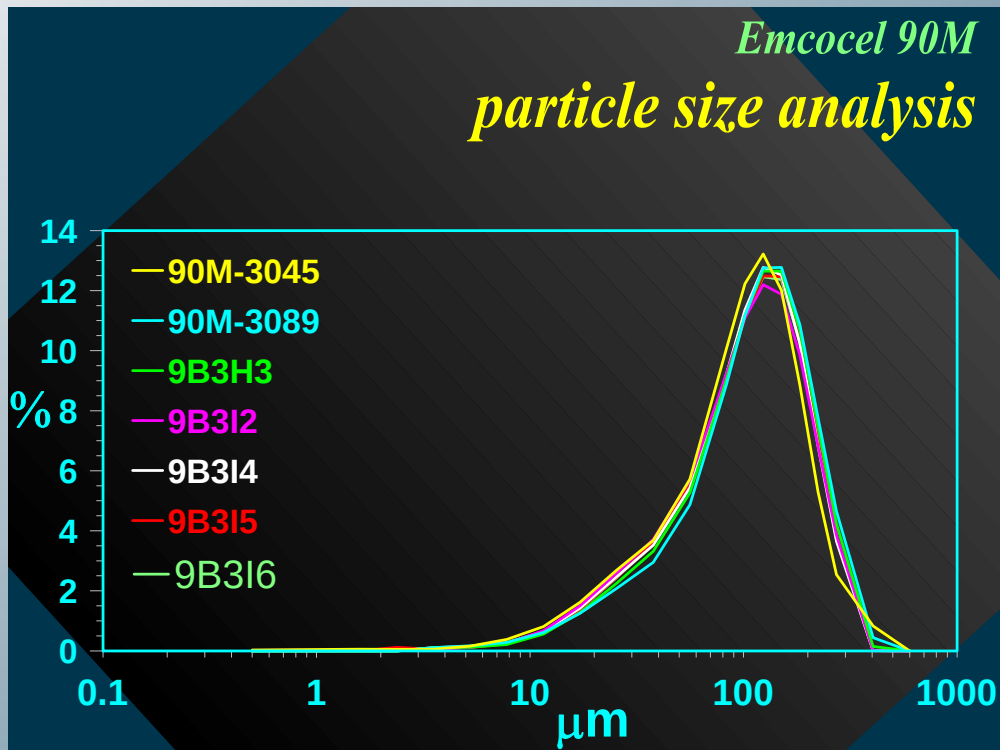
- picks up water in high humidity causing possible tablet softening.
- is a poorly reworkable material (due to destruction of the crystalline structure)
- looses compaction properties when wet granulated
- is sensitive to storage conditions
- Compaction properties: To be addressed in Module 6 - Tabletting/Compaction

Microcrystalline Cellulose Compaction Properties

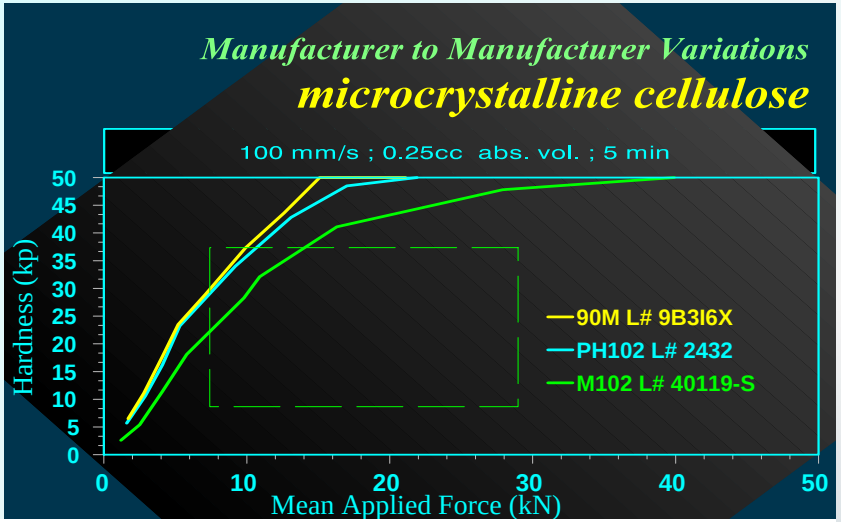
- Emcocel (Mendell)
  - Emcocel 50M
    - USA Lot # 5B312; 5B313; 5B3J1; 5B3H3
    - Finland Lot # 2433; 3544
  - Emcocel 90M
    - USA Lot # 9B312; 9B314; 9B315; 9B3H3
    - Finland Lot # 3045; 3546 (?)
- Avicel (FMC)
  - Avicel PH101
    - Lot # 1342; 1401; 1430
  - Avicel PH102
    - Lot # 2343; 2350; 2432
- Comprecel (Mingtai)
  - Comprecel M101
    - Lot # 40403-S; A30117; 21015
  - Comprecel M101
  - Lot # 40403-S; 40119-S; B30115

Microcrystalline Cellulose:
Batch-to-Batch / Grade-to-Grade / Supplier-to-Supplier Variations





Microcrystalline Cellulose:
Batch-to-Batch / Grade-to-Grade / Supplier-to-Supplier Variations



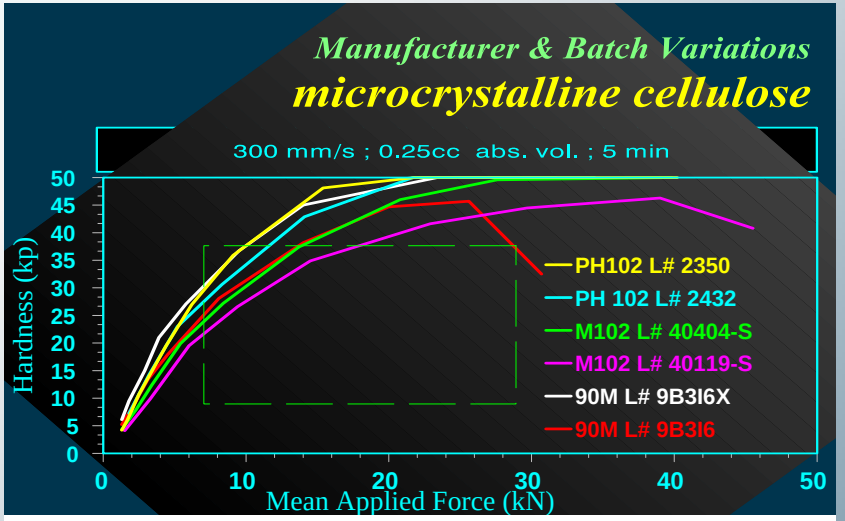


Figure 1

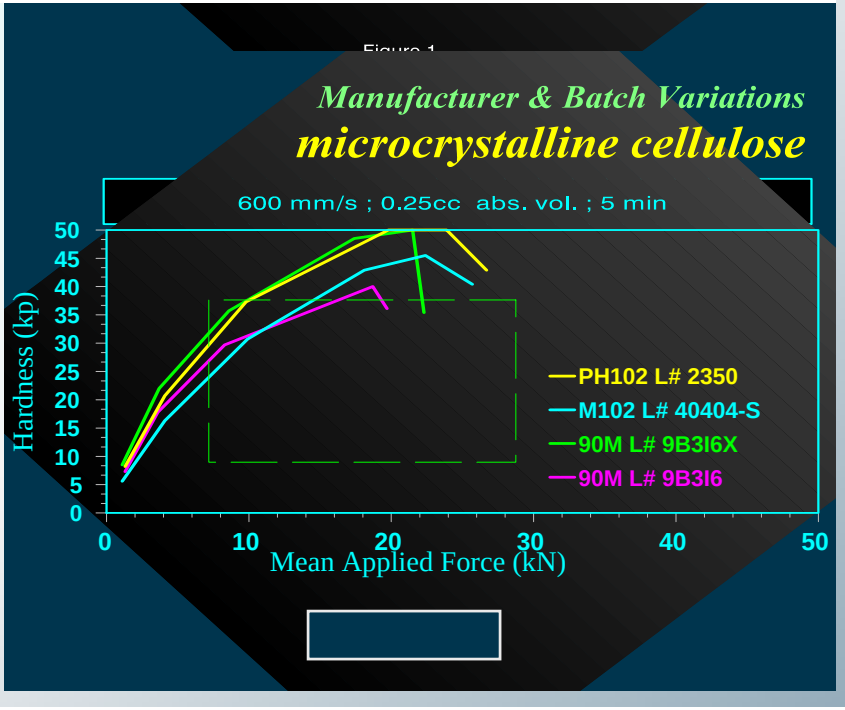
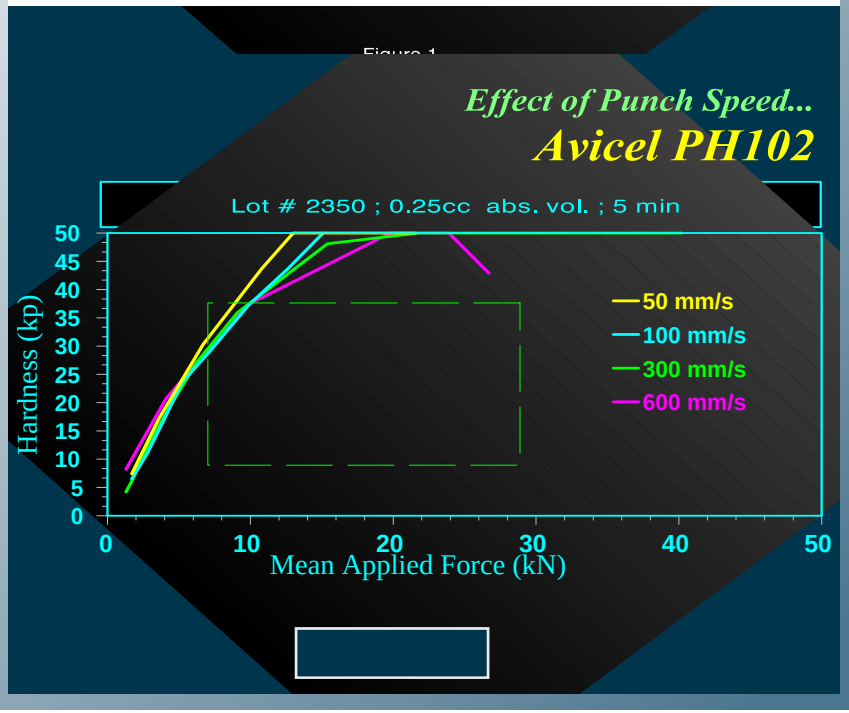


Figure 1



CASE STUDY

Calcium Phosphate

- Miscellaneous Properties
- Batch-To-Batch Variations
- Grade-To-Grade Variations
- Supplier-To-Supplier Variations

Calcium Phosphate

Two forms available:

- Dibasic calcium phosphate dihydrate ($CaHP0_4.2H_2O$)
  - more commonly used form
  - not sensitive to compaction speed
  - not sensitive to compaction pressure
  - surface properties neutral/slightly basic

- Anhydrous dibasic calcium phosphate ($CaHPO_4$)
  - not sensitive to compaction speed
  - sensitive to compaction pressure
  - surface properties more acidic

Two particle size grades available for both:

- Fine-milled (typically <20µm) for wet granulation
- Unmilled/coarse grade (ca. 150 - 200µm) for direct compression

Dibasic Calcium Phosphate Dihydrate

- **Dihydrate salt is nonhygroscopic.** However, under accelerated aging dehydration reaction occurs*. Initiation of dehydration reaction appears to be promoted by:
  1. elevated humidity (microhumidity)
  2. certain actives
  3. elevated temperature (below 100ºC)

$$4CaHPO_4.2H_2O + H_2O \longrightarrow Ca(H_2PO_4)_2 + Ca_3(PO_4)_2 + 9H_2O$$

$$Ca(H_2PO_4)_2 \longrightarrow CaHPO_4 + H_3PO_4$$

$$H_3PO_4 + CaHPO_4.2H_2O \longrightarrow Ca(H_2PO_4)_2 + 2H_2O$$

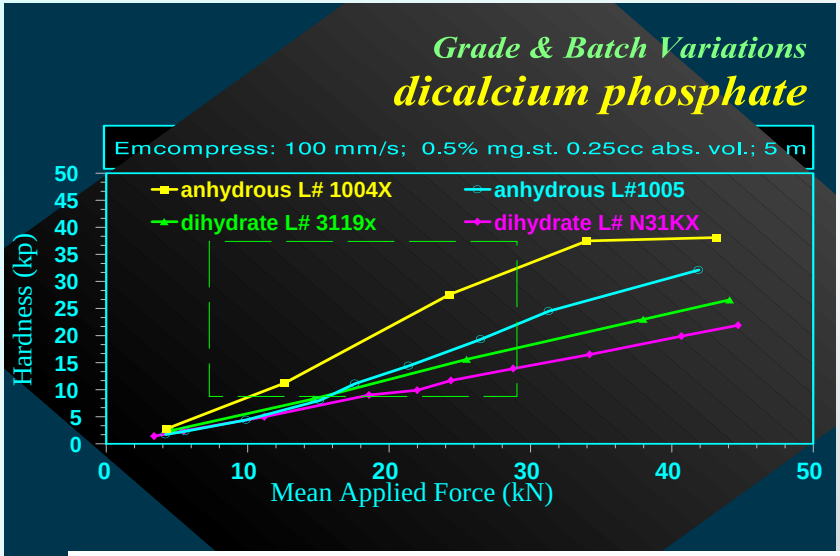
- **There are implications for:**
  1. coating
  2. packaging

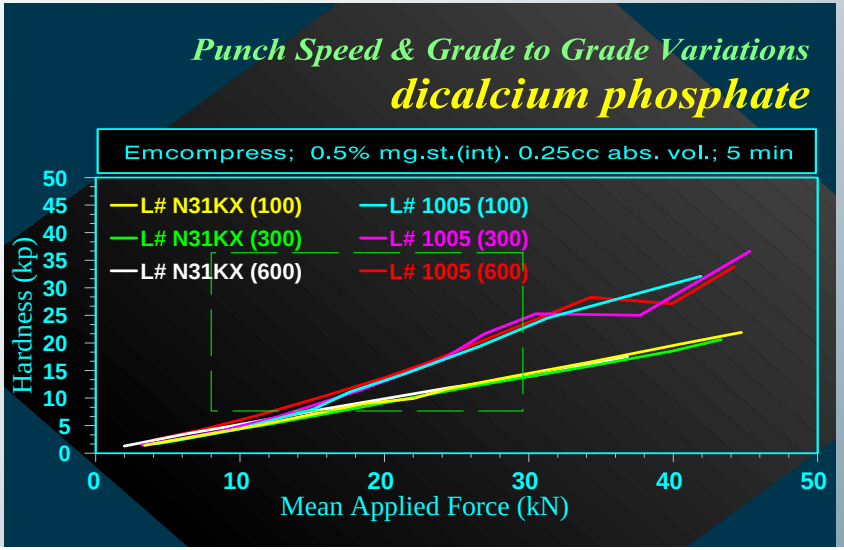
*Dehydration Reaction Scheme (Dugleux and De Sallier-Dupin, 1967)

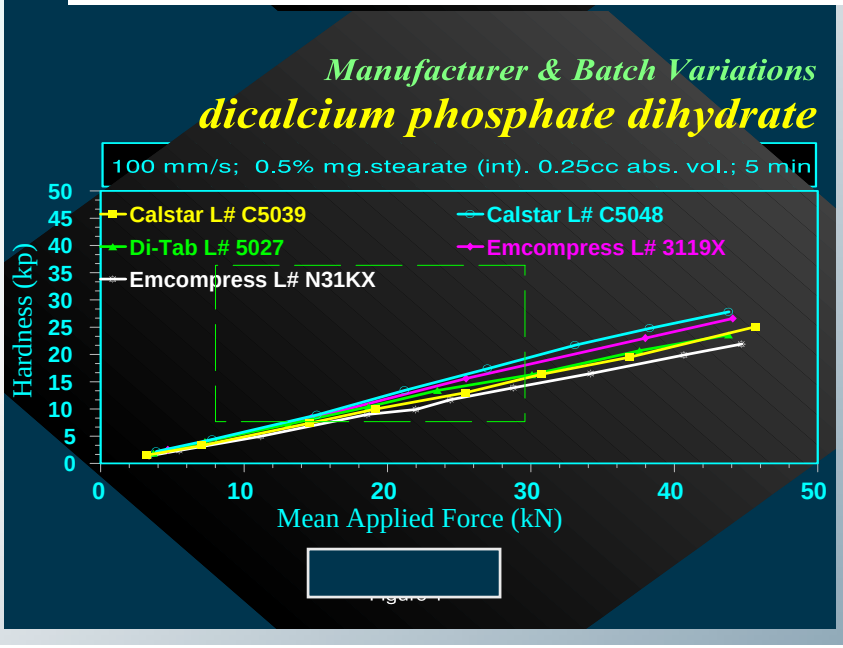
Calcium Phosphate Compaction Properties

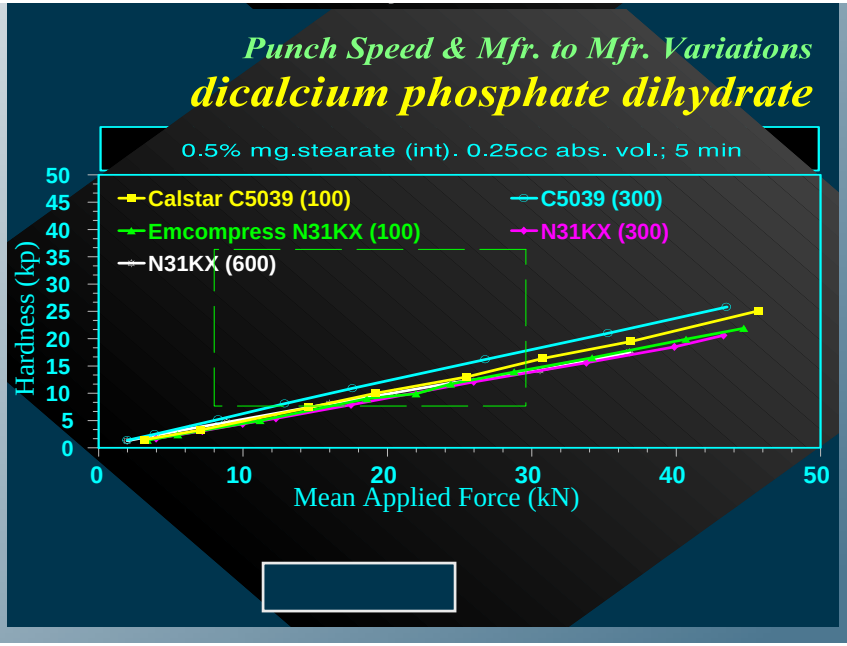
- Emcompress (Mendell)
  - Dihydrate
    - Lot # N31KX; 3119X
  - Anhydrous
    - Lot # 1004X; 1005
- Calstar (FMC)
  - Dihydrate
    - Lot # C5039; C4048
- Di-tab (Rhone-Poulenc)
  - Dihydrate
    - Lot # 5027

Dibasic Calcium Phosphate
Batch-to-Batch / Grade-to-Grade / Supplier-to-Supplier Variations









CASE STUDY

Pre-Gelatinized Starch

- Miscellaneous Properties
- Batch-To-Batch Variations
- Grade-To-Grade Variations

Pre-Gelatinized Starch

- Pre-gelatinized starch
  - requires no/little lubrication (when used in high concentrations)
  - sensitive to lubrication with magnesium stearate (avoid using more than 0.5% magnesium stearate)
  - Highly visco-elastic (which is a concern for use in the core for the film coated tablets)
  - Partially pre-gelatinized (Starch 1500)
    - good direct compression properties
  - Fully pre-gelatinized (National 1551)
    - poor direct compression properties
    - Better wet binder propertied

Pre-Gelatinized Starch

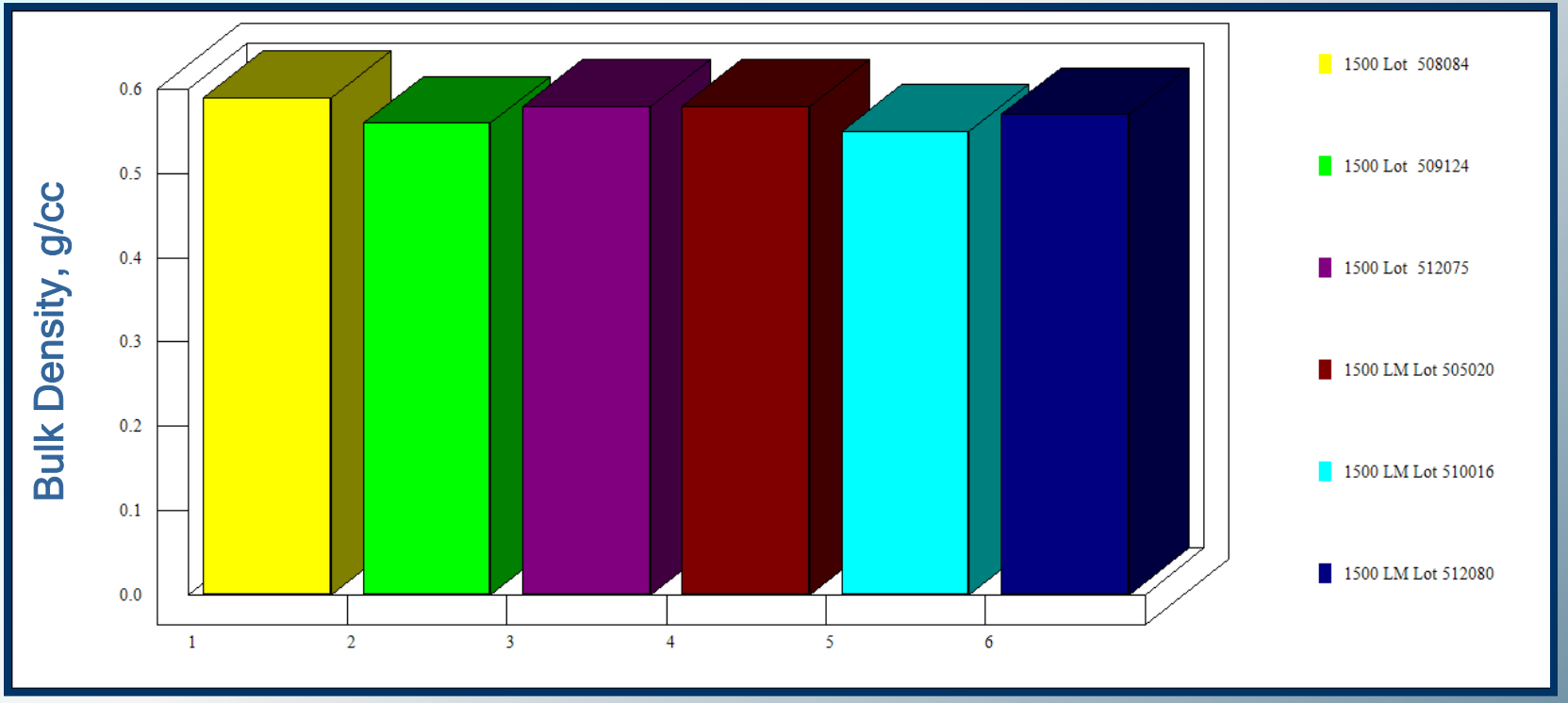
Pre-Gelatinized Starch Case Study – Materials and Method

- Materials

1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

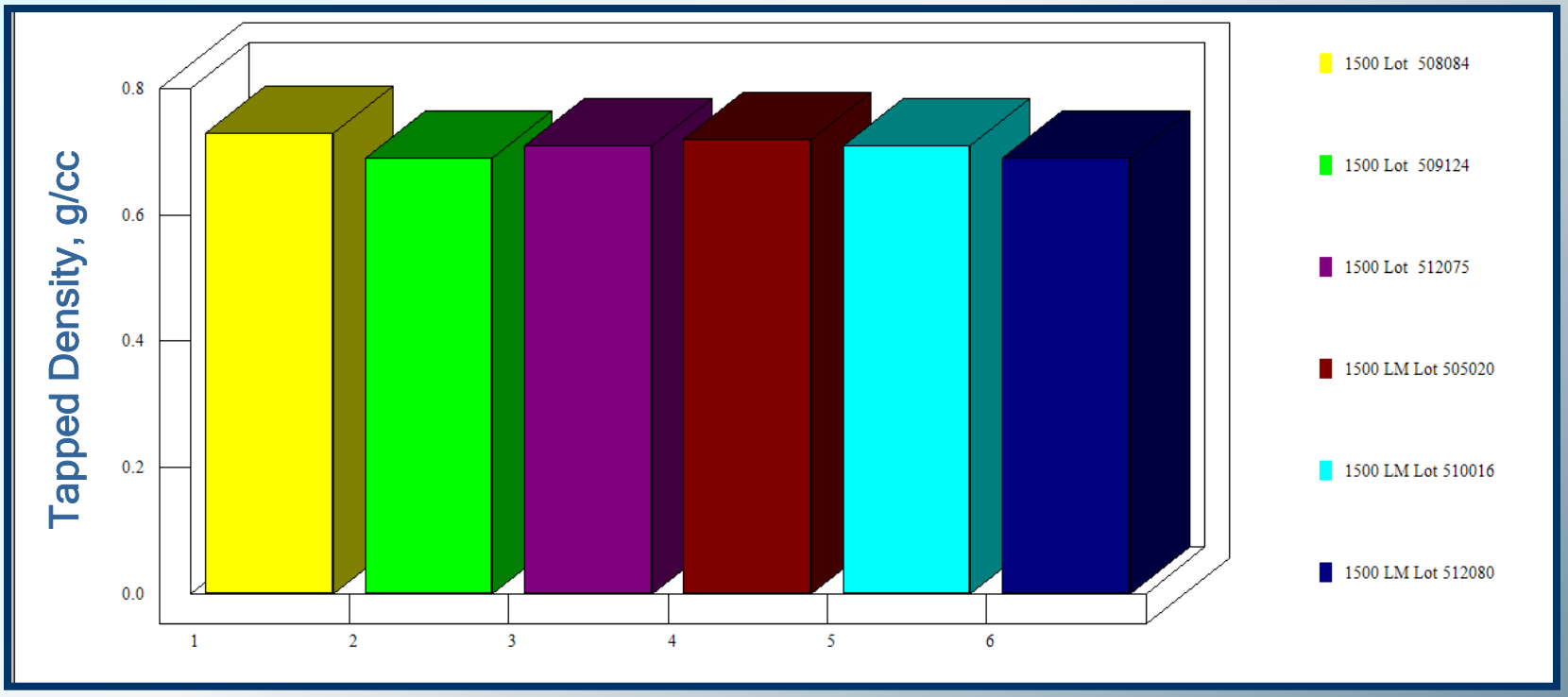
- Moisture Content Analysis (Computrac MAX50)
- Flowability Tests (Pharmatest Flow Tester)
- Density Measurements (Bulk, Tapped, True-(Quantachrome Multipycnometer))
- Particle Size Analysis (Sympatec)
- Compaction Tests:
  - The compaction studies were performed employing an Integrated Compaction Research System (Mand Testing Ltd., Stourbridge, U.K.) fitted with standard 10.3mm round, flat faced BB tooling.
  - The compacts were made using a double ended sawtooth profile at a punch velocities of 100mm/s and 300mm/s at a wide range of applied compaction pressure. The compaction parameters collected were the forces exerted by the upper and lower punches and their displacements. All of the displacement data obtained were corrected for the deformation of the system (consisting of the punches and other machine components associated with the punches). Three to five replicates were obtained for each set of conditions. Following the completion of each set of experiments, the die wall and the punch faces were cleaned with acetone..

Pre-Gelatinized Starch Case Study – Bulk Density (g/cc)



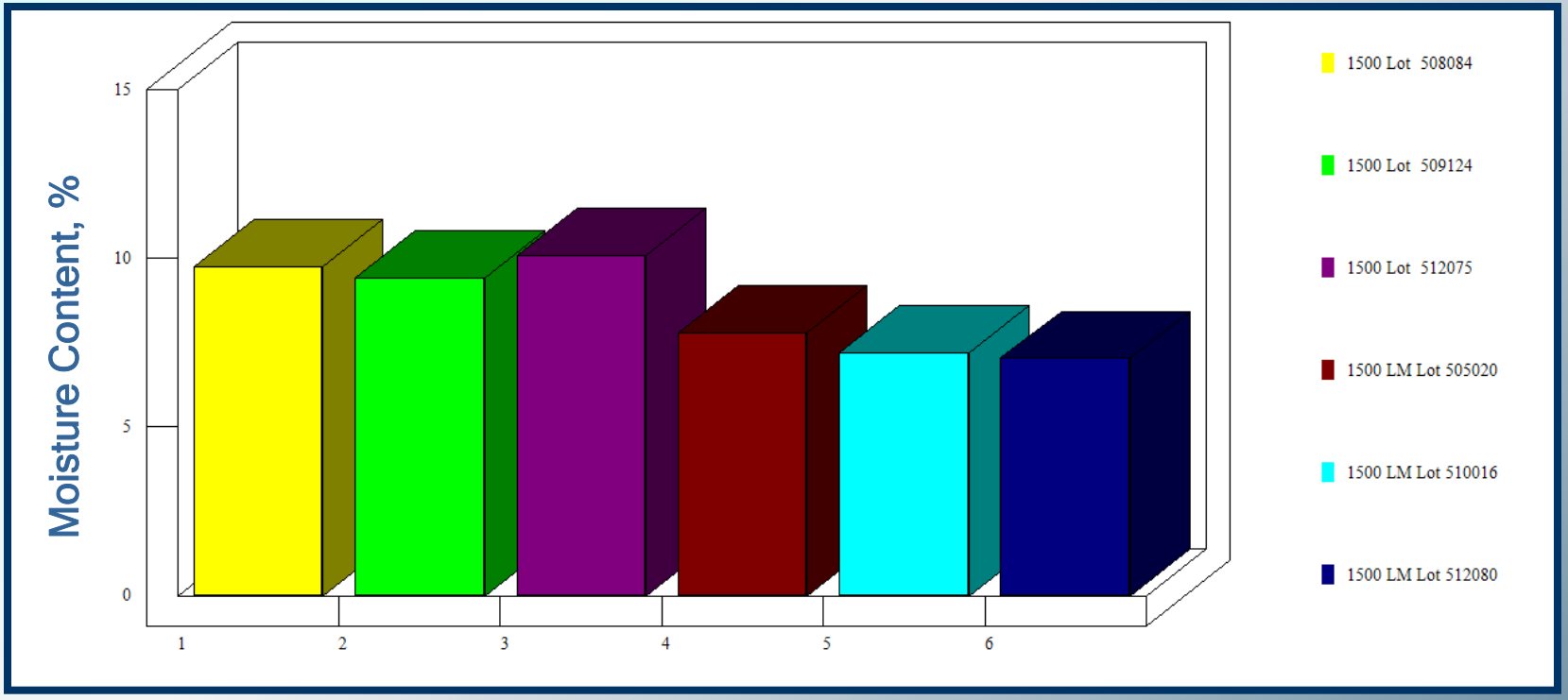
1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

Pre-Gelatinized Starch Case Study – Tapped Density (g/cc)



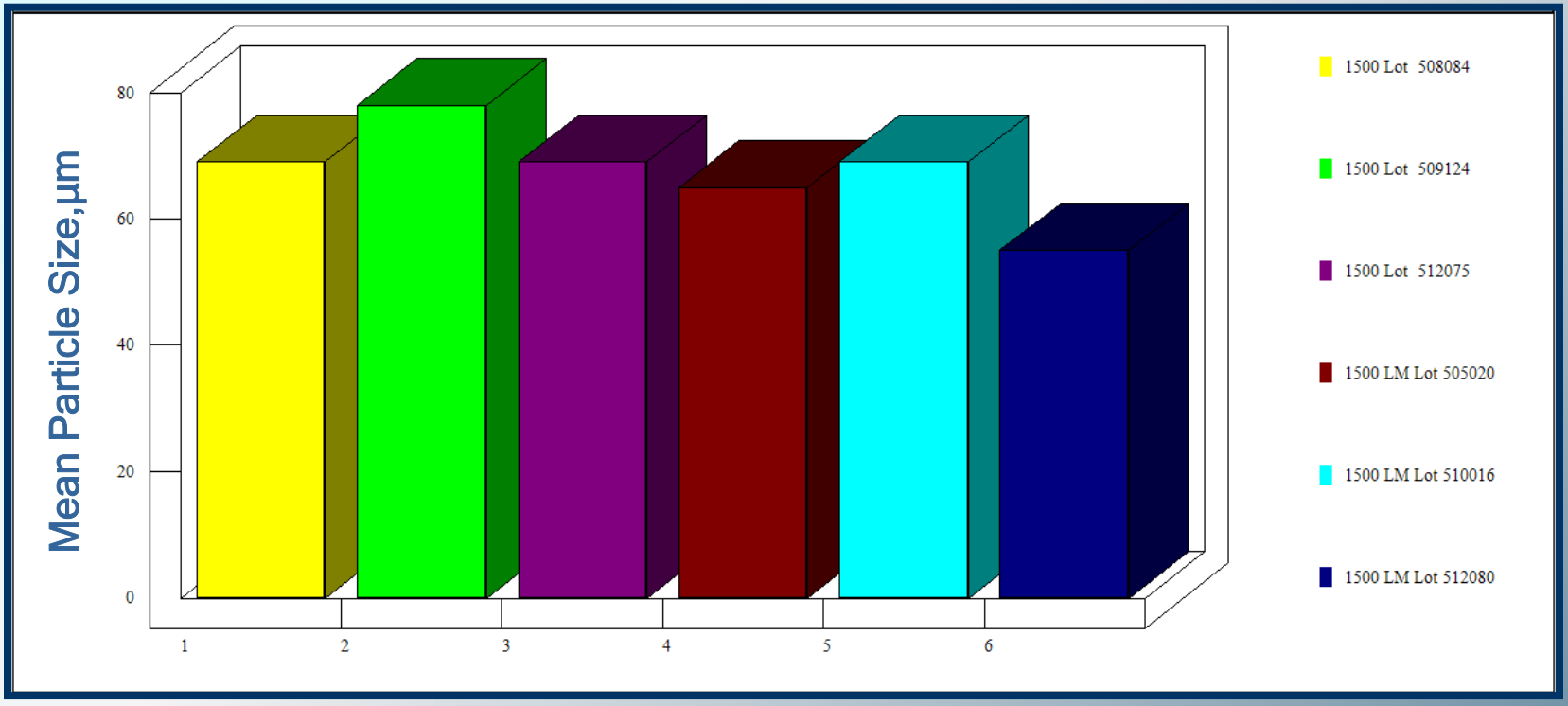
1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

Pre-Gelatinized Starch Case Study – Moisture Content (%)



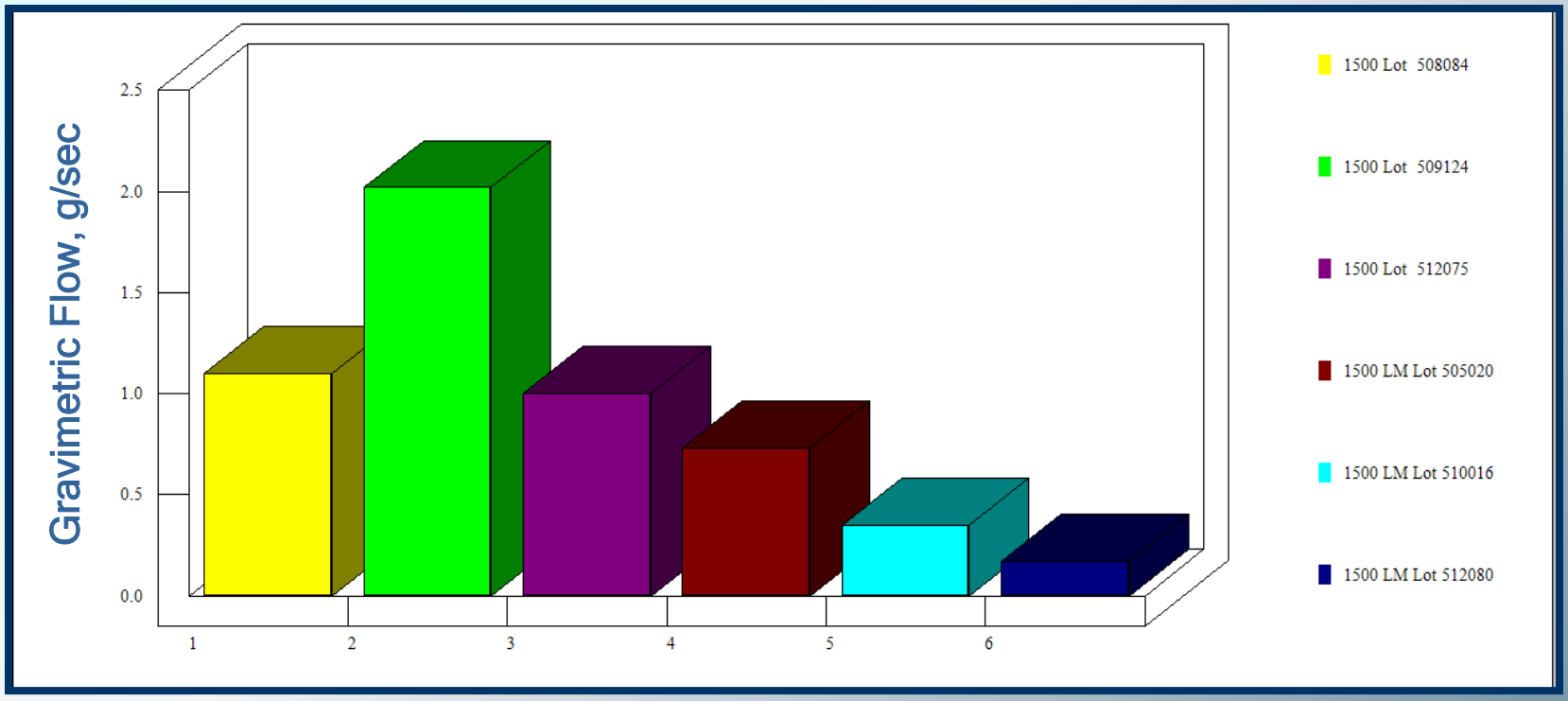
1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

Pre-Gelatinized Starch Case Study – Mean Particle Size (µm)



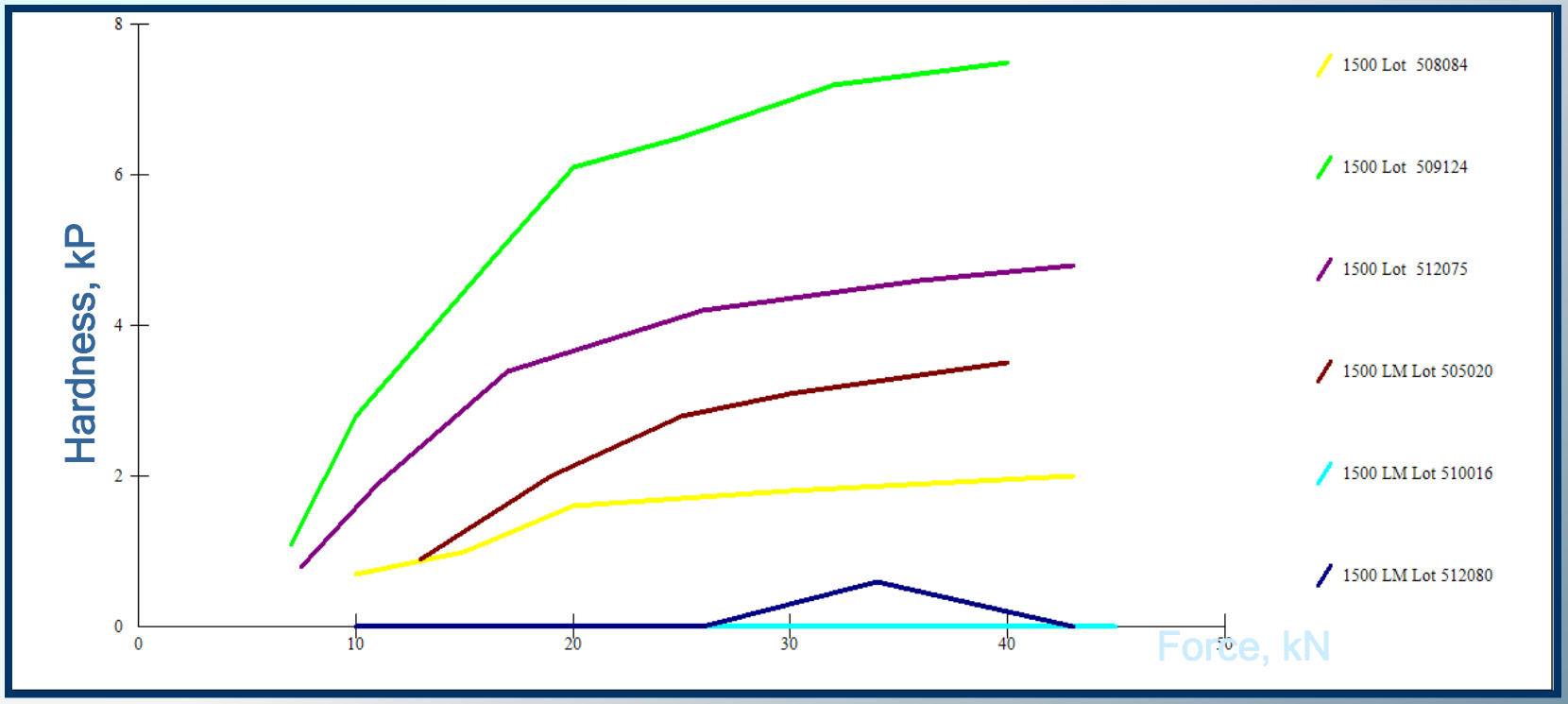
1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

Pre-Gelatinized Starch Case Study – Flow: Gravimetric Flow (g/sec)



1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

Pre-Gelatinized Starch Case Study – Hardness Profile



1500 L# 588084	1500 L# 509124	1500 L# 512075	1500 LM L# 505020	1500 LM L# 510016	1500 LM L# 512080

CASE STUDY

LACTOSE

- Miscellaneous Issues
- Batch-To-Batch Variations
- Supplier-To-Supplier Variations

Lactose

Lactose Case Study – Materials

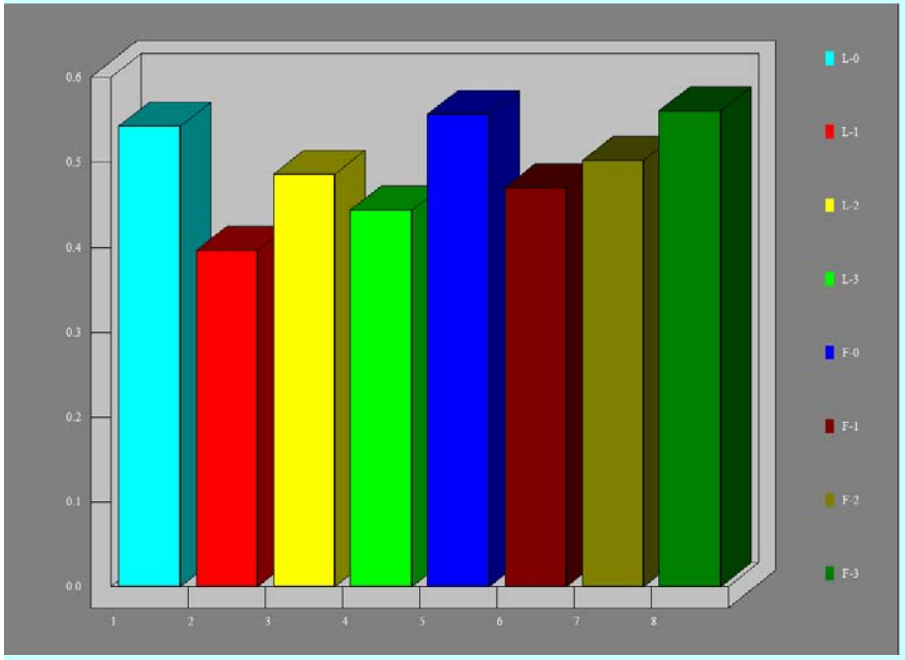
- The following four batches of lactose powders were used in this study:
  - L-0: Lactose 200 mesh (Borculo Whey Products Lot # B630049)
  - L-1: NF Lactose, Monohydrate (Leprino Foods Lot # 709811)
  - L-2: NF Lactose, Monohydrate (Leprino Foods Lot # 554619)
  - L-3: NF Lactose, Monohydrate (Leprino Foods Lot # 709983)

- The model Acetaminophen formulation contained the above excipients at the following concentrations:
  - N-Acetyl-p-amino phenol 20.26%
  - lactose 56.74%
  - microcrystalline cellulose 20.67%
  - polyvinylpyrrolidone 1.82%
  - magnesium stearate 0.51%

Lactose Case Study – Methods

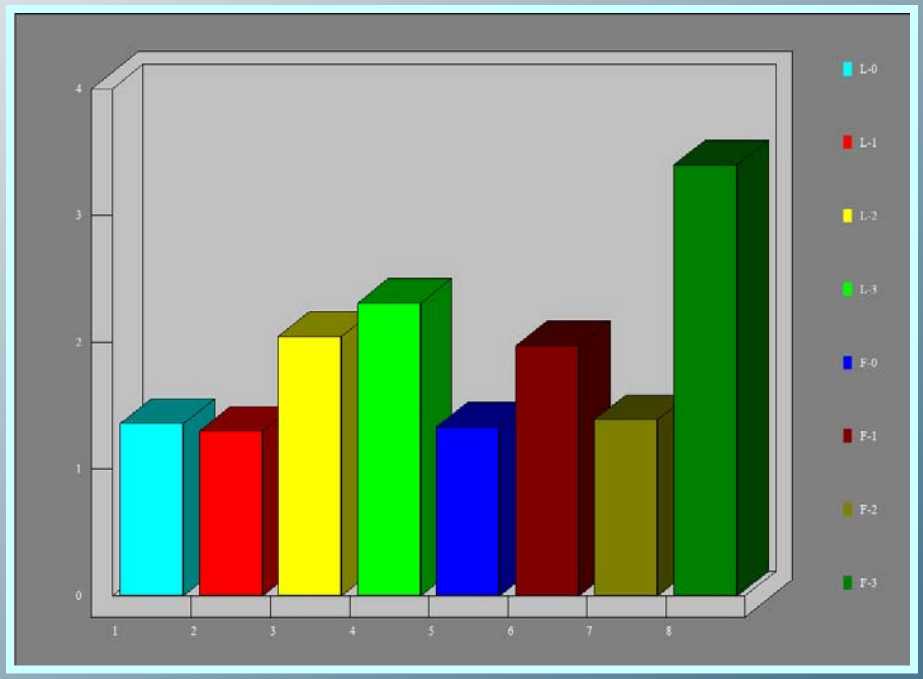
- Moisture Content Analysis (Computrac MAX50)
- Flowability Tests (Pharmatest Flow Tester)
- Density Measurements (Bulk, Tapped, True-(Quantachrome Multipycnometer))
- Particle Size Analysis (using an ATN sonic sifter)
- Granulation: (A 5-lt Baker-Perkins high-shear mixer granulator)
- Compaction Tests:
  - The compaction studies were performed employing an Integrated Compaction Research System (Mand Testing Ltd., Stourbridge, U.K.) fitted with standard 10.3mm round, flat faced BB tooling.
  - The samples which contained an internal lubricant were prepared by mixing 0.5% of previously sifted (through #80 mesh size) magnesium stearate with the material (excipient) for three minutes using a mixer (Turbula Type T2C, Glen Mills Inc., N.J.) at 42rpm. During mixing, the containers were filled to a maximum of two-thirds of their capacity. The compacts were made using a double ended sawtooth profile at a punch velocities of 100mm/s and 300mm/s at a wide range of applied compaction pressure. The compaction parameters collected were the forces exerted by the upper and lower punches and their displacements. All of the displacement data obtained were corrected for the deformation of the system (consisting of the punches and other machine components associated with the punches). Three to five replicates were obtained for each set of conditions. Following the completion of each set of experiments, the die wall and the punch faces were cleaned with acetone.
  - Additional post-compaction tests (for the tablets made from granulated formulations) included the disintegration (PharmaTest automated disintegration apparatus) and friability (Roche Friabiltor) tests.

Lactose - Batch/Supplier Variation (1)



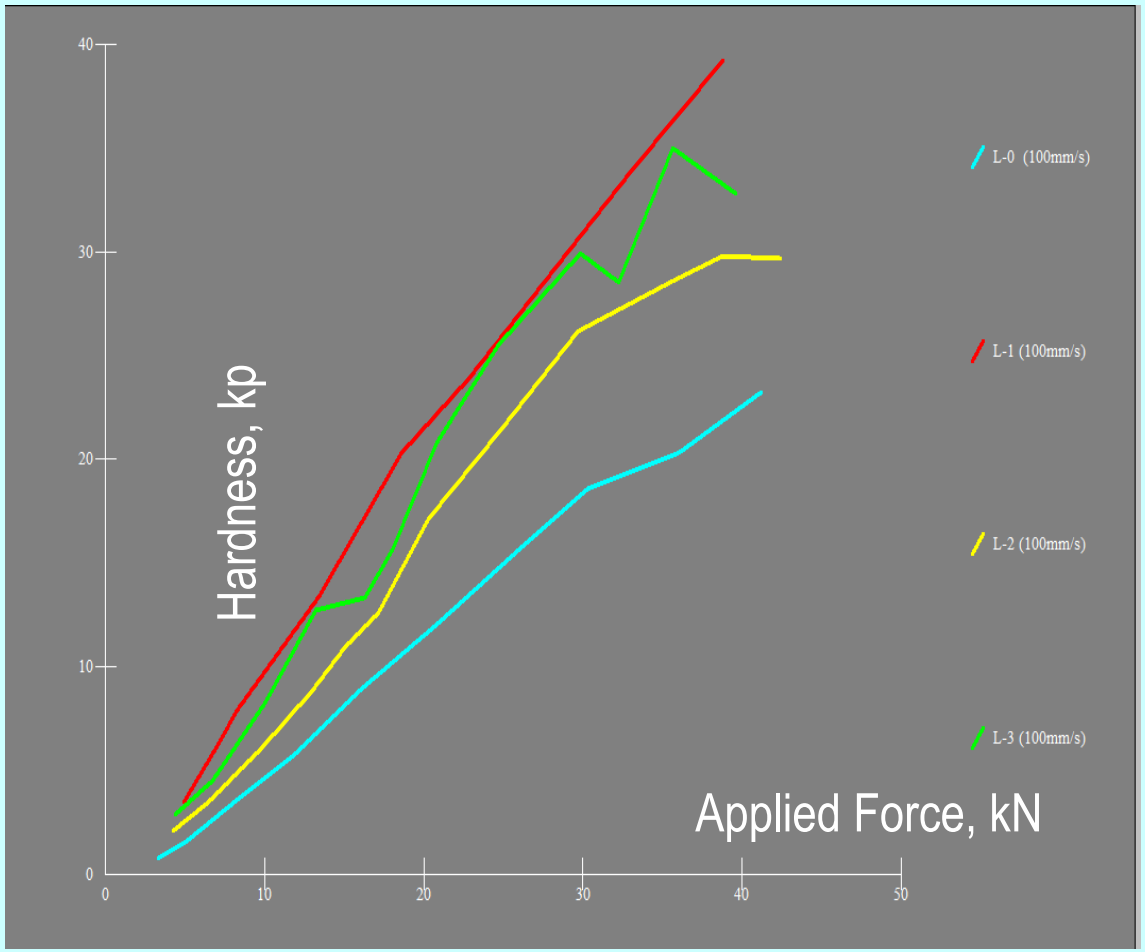
Bulk Density (g/cc)

Moisture Content Analysis

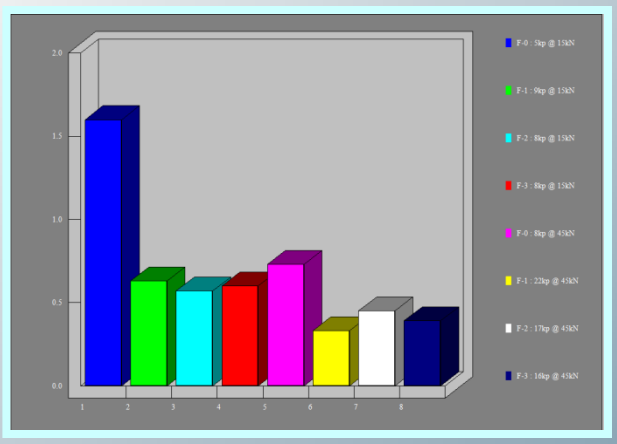


Lactose - Batch/Supplier Variation (3)

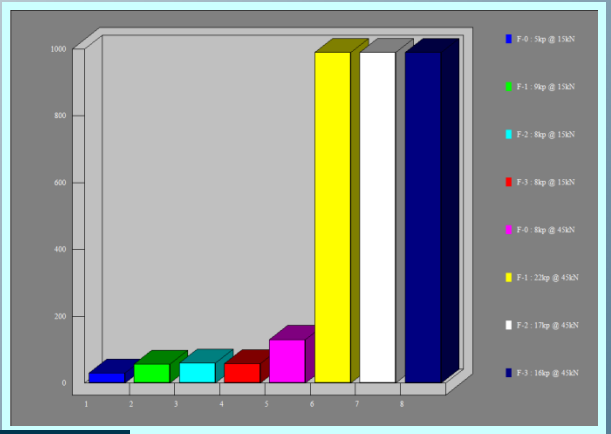
Hardness Profile (Tablets made @ 100 mm/sec)



% Friability (@ 100 mm/sec)

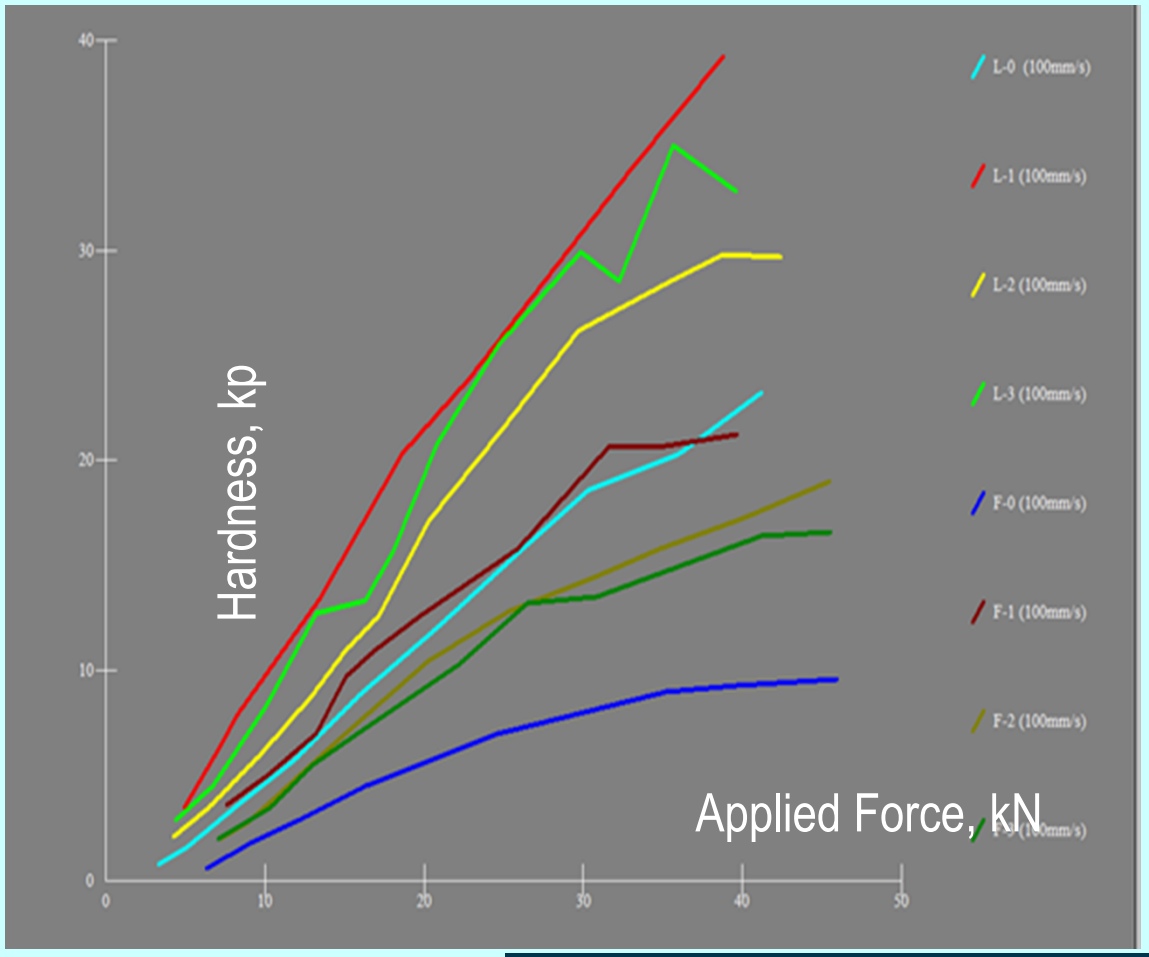


Disintegration Time, sec (@ 100 mm/sec)

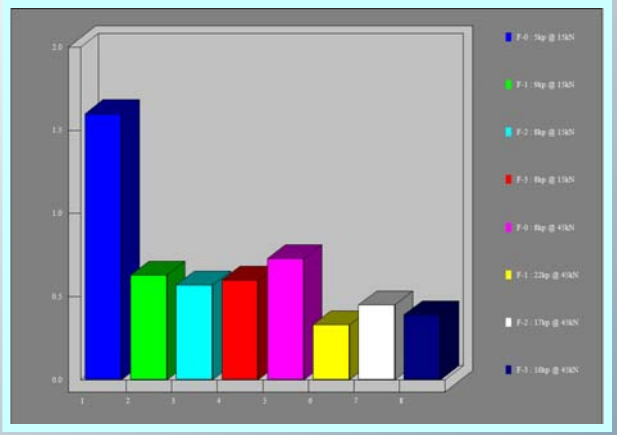


Lactose - Batch/Supplier Variation (3)

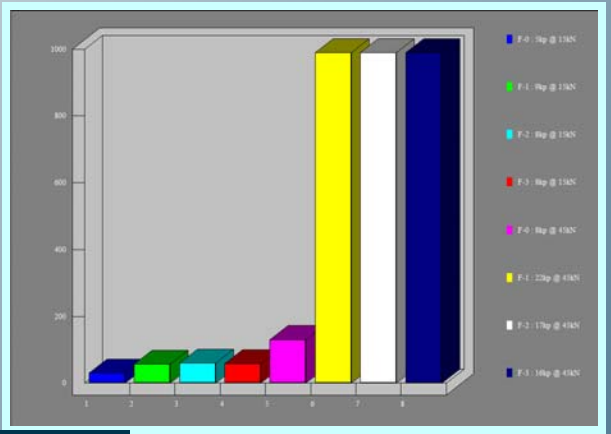
Hardness Profile (Tablets made @ 100 mm/sec)



% Friability (@ 100 mm/sec)



Disintegration Time, sec (@ 100 mm/sec)



L0 L1 L2 L3

F0 F1 F2 F3

CASE STUDY
MAGNESIUM STEARATE

- Miscellaneous Properties

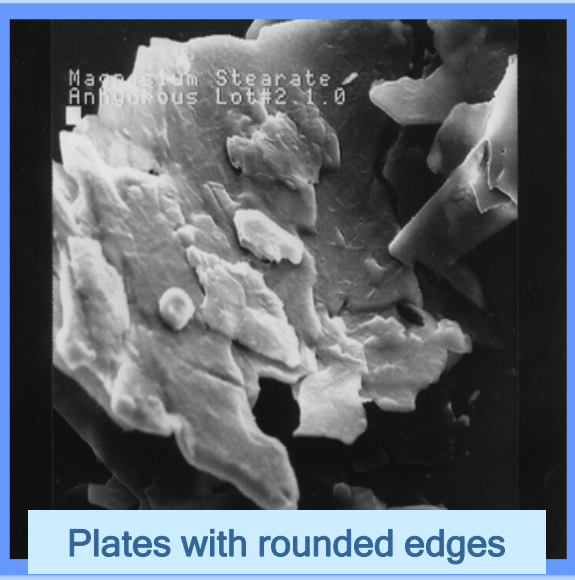
Problems Associated with Magnesium Stearate

- exhibits supplier to supplier variation
- exhibits batch to batch variations
- may retard the dissolution of a drug
- may increase the tablet friability
- may reduce the strength of the compacts
- sensitive to mixing time
- difficult to determine the ‘right amount’

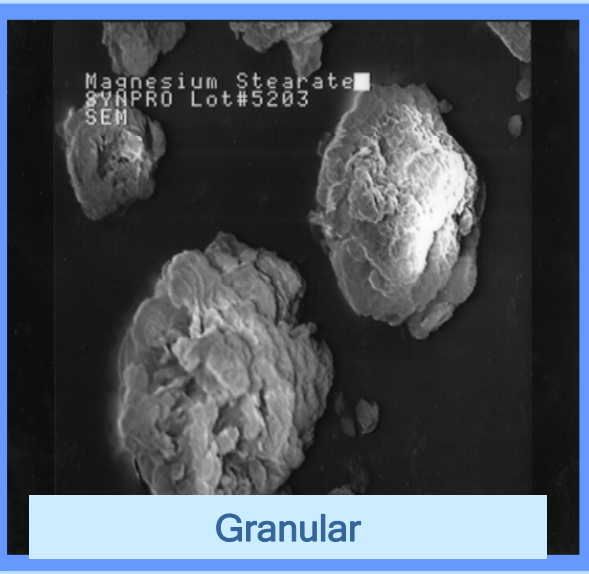
Magnesium Stearate – Typical Properties

- Particle Density (g/ml) → 1.03 – 1.08
- Bulk Volume (ml/g) → 3.0 – 8.4
- Tapped Volume (ml/g) → 2.5 – 6.2
- Melting Point (°C) → 88.5
- Specific Surface Area (m^2/g) → 2.45 – 7.92 (USP)
  (16.0) (BP)
- LOD → 4% (USP)
  → =< 6% (BP)
- Pseudo polymorphs

Magnesium Stearate - Morphology



Plates with rounded edges



Granular

Plate like - stacked sheets

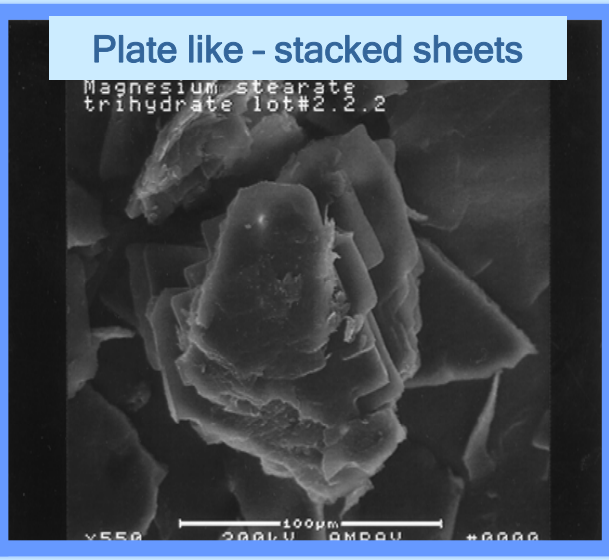
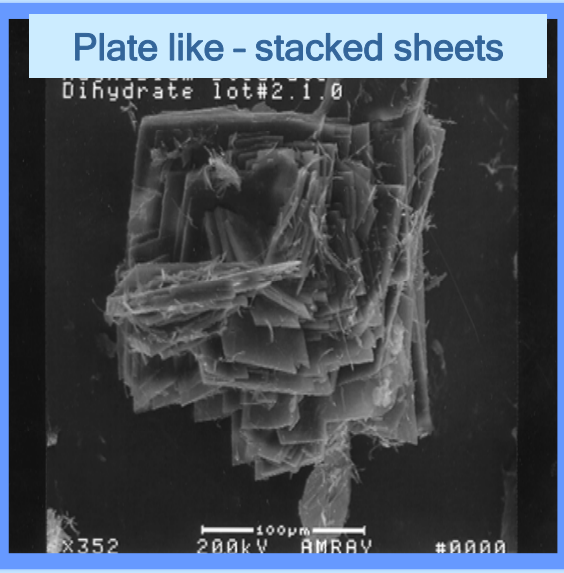


Plate like - stacked sheets

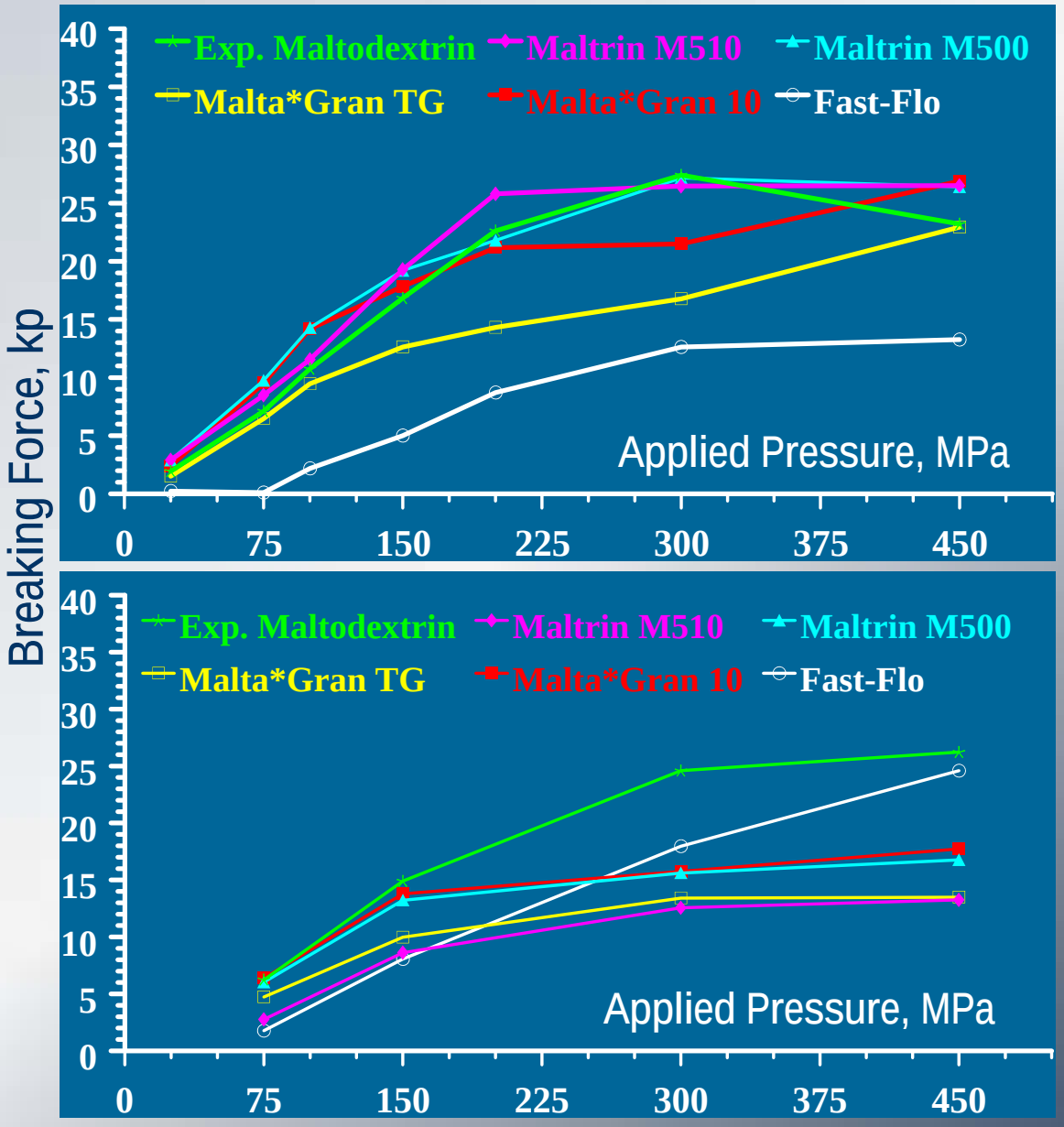


Magnesium Stearate
Maltodextrin Case Study

Materials:

- Experimental maltodextrin: Roller Compacted
- Maltrin M500: Spray dried
- Maltrin M510: Fluidized bed agglomerated
- Malta*Gran TG: Fluidized bed agglomerated
- Malta*Gran 10:Fluidized bed agglomerated

Magnesium Stearate
Maltodextrin Case Study



Unlubricated, 100 mm/s,

Material	SSA(m^2/g)
Exp. Maltodextrin	1.73
Maltrin M510	0.31
Maltrin M500	0.54
Malta Gran TG	0.40
Malta Gran 100	.50

Lubricated (0.5% Mg Stearate), 100 mm/s,

Magnesium Stearate Maltodextrin Case Study

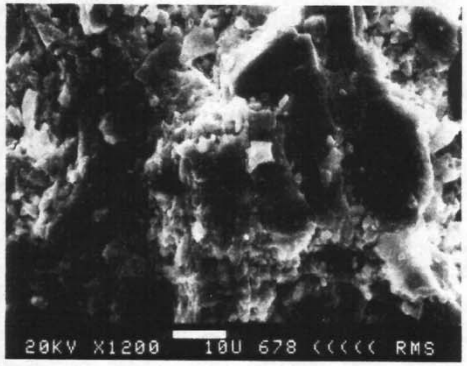


FIGURE 1
Scanning Electron Photomicrographs of Experimental Maltodextrin

FIGURE 4
Scanning Electron Photomicrographs of Malta*Gran TG

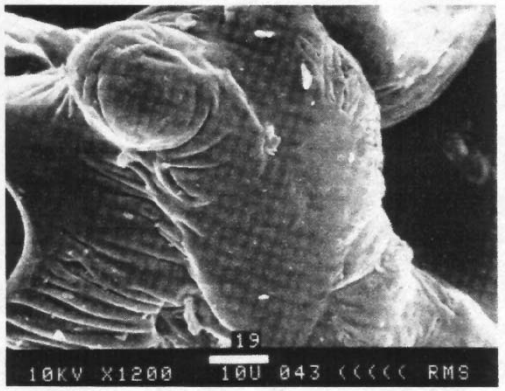


FIGURE 2
Scanning Electron Photomicrographs of Maltrin M510

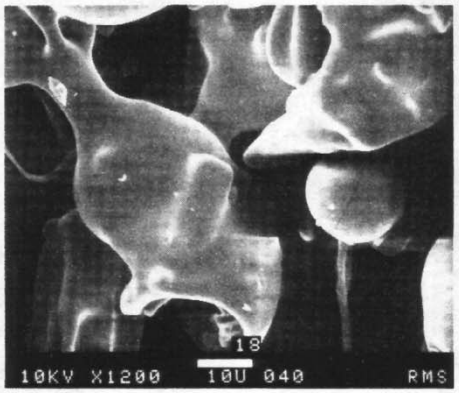


FIGURE 3
Scanning Electron Photomicrographs of Maltrin M500

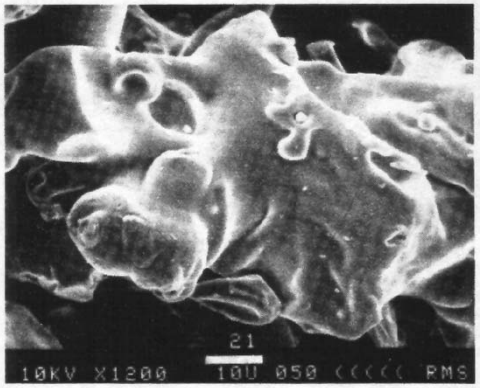


FIGURE 5
Scanning Electron Photomicrographs of Malta*Gran 10

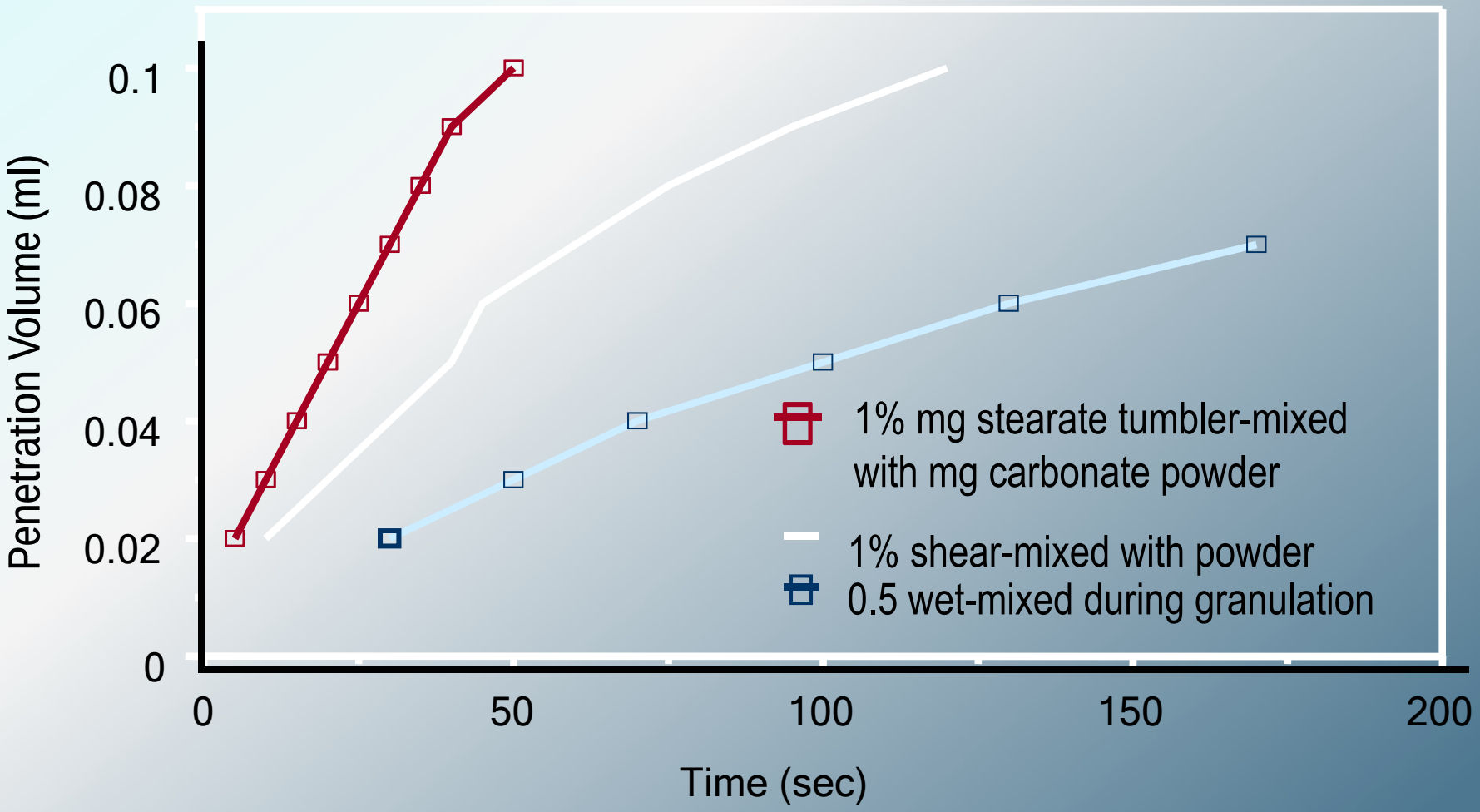
LUBRICATION EFFICIENCY
Coefficient of Lubricant Efficiency [R= Fl / Fa= Pl / Pa]

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
Magnesium Stearate	-	0.83	0.86	0.88

* formulation contains sulphatiazole

Effect of the lubricant incorporation method:

Water penetration into tablets containing lubricant added in different ways



EXCIPIENT SELECTION

PROCESS CONCERNS

e.g. Film Coating

- Super Disentagrants
- Temperature Sensitive – Emcompress
- Viscoelastic materials
- High level of lubricants

- Magnesium stearate
  - pseudopolymorphs

PROCESS DEVELOPMENT

Critical Variables

& Risk Analysis

Process Steps, Control Variables & Measured Responses:

Sizing:
(Mill/Sieve)

Control Variables:
Screen Type
Screen Size
Feed Rate
Impeller Type
rpm

Measured Responses
Distribution
Loose Density
Packed Density

Blending:
(V-Blender)

Control Variables:
Load Size
rpm
Blending Time

Measured Responses
Blend Uniformity
Flow Characteristics

Process Steps, Control Variables & Measured Responses:

Granulation:
(High Speed Mixer/Granulator)

Control Variables:
Load Size
Amount of Granulating Agent
Solvent Addition Rate
rpm
Granulation Time

Measured Responses
Density
Yield

Drying:
(Fluid Bed Dryer)

Control Variables:
Initial Temperature
Load Size
Drying Temperature Program
Air Flow Program
Drying Time
Cooling Time

Measured Responses
Density
Moisture Content
Yield

Process Steps, Control Variables & Measured Responses:

Sizing:
(Mill/Sieve)

Control Variables:
Screen Type
Screen Size
Feed Rate
Impeller Type
rpm

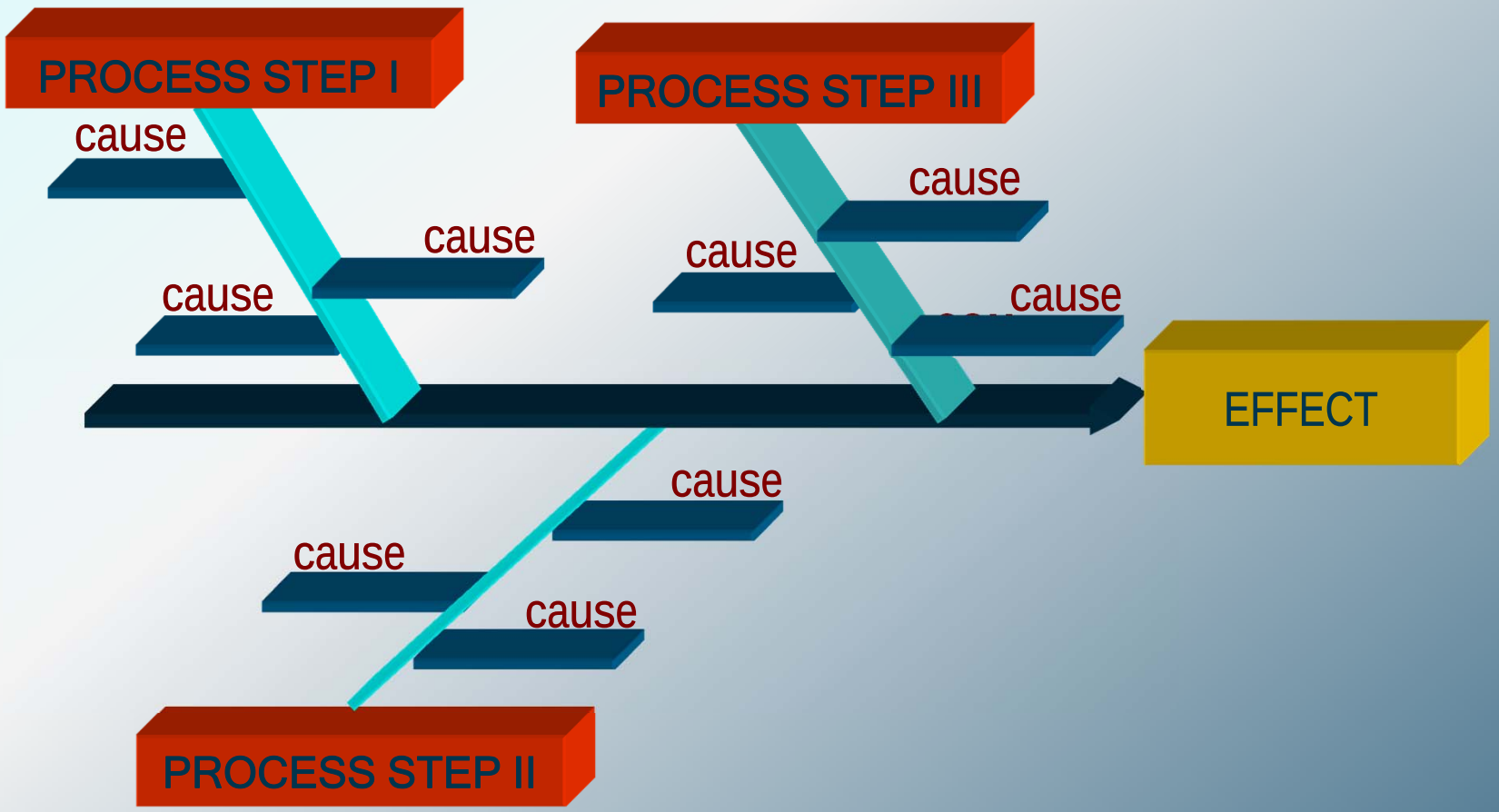
Measured Responses
Granule Size
Distribution
Loose Density
Packed Density

Tableting:
(High Speed Rotary with Precompression)

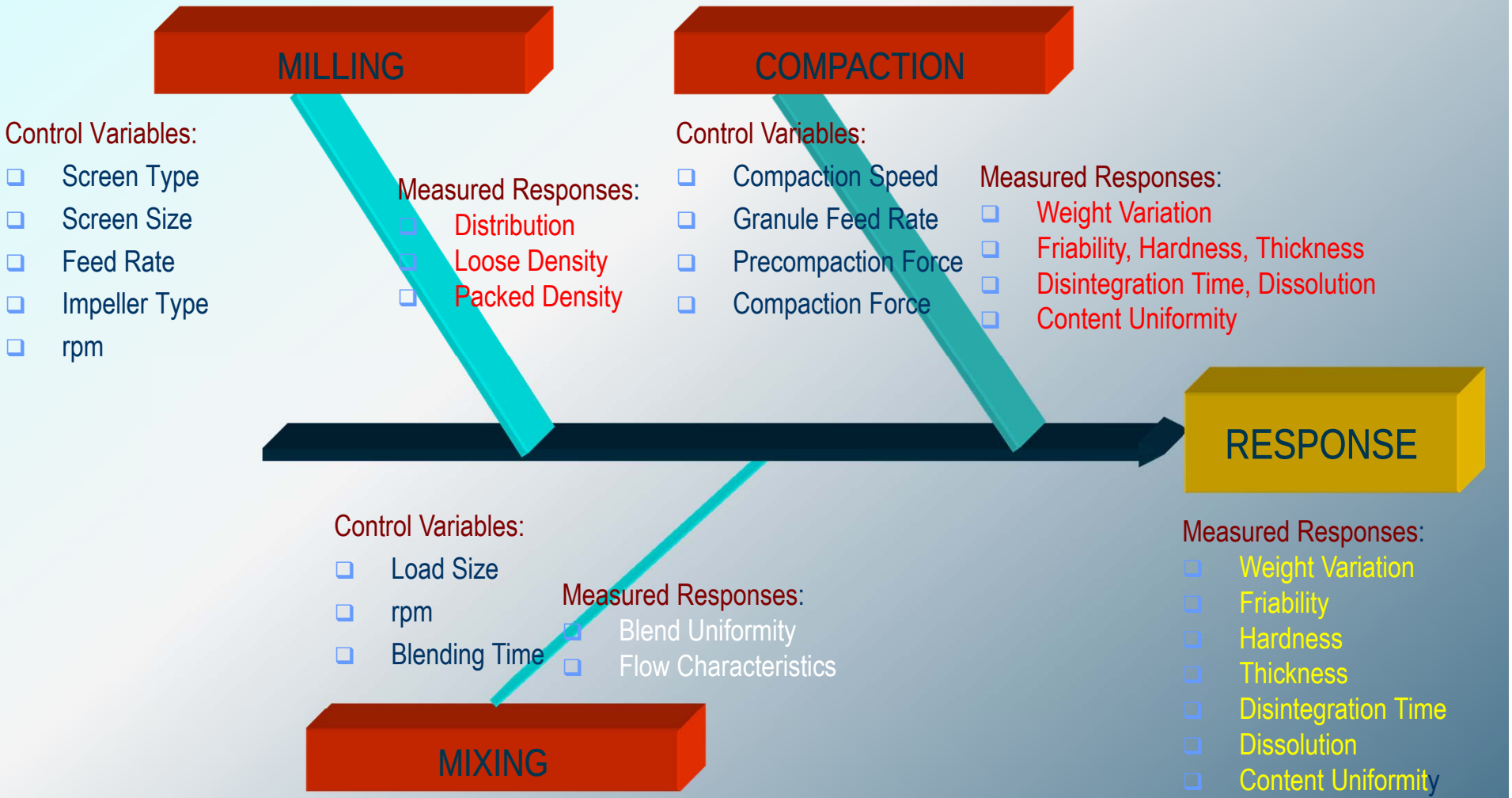
Control Variables:
Compaction Speed
Granule Feed Rate
Precompaction Force
Compaction Force

Measured Responses
Weight Variation
Friability, Hardness, Thickness
Disintegration Time, Dissolution
Dosage Form Uniformity

Cause-Effect Diagrams
(Ishikawa Diagrams, Fishbone Diagrams)



Cause-Effect Diagrams
(Ishikawa Diagrams, Fishbone Diagrams)



Influence matrix for variables & responses

	Variable	Preblend Uniformity	Power Load	Moist. %	Size Distr.	Blend Uniformity	Hardness	Friability	Dosage Form Uniformity
Preblending	rpm	S			N	W	N	N	W
	time	S			N	W	N	N	W
Granulating	rpm		S	N	W	W	W	N	W
	W (solv)		M	W	M	W	W	W	W
	Time		M	N	M	W	W	W	W
Drying	Temp.			S		N	N	N	N
				S	M	N	N	N	N
Sizing	Screen Size				S	W	N	M	W
Blending	Time					S	M	N	S
Tableting	Speed						W	W	W
	Force						S	S	W

N: none W: weak

M: moderate S: strong

RISK ANALYSIS

Matrix 1		Probability of occurence of harm		
Severity of harm		**Low (1)**	**Medium (2)**	**High (3)**
	High (3)	2	3	3
	Medium (2)	1	2	3
	Low (1)	1	1	2

Matrix 2		Probability of detection		
From matrice 1		**Low (1)**	**Medium (2)**	**High (3)**
	High (3)	Q	Q	C
	Medium (2)	Q	C	-
	Low (1)	C	-	-

Note: 'Q' = Qualification (critical), 'C' = Commissioning (non-critical), '-' = Acceptable

Process Steps, Control Variables & Measured Responses:

Addition of Raw Material
(Active + Excipients)

- Control Variables:
  - Blending Time
  - rpm
  - Load Size
  - Order of Addition
- Measured Responses
  - Blend Uniformity

Granulation
(High Speed Mixer/Granulator)

- Control Variables:
  - Load Size
  - Amount of Granulating Agent
  - Solvent Addition Rate
  - rpm
  - Granulation Time
- Measured Responses
  - Density
  - Yield

Drying:
(Fluid Bed Dryer)

- Control Variables:
  - Initial Temperature
  - Load Size
  - Drying Temperature Program
  - Air Flow Program
  - Drying Time
  - Cooling Time
- Measured Responses
  - Density
  - Moisture Content
  - Yield

Sizing:
(Mill/Sieve)

- Control Variables:
  - Screen Type
  - Screen Size
  - Feed Rate
  - Impeller Type
  - rpm
- Measured Responses
  - Granule Size Distribution
  - Loose Density
  - Packed Density

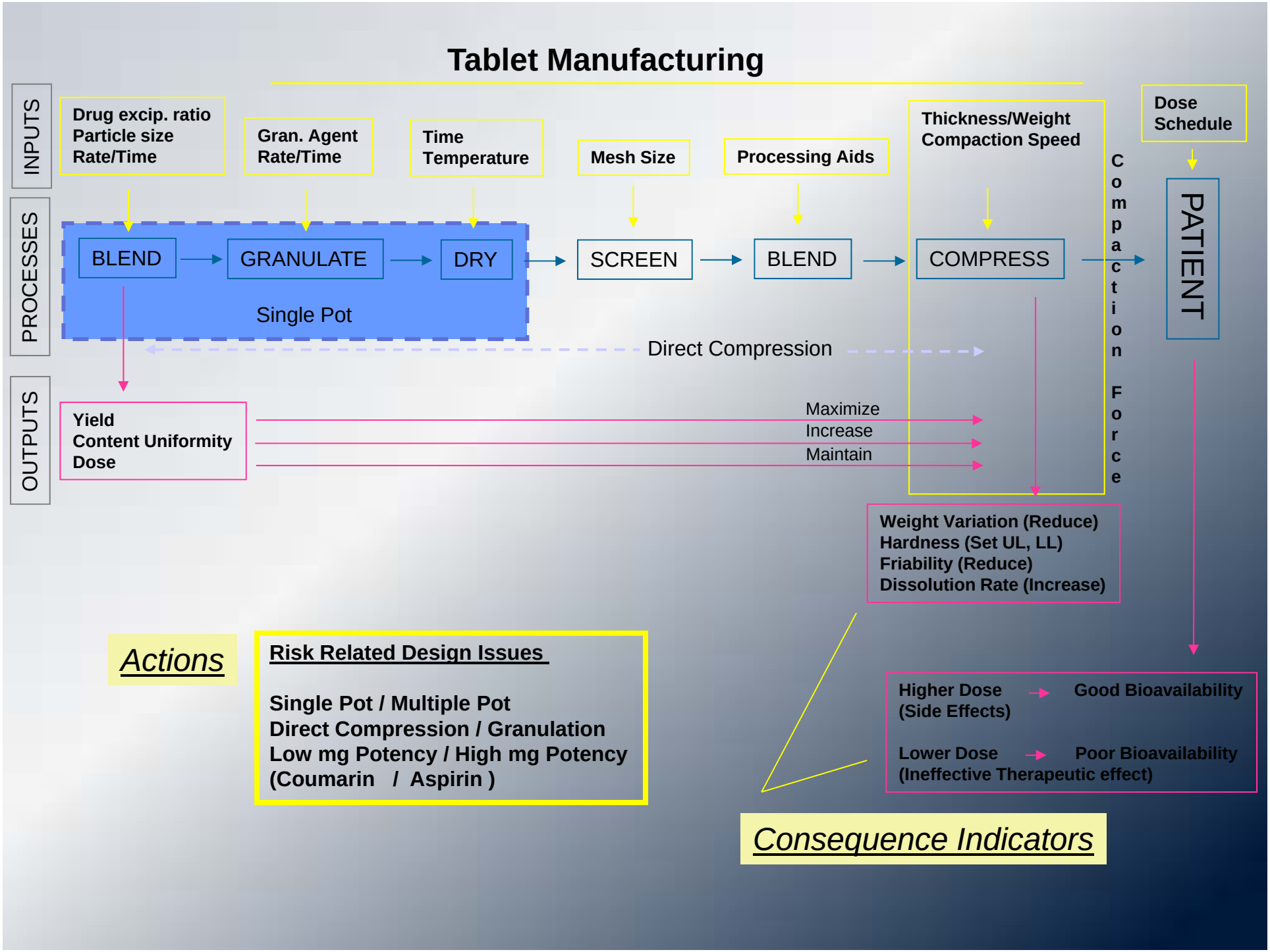
Blending:
(V-Blender)

- Control Variables:
  - Load Size
  - rpm
  - Blending Time
- Measured Responses
  - Blend Uniformity
  - Flow Characteristics

Tableting:
(High Speed Rotary with Precompression)

- Control Variables:
  - Compaction Speed
  - Granule Feed Rate
  - Precompaction Force
  - Compaction Force
- Measured Responses
  - Weight Variation
  - Friability, Hardness, Thickness
  - Disintegration Time, Dissolution
  - Dosage Form Uniformity

Tablet Manufacturing

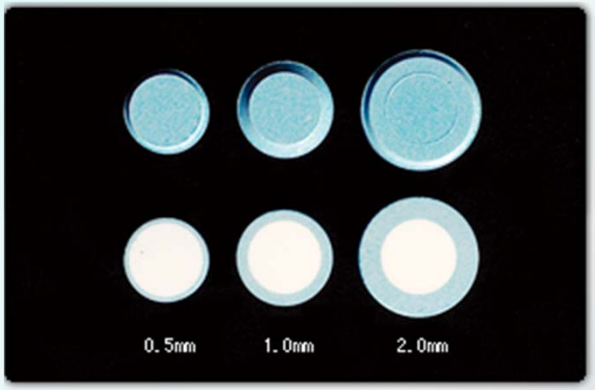


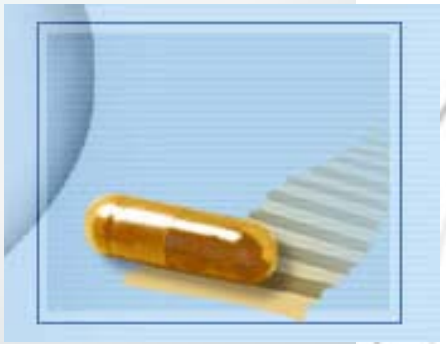
PROCESS DEVELOPMENT

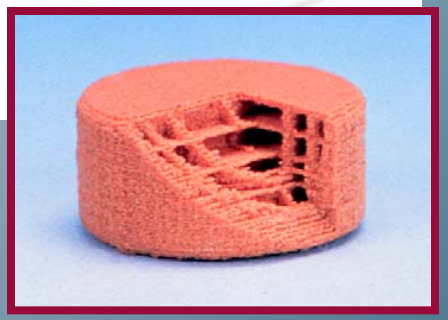
Innovative Approaches

Many of the Novel Drug Delivery Systems Require Innovative Processes

Novel drug delivery systems utilize control over position, composition, and microstructure of (polymeric) materials to control drug release



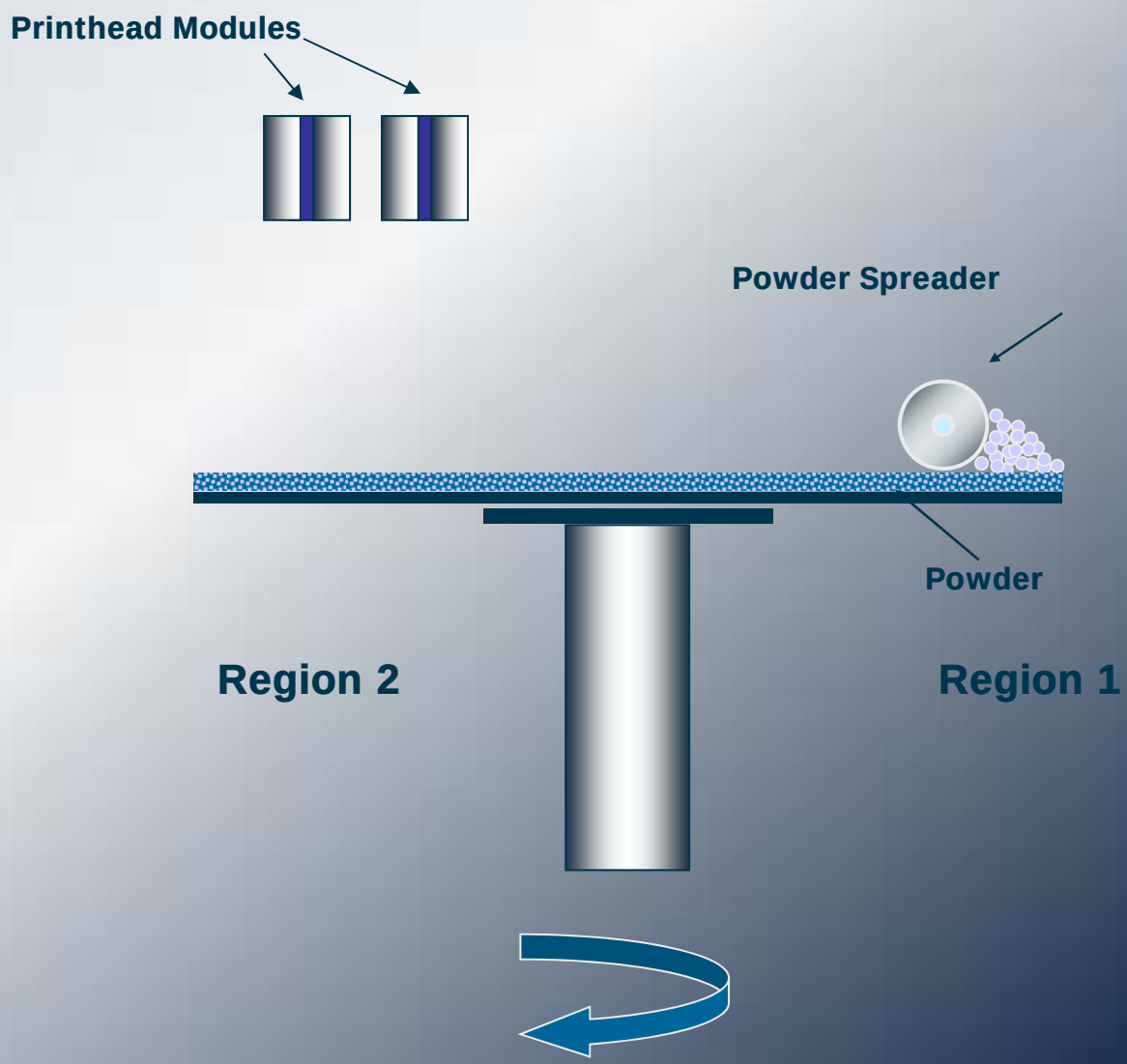




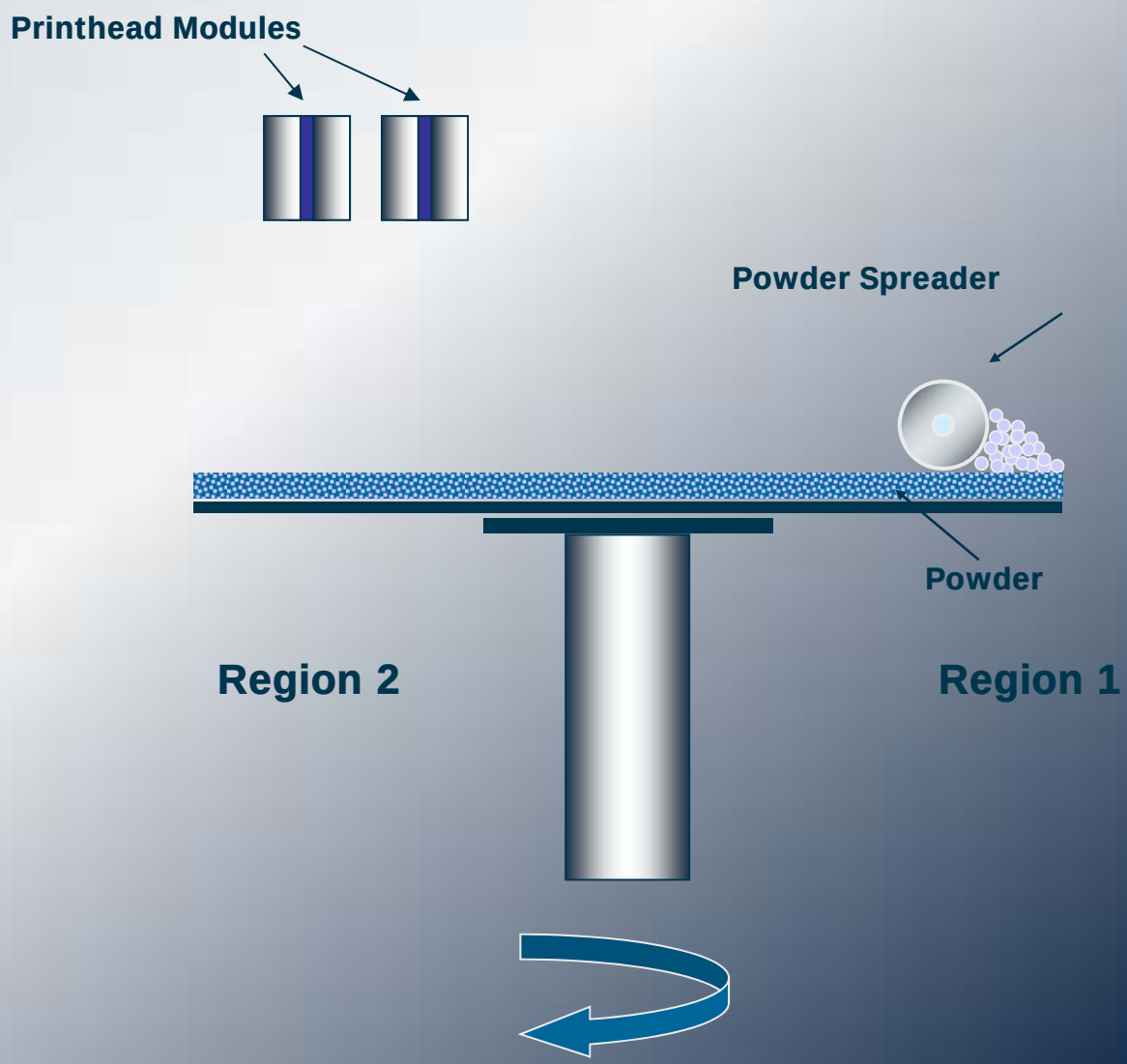
Three Dimensional Printing (3DP)

- Aprecia Pharmaceuticals (Langhorne, PA)
  - www.aprecia.com
- Process Overview
  - Computer Aided Design and Manufacturing (CAD/CAM)
  - Adaptation of ink-jet printing technology
  - Powder spreading
  - Selective deposition of “binder”
  - Layer-by-layer build process
  - Drying and Retrieval
- Process Variables
  - Binder droplet size
  - Droplet placement
  - Layer thickness
  - Printing strategy
  - Internal architecture

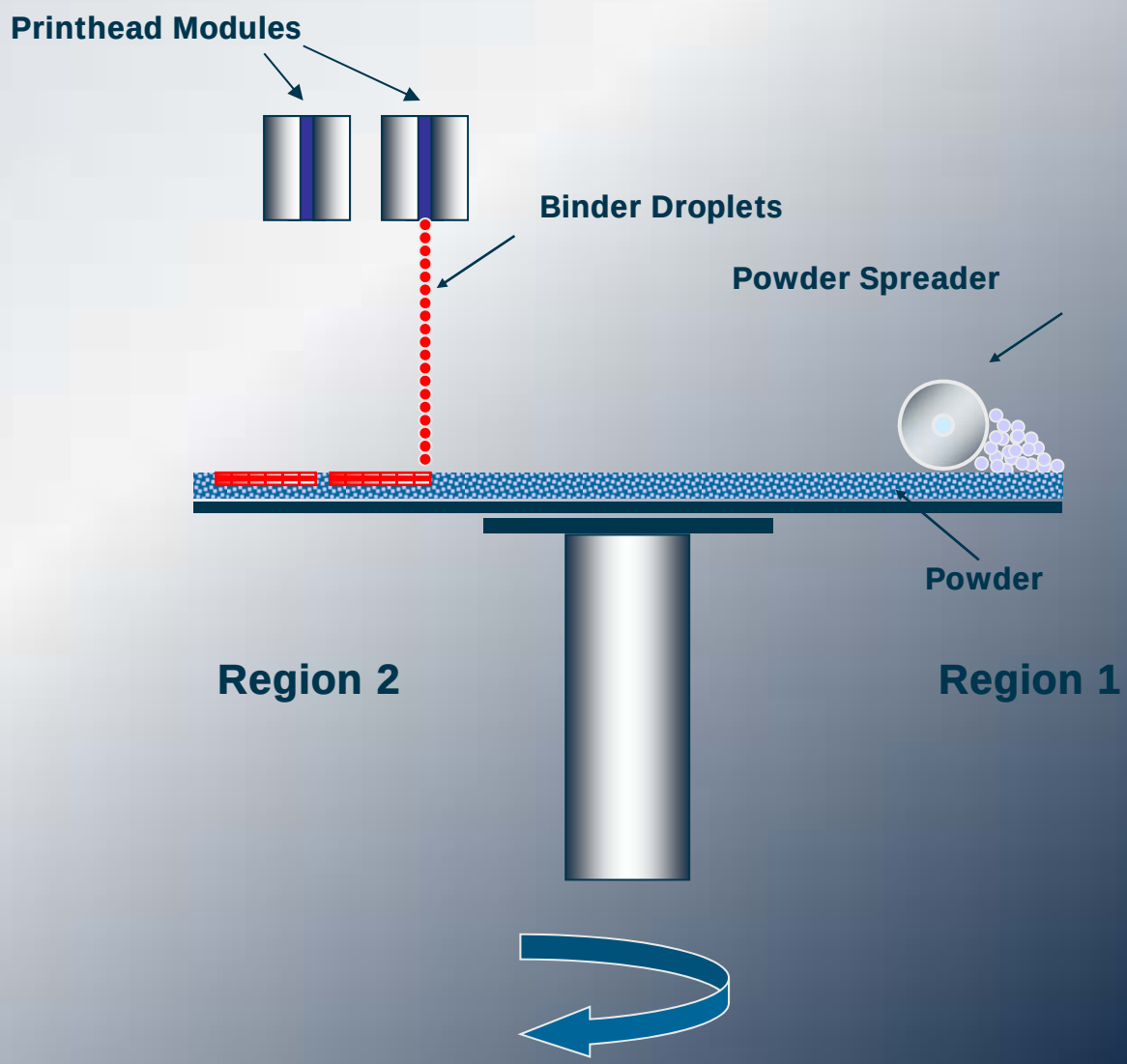
3DP Process Fundamentals



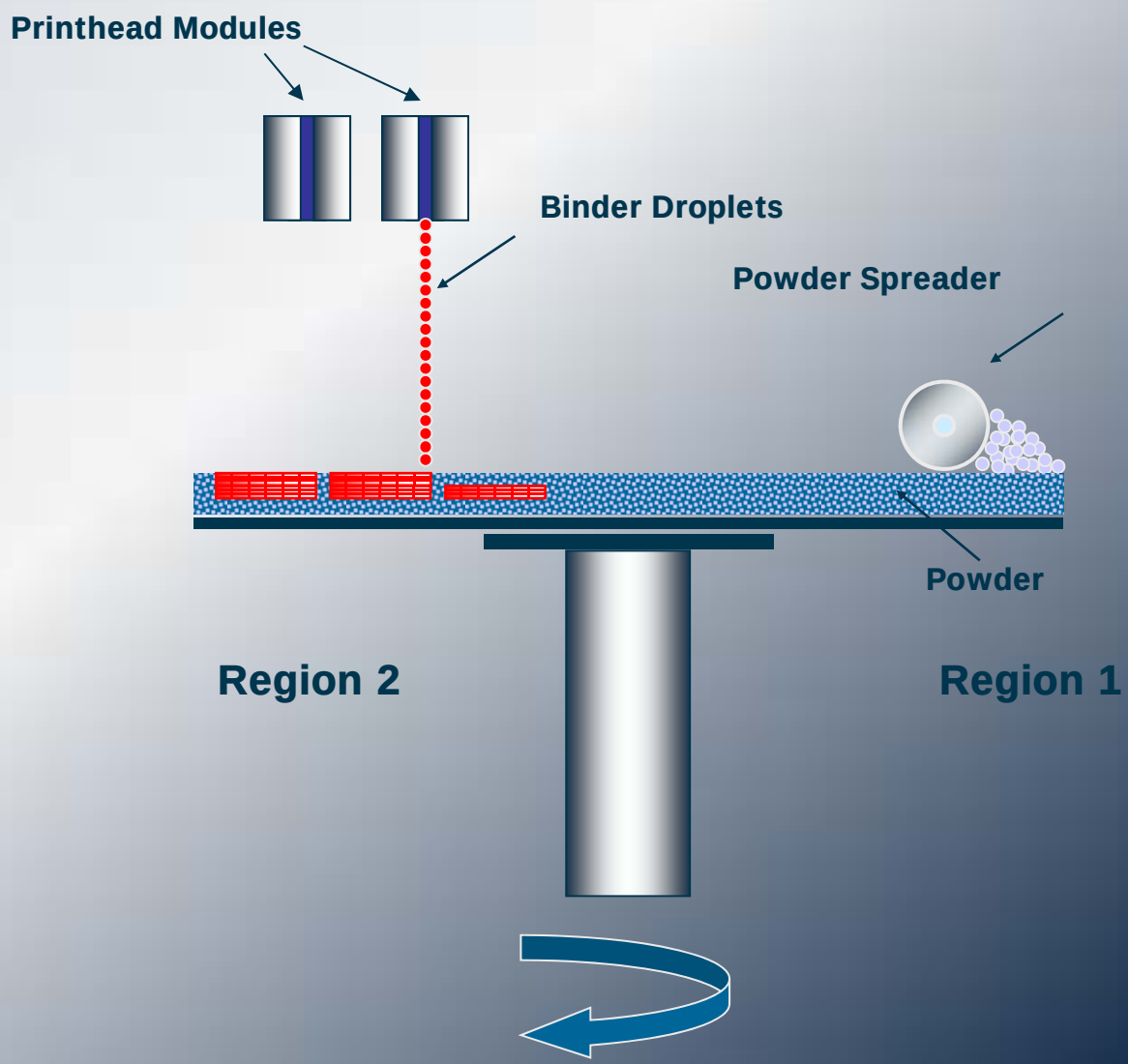
3DP Process Fundamentals



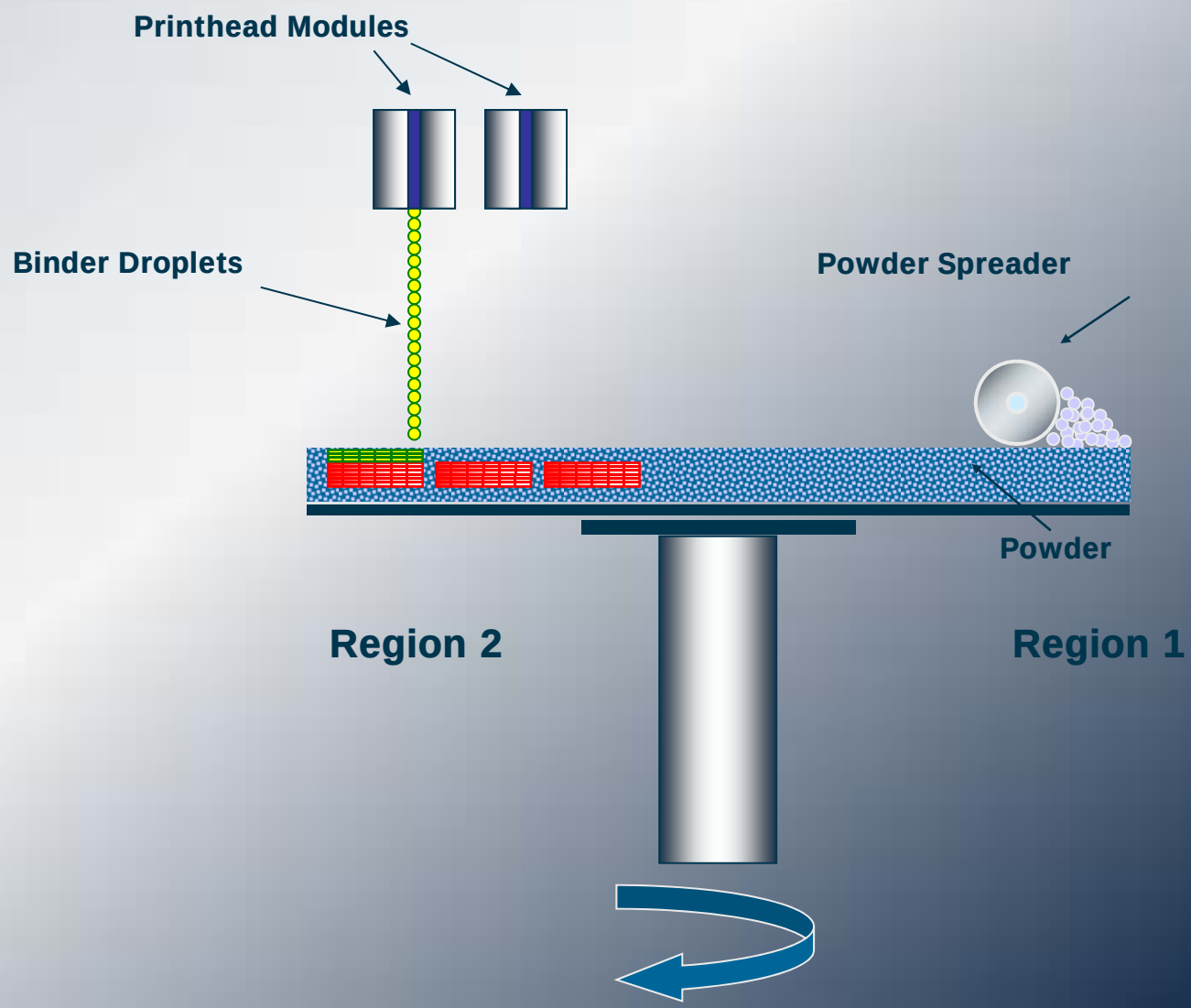
3DP Process Fundamentals



3DP Process Fundamentals



3DP Process Fundamentals



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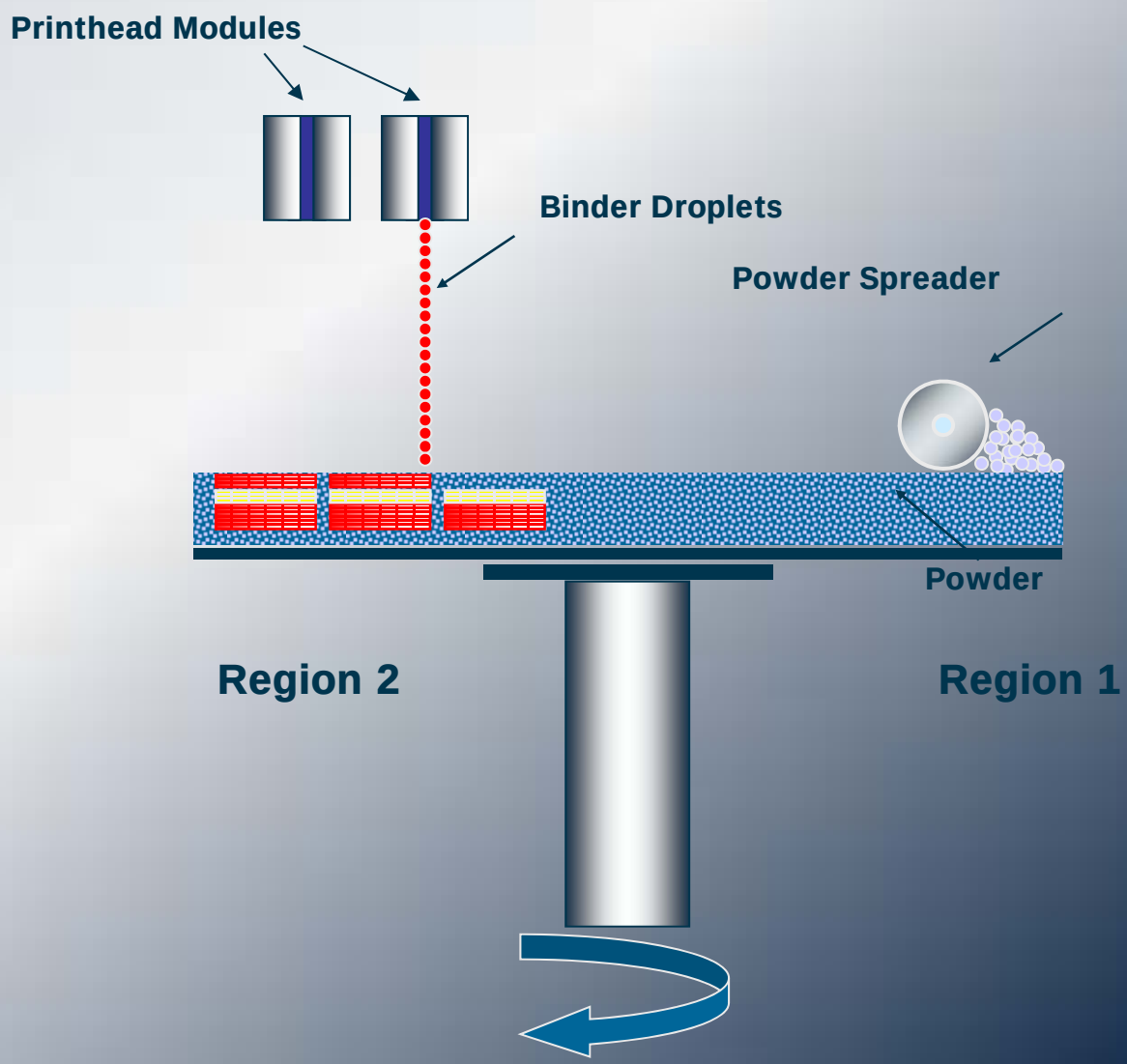
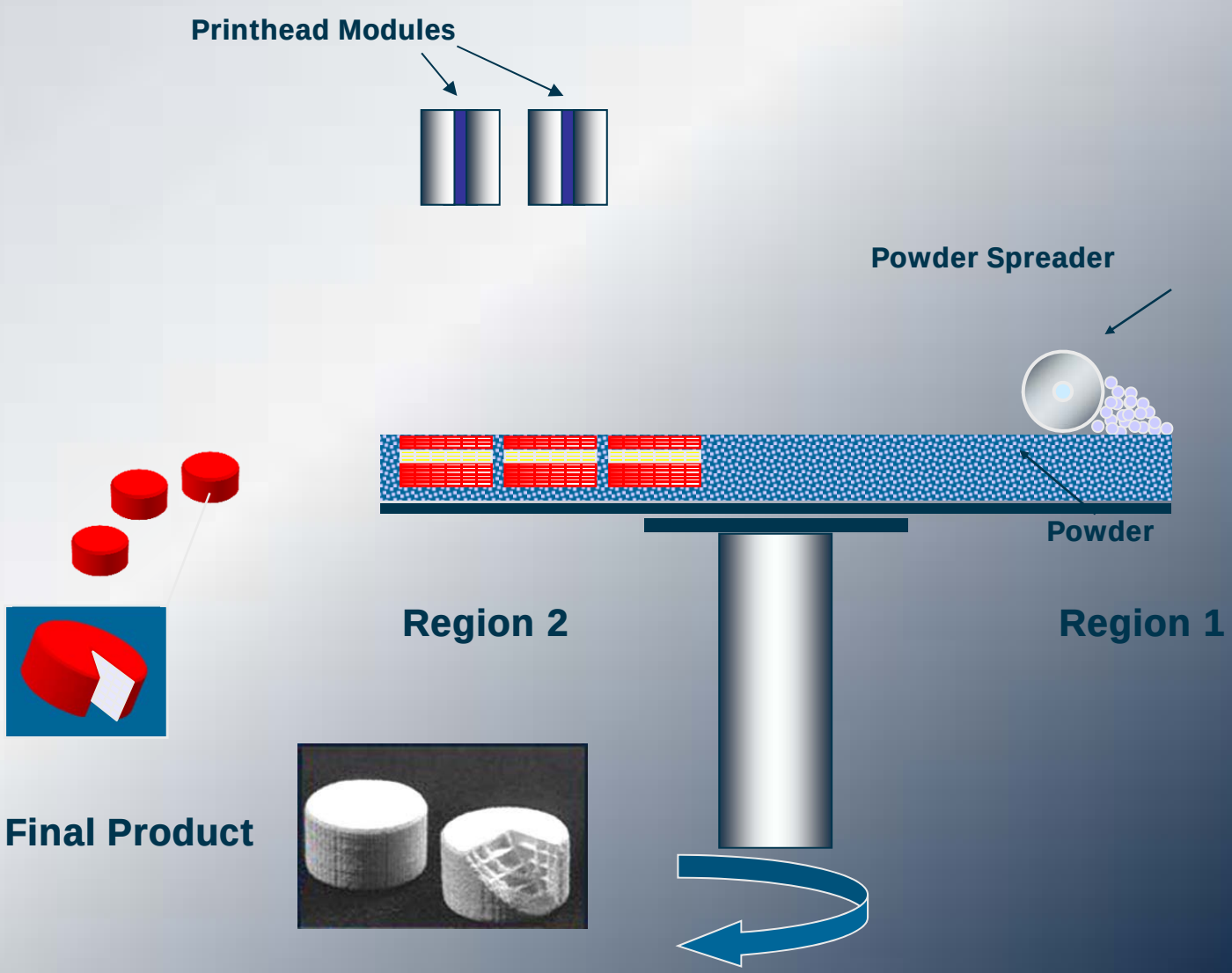


3DP Process Fundamentals



PROCESS DEVELOPMENT

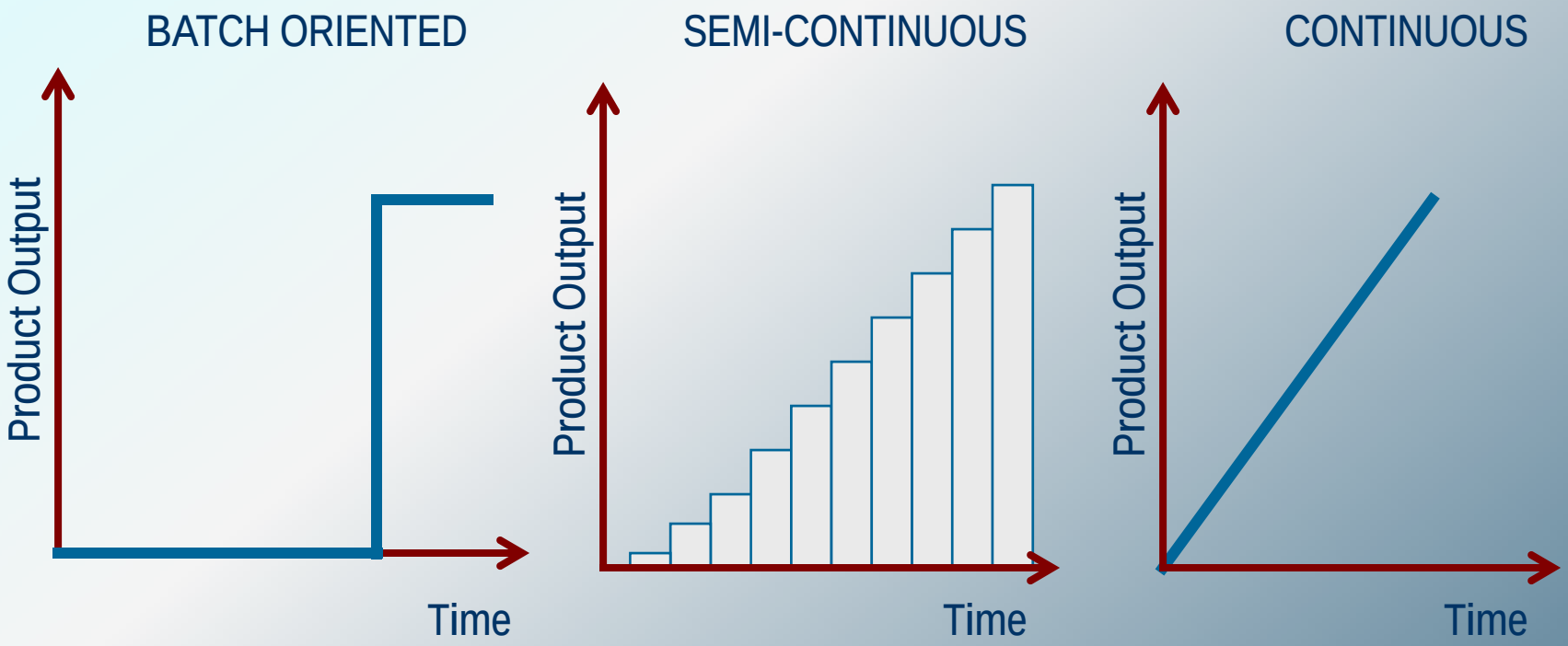
FRAMEWORK FOR INNOVATION

Framework for Innovation

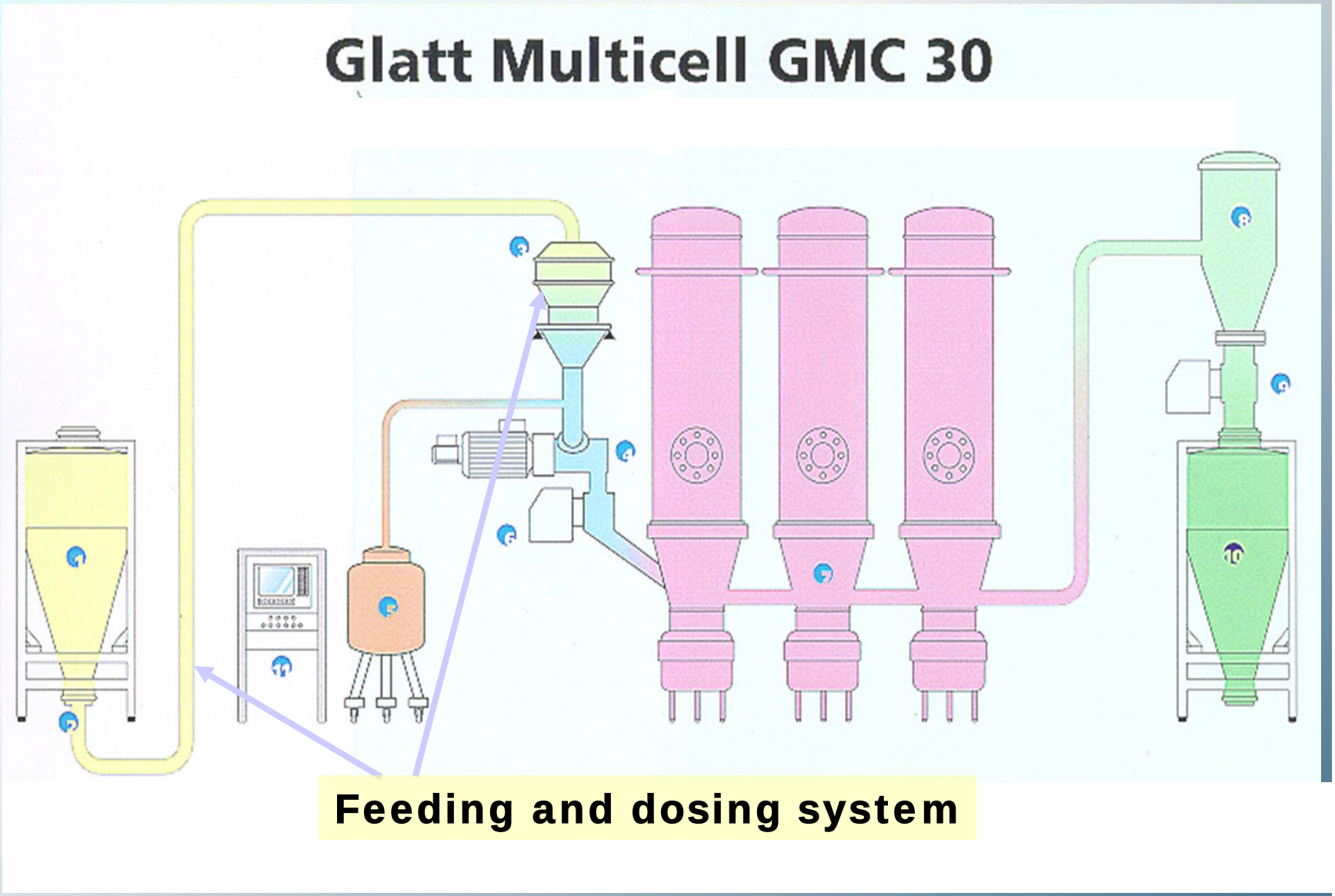
Development of new solid oral dosage technologies should focus on four targets:

- **Move away** from batch concepts to full continuous processes for manufacturing.
- **Optimize** manufacturing processes with regard to floor space and cycle times.
- **Support** parametric release through in-line testing.
- **Minimize** scale-up requirements during drug product development.

Product Output for Batch, Semi-Continuous and Continuous Processing



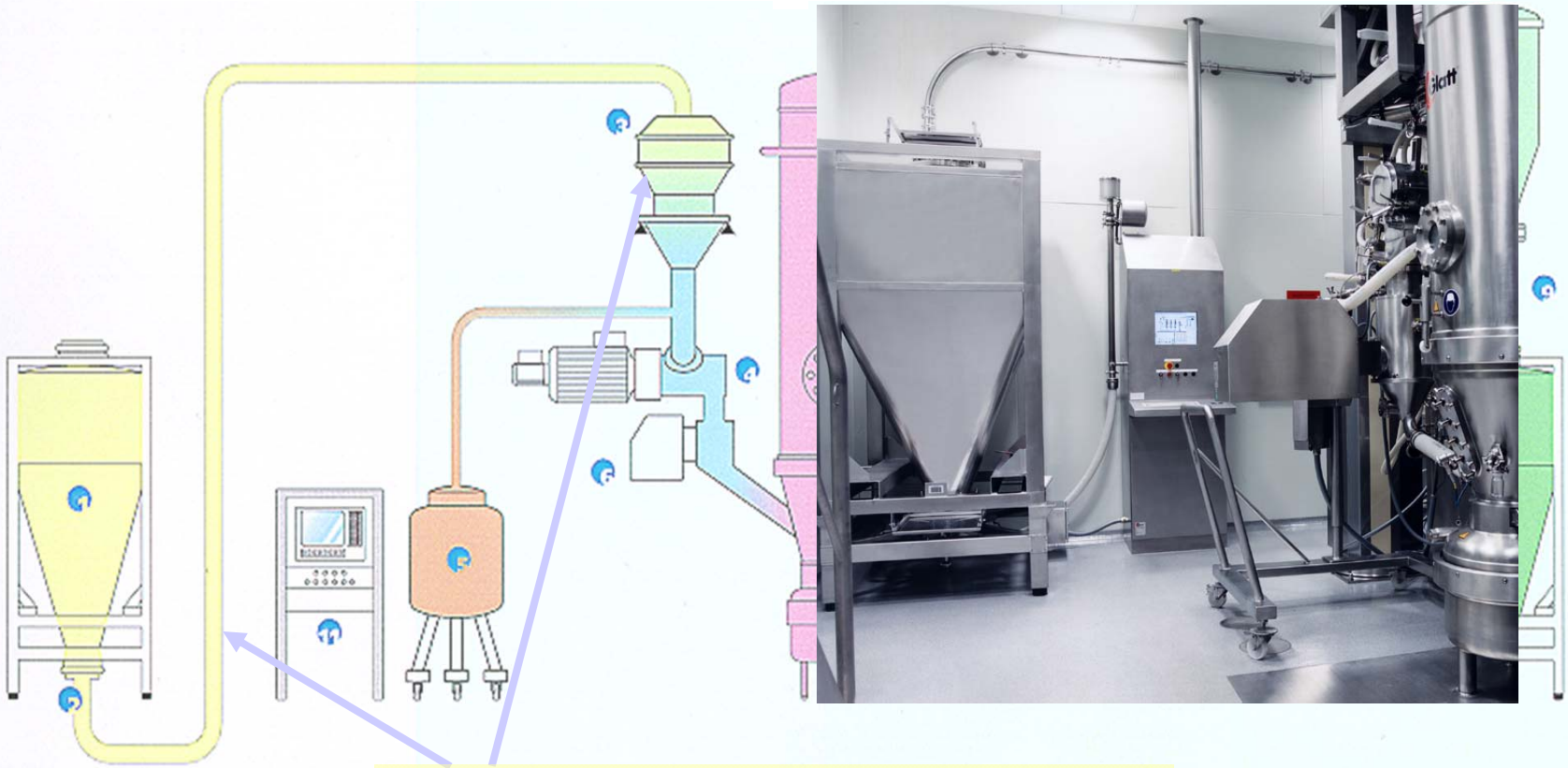
Semi continuous granulation and drying process



Courtesy of Prof. H. Leuenberger

Semi continuous granulation and drying process

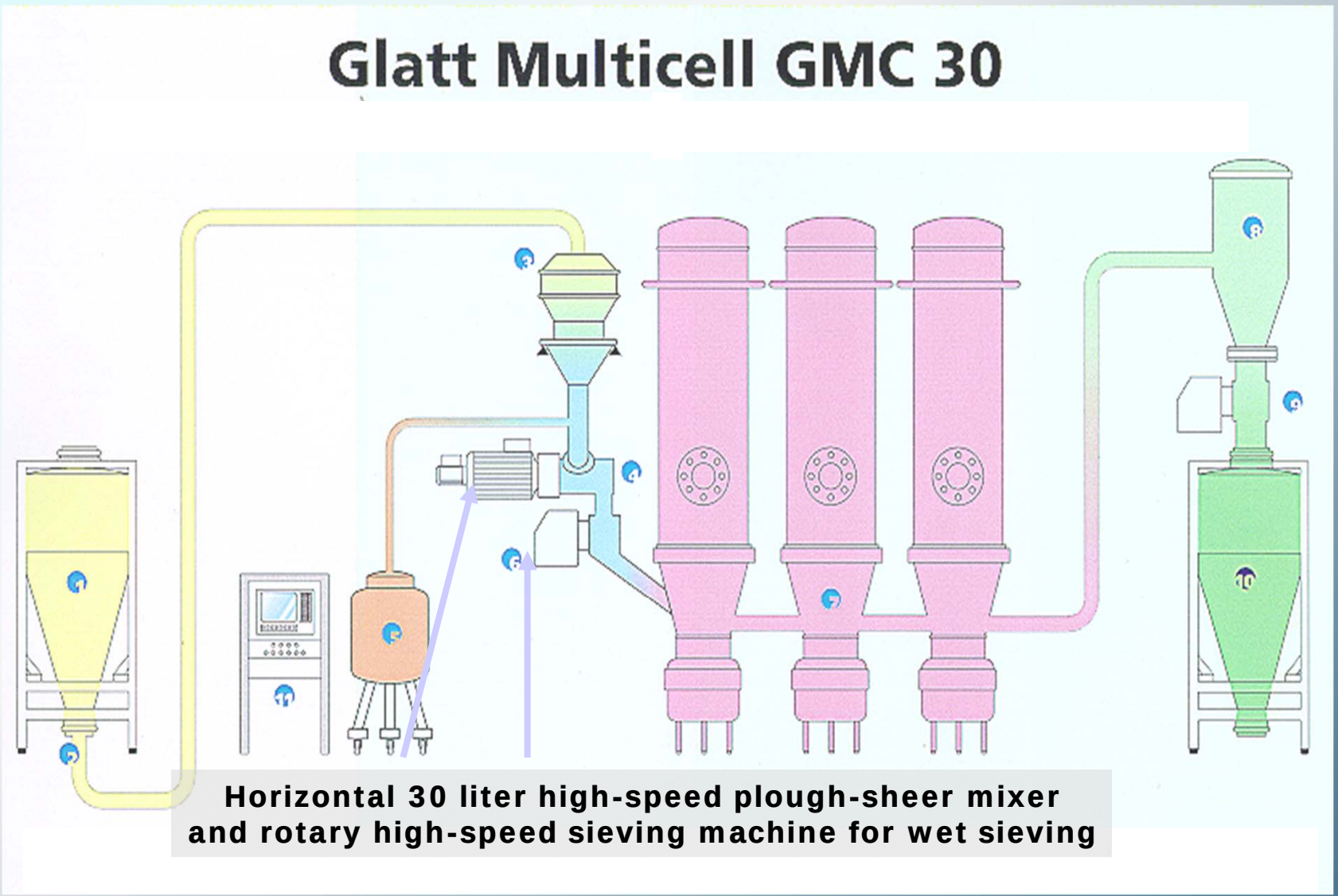
Glatt Multicell GMC 30



Feeding and dosing system

Courtesy of Prof. H. Leuenberger

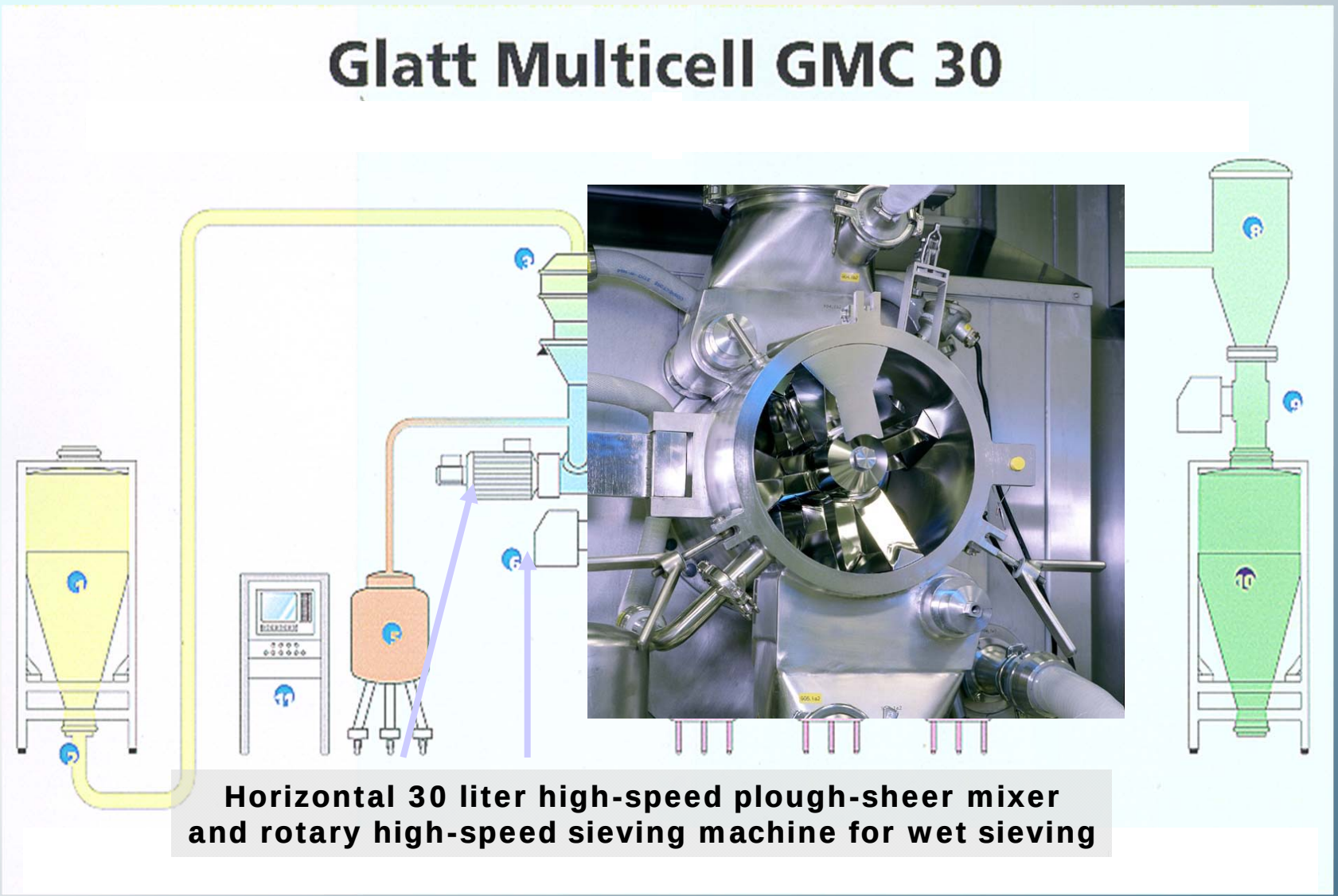
Semi continuous granulation and drying process



Horizontal 30 liter high-speed plough-sheer mixer and rotary high-speed sieving machine for wet sieving

Courtesy of Prof. H. Leuenberger

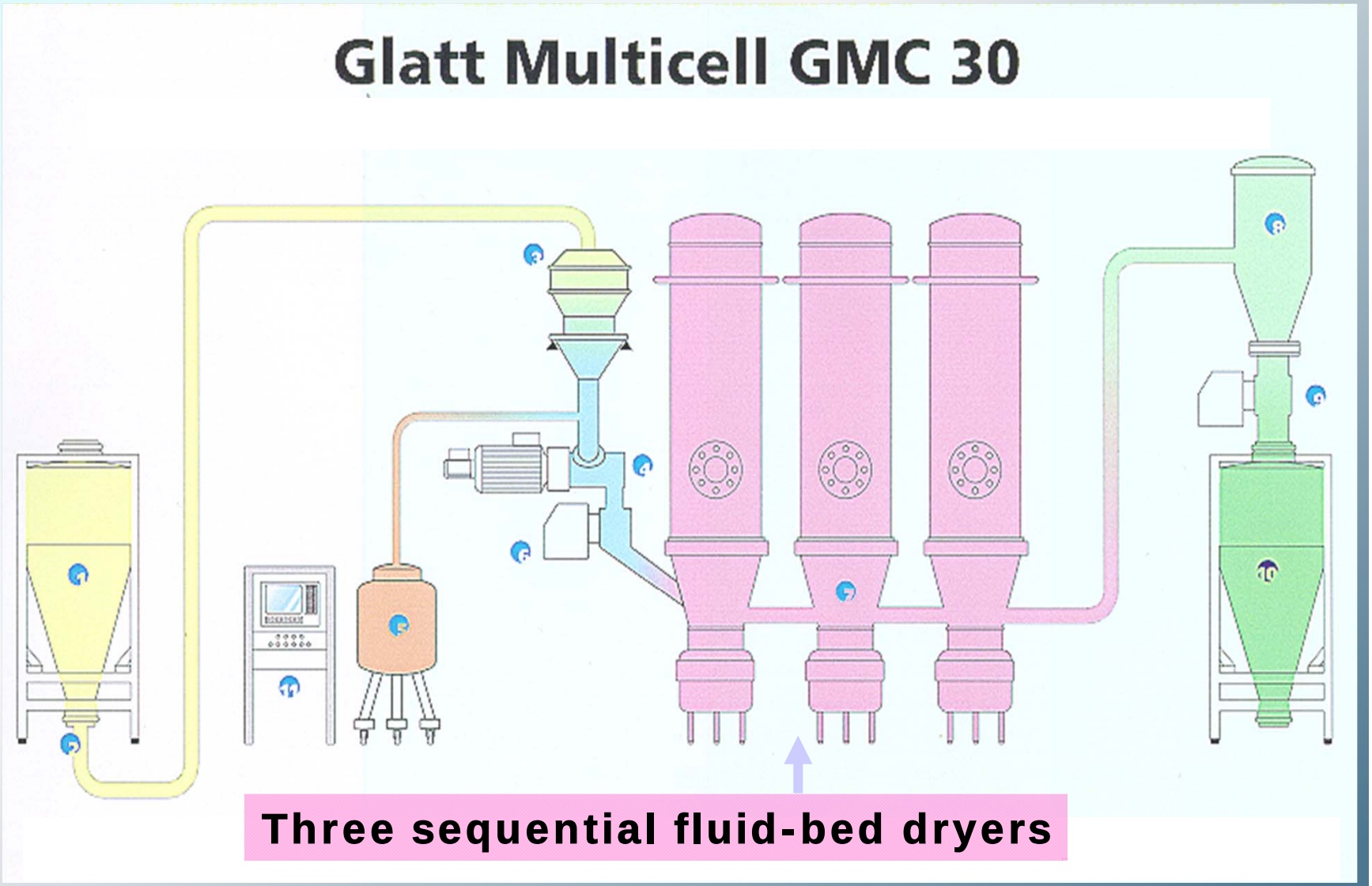
Semi continuous granulation and drying process



Horizontal 30 liter high-speed plough-sheer mixer and rotary high-speed sieving machine for wet sieving

Courtesy of Prof. H. Leuenberger

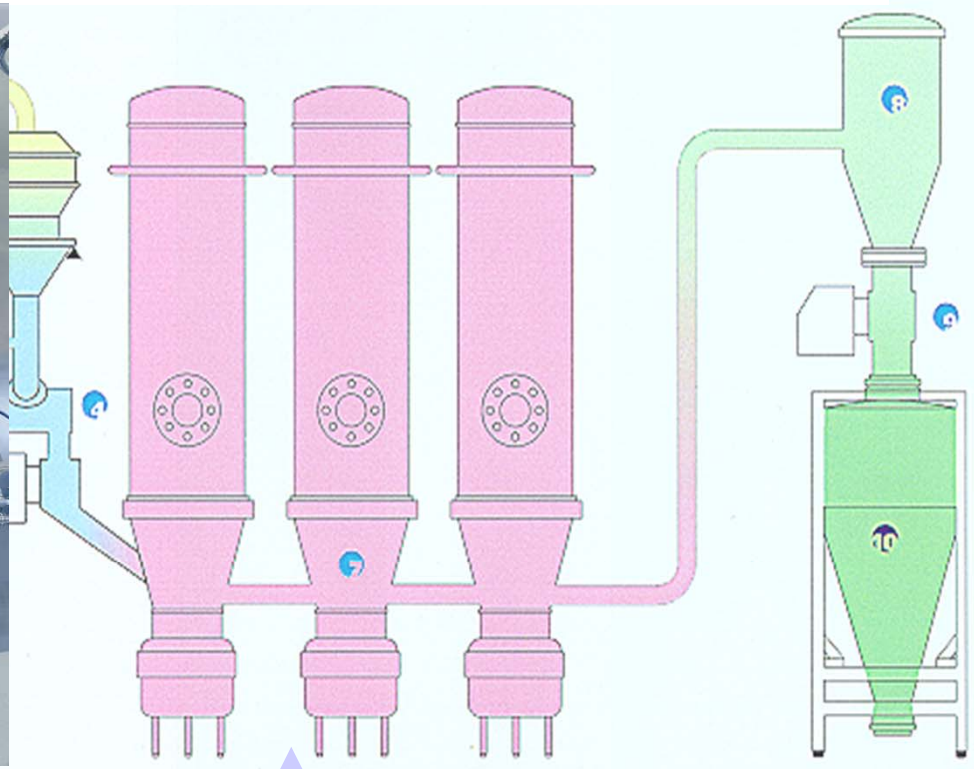
Semi continuous granulation and drying process



Courtesy of Prof. H. Leuenberger

Semi continuous granulation and drying process

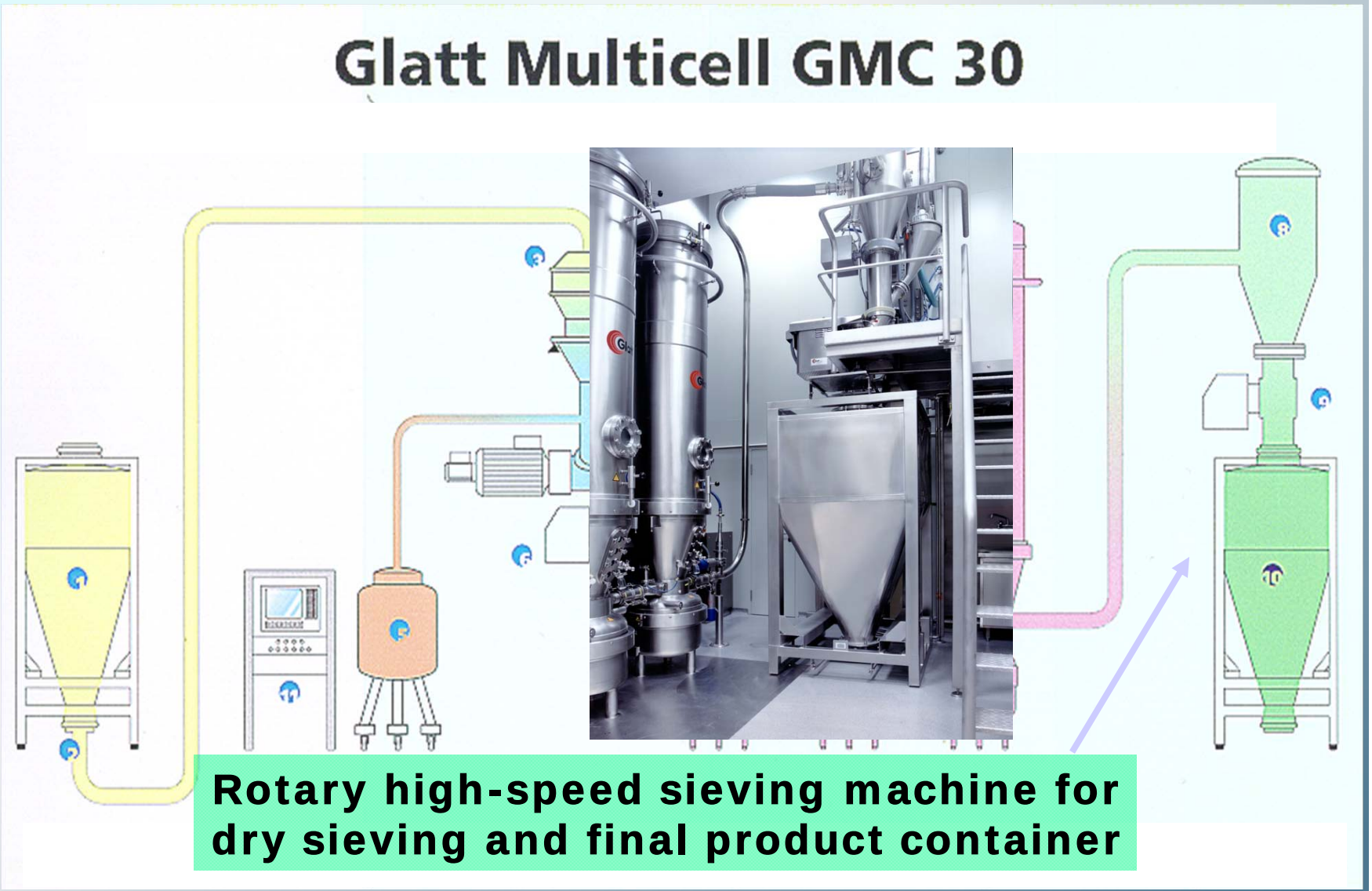
Glatt Multicell GMC 30



Three sequential fluid-bed dryers

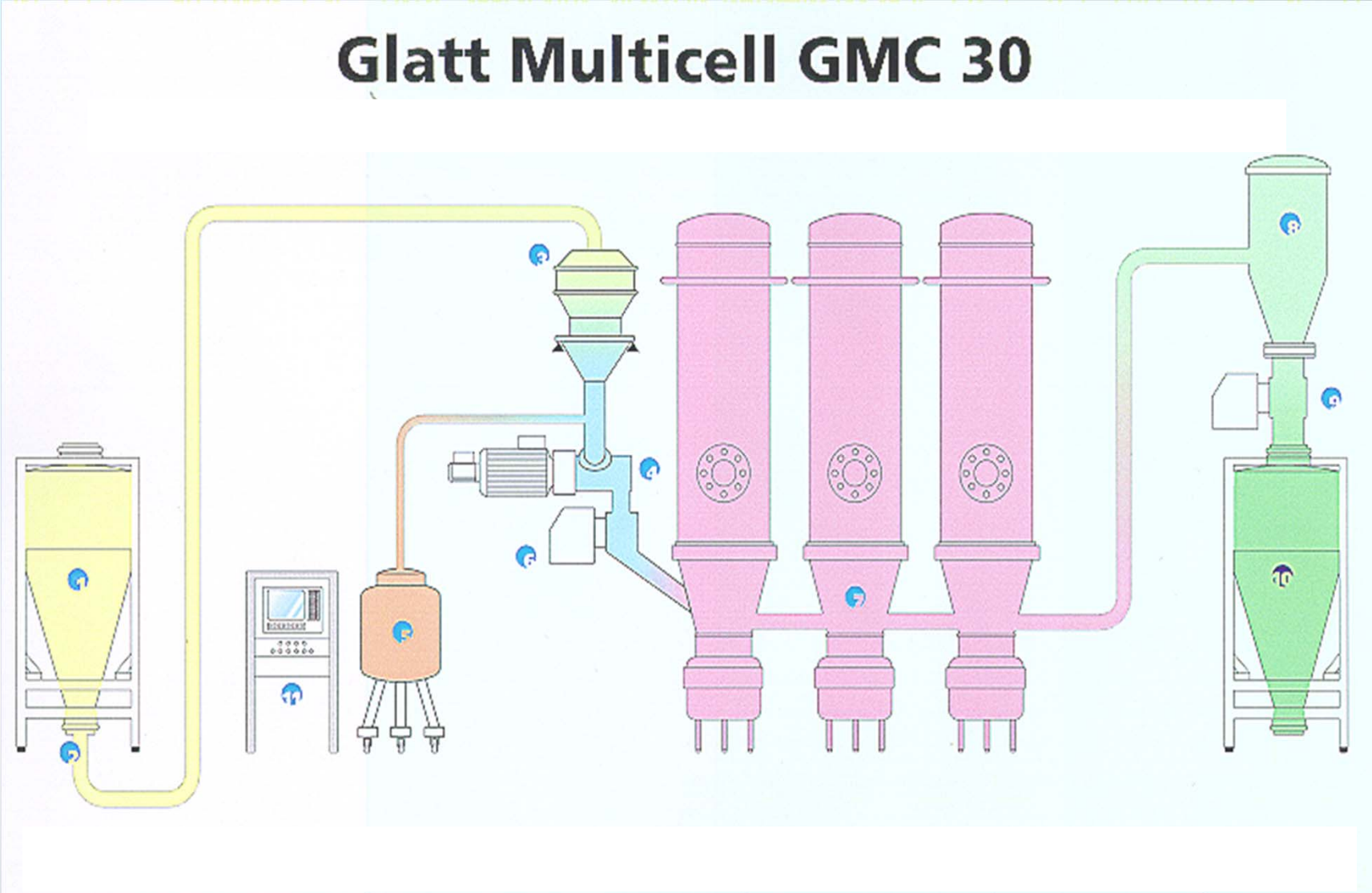
Courtesy of Prof. H. Leuenberger

Semi continuous granulation and drying process



Courtesy of Prof. H. Leuenberger

Semi continuous granulation and drying process



Courtesy of Prof. H. Leuenberger

Batch Process vs Continuous Process

Technology	Lödige 900 / WSG 300	Multicell	
Process	Batch process	Continuous process	
Batch size	Fixed to equipment capacity	Flexible depending on process time	
Mode of operation	Manual-driven and monitored	Almost lights-out-operated	
Floor space	130 m²	100 m²	-23%
Investment	1,6 Mio. US$	2 Mio. US$	+25%
Volume of equipment	900 l (270 +/- 50 kg)	30 l (8 +/- 2 kg)	
Output	55 kg/h	96 kg/h	+75%
Overall output	10 kg/24 h/m²	20 kg/24 h/m²	+100%

Any Questions?

Metin.Celik@pt-int.com

Material Processing Technologies

IDEX MATERIAL PROCESSING

Pharmaceutical Technologies International, Inc.
Princeton, New Jersey, USA

Particle Size Reduction
MILLING TECHNOLOGY

Presented by:

Mina Ibrahim, P.Eng., MBA

Product Manager, Quadro Solids Division

QUADRO
Leading Process Equipment Innovation

FITZPATRICK®

Microfluidics

Agenda

1. INTRODUCTION TO QUADRO, MPT, & IDEX
2. SIZE REDUCTION OVERVIEW
3. EVOLUTION OF MILLING TECHNOLOGY
4. OVERVIEW OF COMMON MILLING TECHNOLOGIES
5. CONICAL MILLING TECHNOLOGY
6. MILL SELECTION CRITERIA

About Quadro

- **History: Since 1976**
- **Manufacturing: 45,000 ft^2 (4180 m^2)**
- **Employees: 93**
- **In-house Engineering**
- **Machining, Welding, Polishing, Electrical, Assembly**
- **ISO Registered, cGMP**
- **R&D Center**

About Quadro

- **Part of IDEX Corporation since 2007**
- **Member of Material Processing Technologies (MPT) platform along with**
  - **The Fitzpatrick Company, Illinois**
  - **Microfluidics, Mass.**
  - **Matcon, UK**

Size Reduction Overview

Advantages of Compressed Tablets (Oral Solid Dosage)

- Accurate dosage of medicament
- Easy to transport - bulk and by patient
- Uniform final product - weight and appearance
- Usually more stable than liquid medicines
- Release rate of drug can be varied
- Mass production - simple and quick & low cost

Size Reduction Overview

Size reduction is an essential process requirement in the practice of Solid Dosage Preparation

The capability to produce a tight particle distribution suitable for compaction and dissolution is directly dependent on the mechanism selected for size reduction

Size Reduction Overview

Tablet Manufacturing

- **Objectives**
  - Uniformity
  - Potency
  - Batch to batch reproducibility
  - Damage resistance
  - Lack of defects

- **How**
  - ✓ Powders must flow
  - ✓ Powders must compress
  - ✓ Particles must lock together
  - ✓ PSD control → Weight control

Size Reduction Overview

Common Tableting Problems

Capping

Sticking

Chipping

Breaking

Discoloring

Tablet weight is the key to controlling hardness and friability.

Controlling tablet weights within a tight range will contribute to better tablet hardness and friability.

Porosity

Key weight control factors are product uniformity in particle size & density

Size Reduction Overview

Why Size Reduce

- Increase Surface Area
- Create Homogeneity
- Control Bulk Density
- Prepare Products for Post Processes

- Specifically for Tablets:
  - Increase bioavailability
  - Improve Flow
  - Reduce Segregation
  - Enhance Drying
  - Control Particle size
  - Repeatability – Batch to Batch

What Affects Size Reduction?

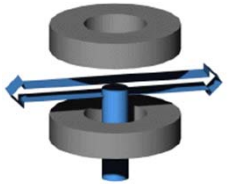
- Mechanical – Sizing Method (Type of Equipment)
- Fracture Mechanics of Particles – Types of Granules
- Properties of OSD ingredients:
  - **Active Pharmaceutical Ingredient (API)**
  - **Excipients - Inactive "helpers":**
    - Anti-adherents/Lubricants: e.g. Magnesium Stearate
    - Binders
      - Wet: Gelatin, Starch, Sucrose, Glycol (dissolved in water or alcohol)
      - Dry: MCC, Polyethylene Glycol
    - Fillers: Lactose, Sorbitol, Calcium Carbonate
    - Flavouring/Colouring
    - Preservatives: Benzoic Acid, Cresol, Parabens, etc.
- Other physical properties – friability, toughness, abrasiveness, corrosiveness, etc.

Common Size Reduction Mechanisms

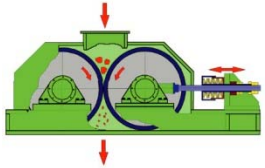
Size reduction equipment is available in many different designs, however, they all stem from four basic principles:

- **IMPACT:** particle concussion by a single force
- **COMPRESSION:** particle disintegration by two rigid forces
- **SHEAR:** produced by particle to particle interaction
- **ATTRITION:** arising from particles scraping against one another or against a rigid surface

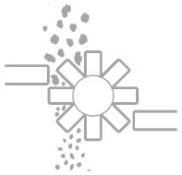
EVOLUTION OF MILLING TECHNOLOGY



Stone Grinder

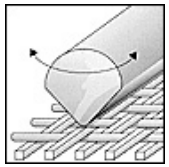


Roll Crusher



Lump Breaker

Hammer Mill



Oscillator

Tornado Mill

Approx. 50 Years

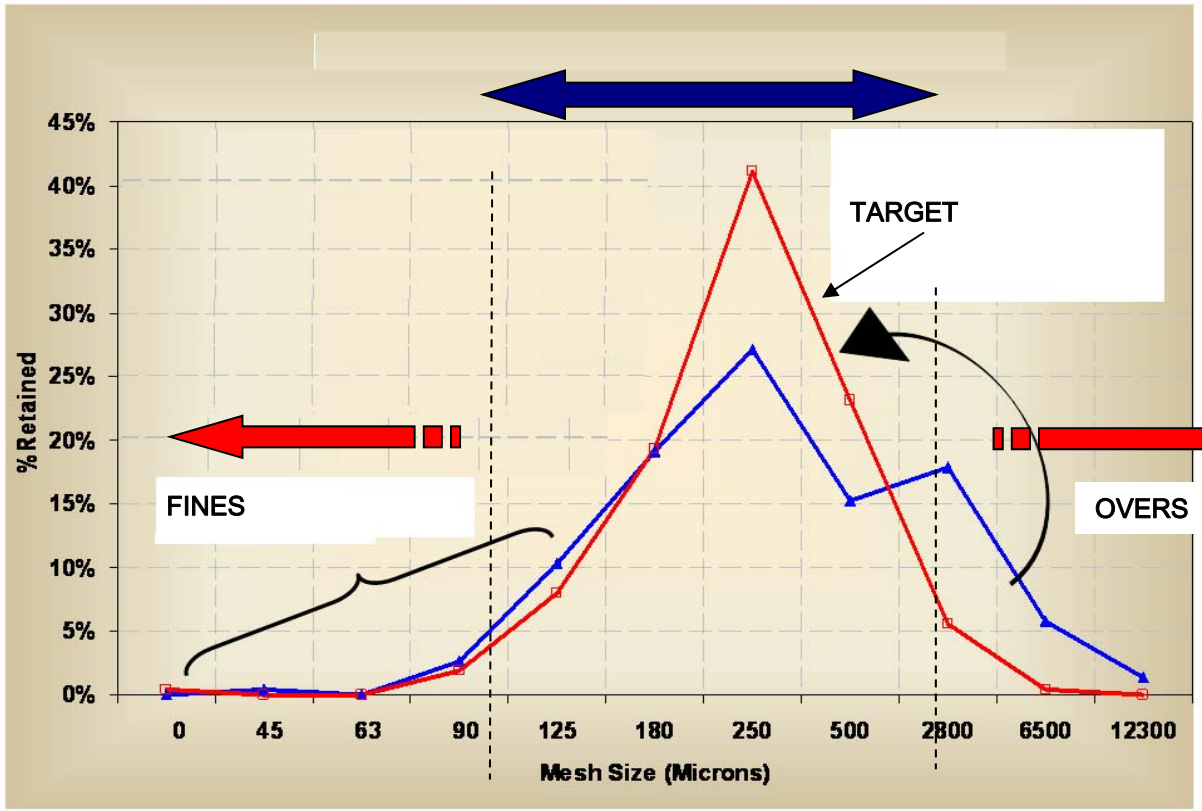
Conical Screen Mill

The most common method over the last 30 years

Approx. 80 Years of recorded history

Milling

One of the most essential process requirements in the practice of Solid Dosage Manufacturing

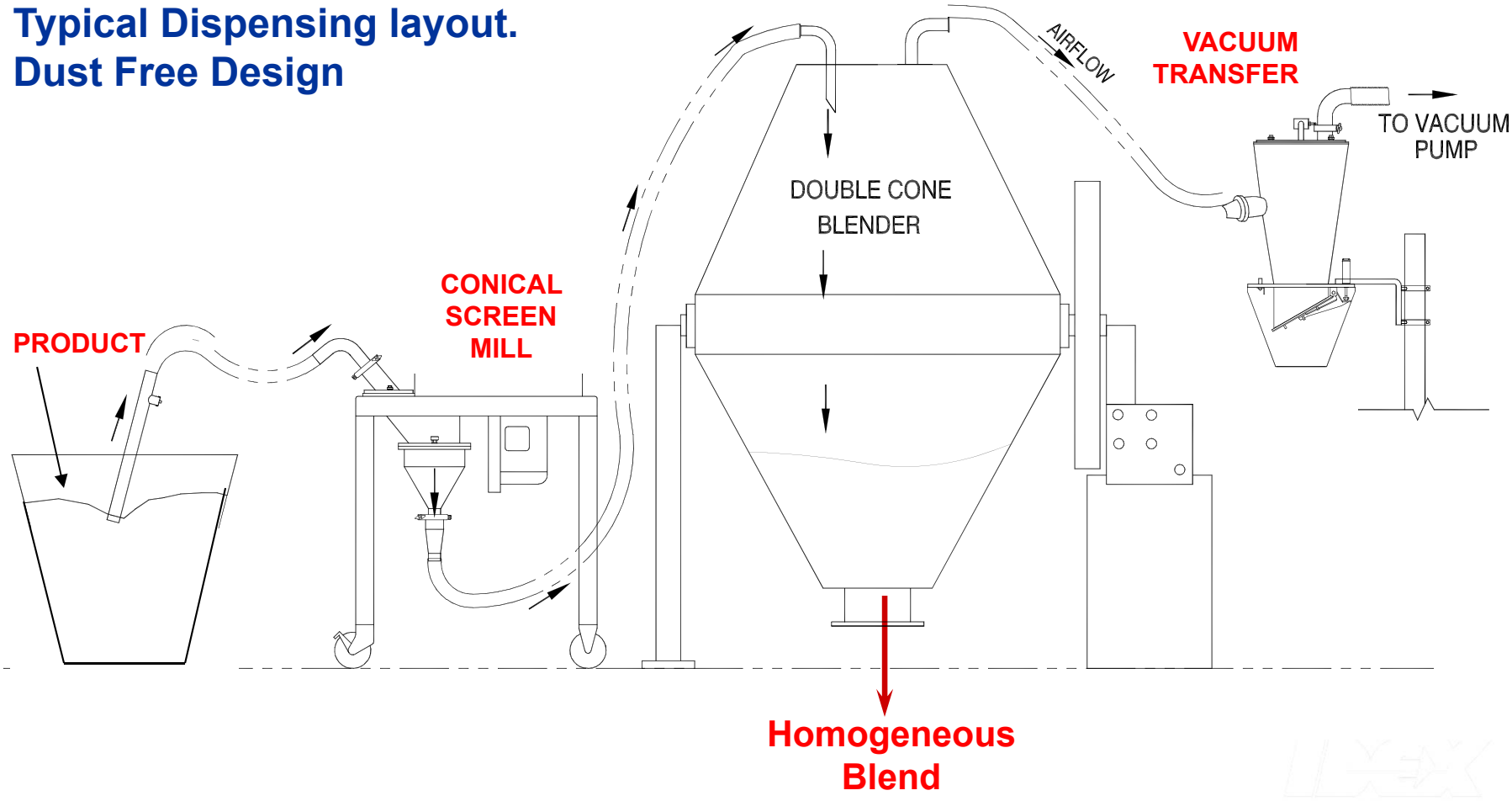


Common Milling Applications in the Manufacturing Process

- Dispensing – **De-agglomeration and security screen**
- Pre-Milling – **Particle Size Distribution**
- Post Granulating – **De-agglomeration/Dispersion**
- Dry Milling – **Sizing Dried Blend**
- Final Milling – **Size/De-lump/Calibrate**
- Reclaim - **Off-Spec Tablets/Compacts**

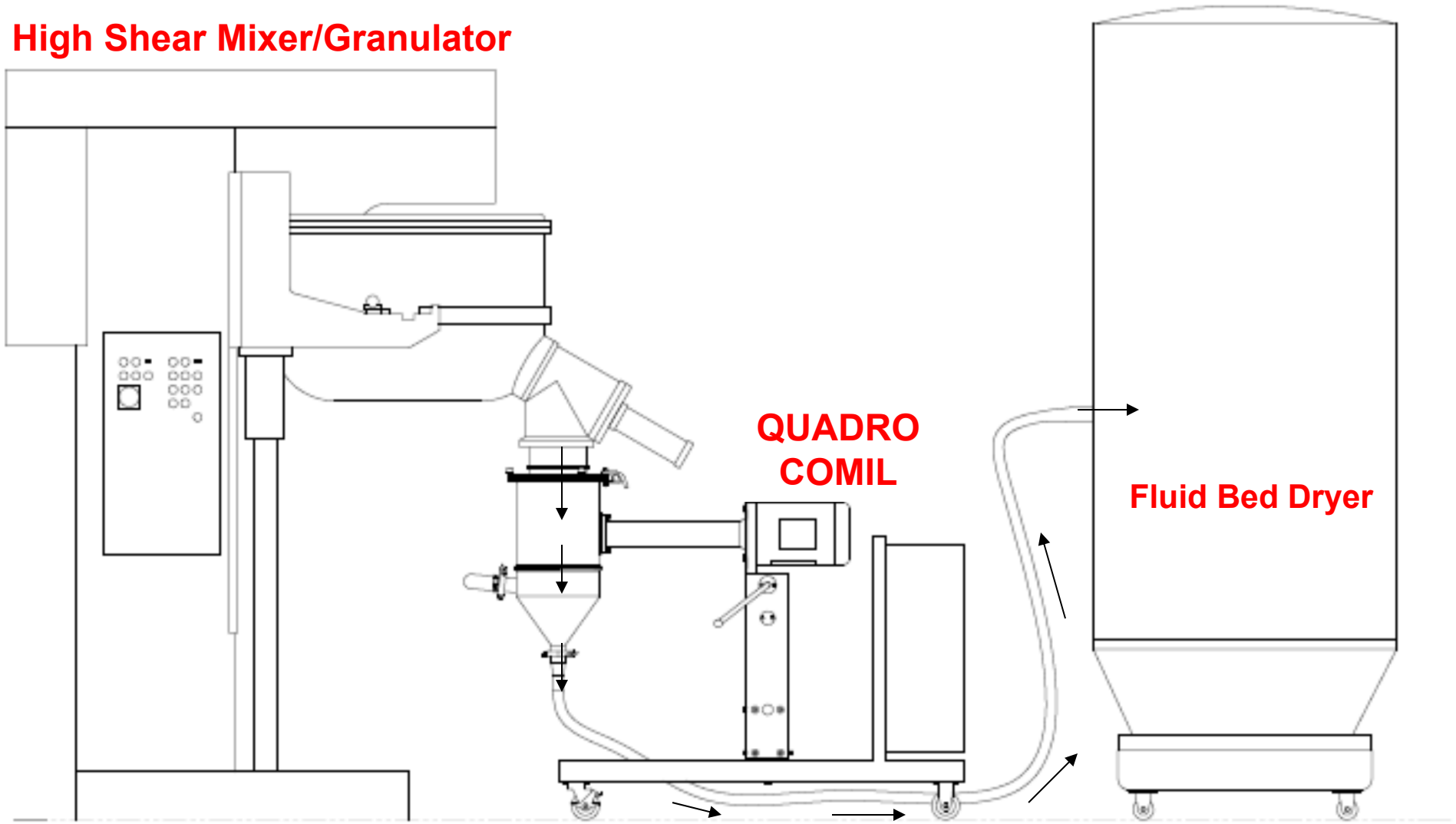
Milling

Typical Dispensing layout.
Dust Free Design



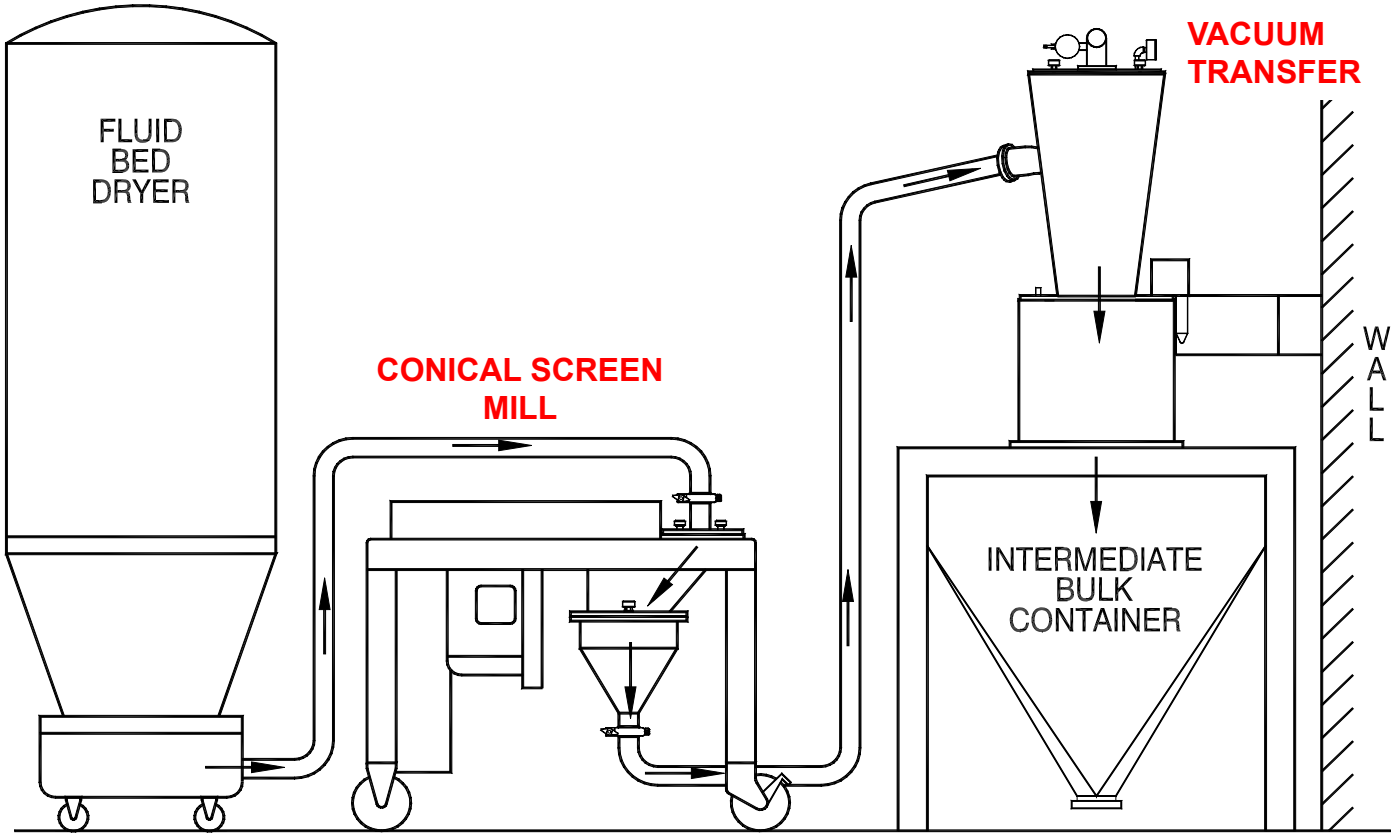
Milling

Wet Dispersion Prior To Drying - Typical Integrated Design



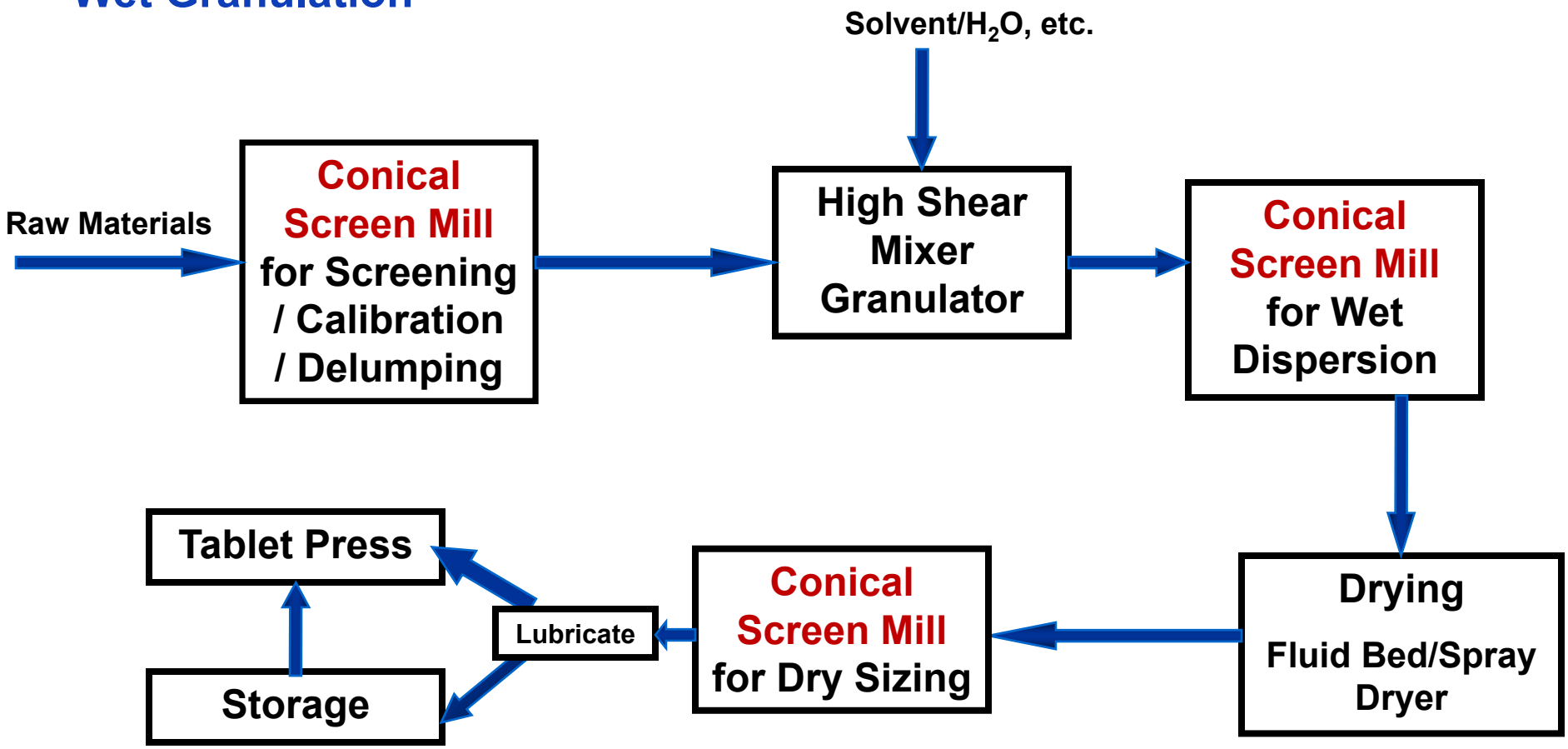
Milling

Dry Milling After Fluid Bed Dryer
Typical Integrated Design c/w Vacuum Transfer



Tablet Manufacturing

Wet Granulation



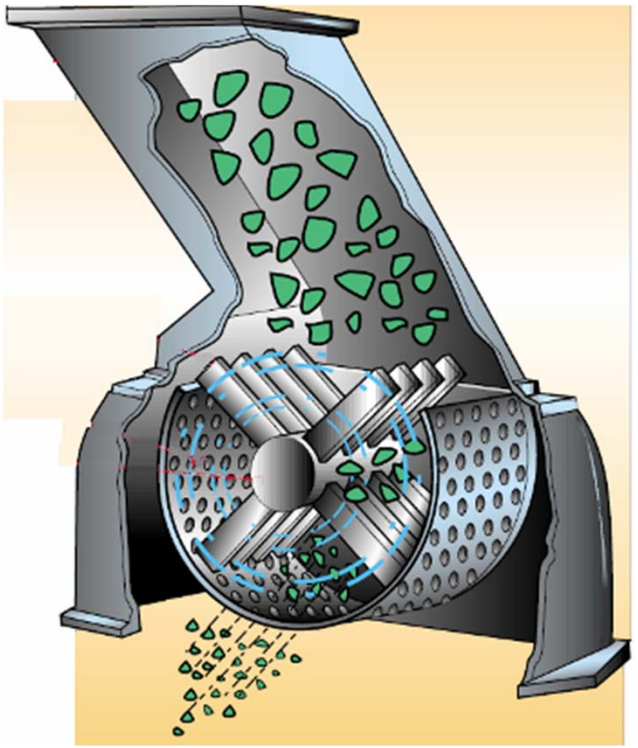

GEA
Comil U20
Wet Milling - Direct Discharge

Fully Integrated Solid Dosage Preparation Plant
(Class 100,000 Room)

Wet Milling - Direct Discharge

Hammer Mill

- High shear mechanism
- Various In-feed designs
- Variable speed, blade & hammer assembly
- 120° discharge area
- Common output range (6” – 12” – 30” wide screens)

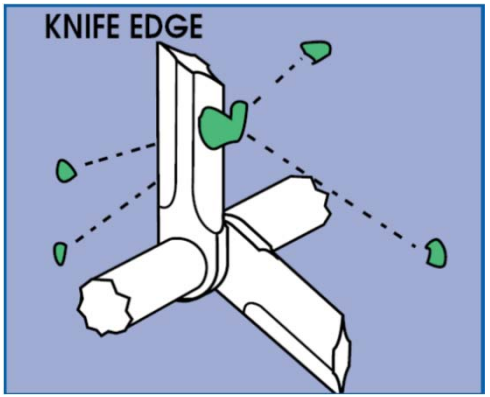


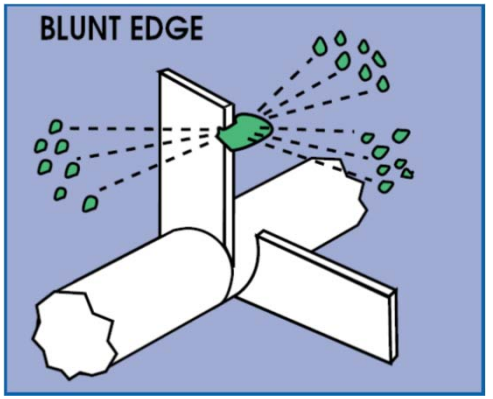
Milling Technologies

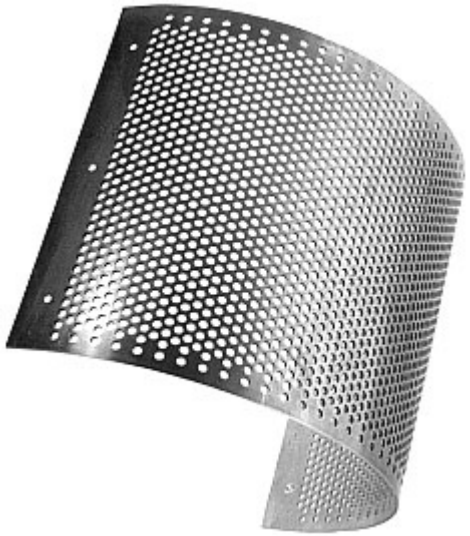
Hammer Mill Cont…

Blade & Screen Types

- The blade assembly is reversible.
- The most common blade arrangement is one blunt edge and one knife edge.
- Product can be hammered or cut.
- Hardened Blades available for abrasive applications







Milling Technologies

Hammer Mill Cont…

- Hammer Mills require control feed.
- Changes in feed rates may change product retention time.
  - **will effect products that can easily dense**
  - **increased fines & friction**
  - **will effect products with low melting temperature**

Milling Technologies

Hammer Mill Cont…

Advantages

- Wide range in Size
- Medium to High Shear
- Vertical/Horizontal Designs
- Blades/Screens Interchangeable
- Suitable for Milling Hard Materials

Disadvantages

- High Noise Levels
- % Fines High
- Must be control-fed
- Belt Slip Common
- High Dusting
- Ventilation Requirement
- Screen change complex
- Difficult to Scale-Up

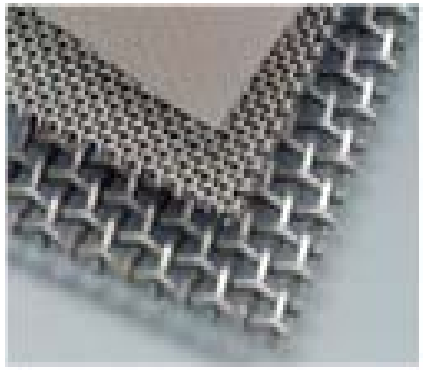
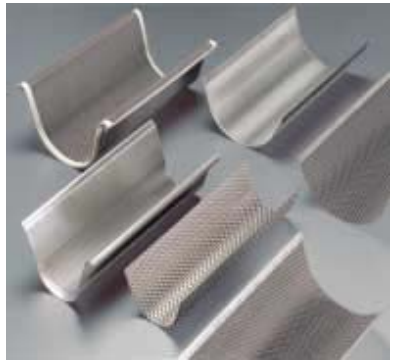
Oscillator

- This machine was commonly used in the past for low shear applications.
- Some similar designs are continuous and do not oscillate.
- Suitable for low volume manufacturing.

Oscillator Cont…

- Uses mesh screens, not perforated plates.
- Cast Body
- Discharge - tray or drum
- High Wear rate.



Oscillator Cont…

Advantages

- Gentle
- Easy to operate
- Fixed speed
- Low cost equipment
- Low Tech Functions
- Portable

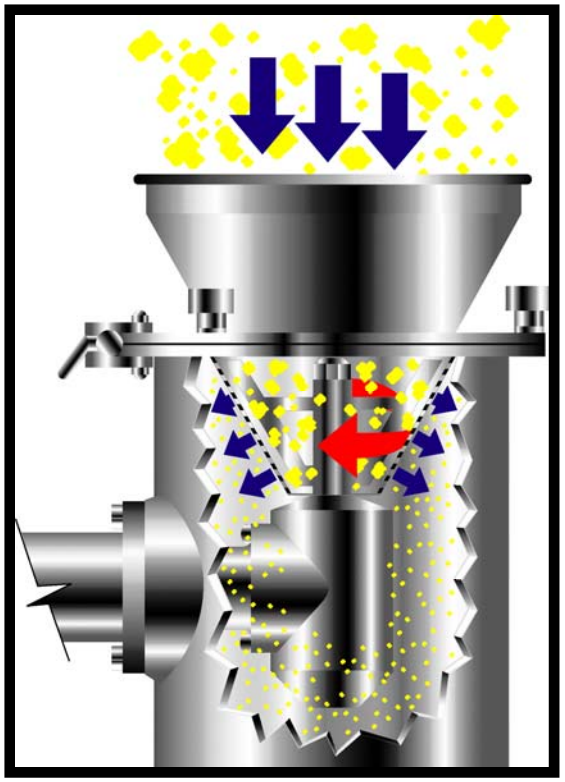
Disadvantages

- Low Capacity
- Metal to Metal contact
- Non GMP design
- Not suitable for integrated processes
- Cleaning - complex
- Loss of Active material

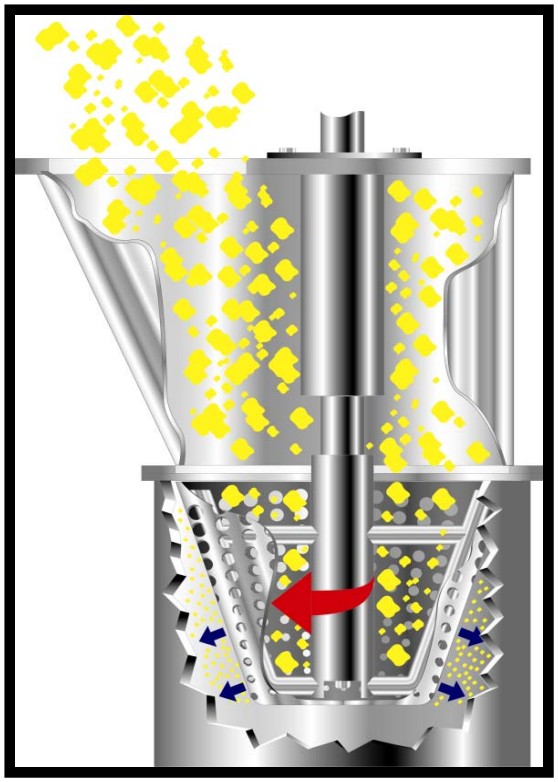
Conical Milling

- Infeed falls into conical screen chamber
- Rotating impeller imparts vortex flow pattern to infeed material
- Centrifugal acceleration forces particulates to screen surface
- Particles are continuously delivered to “action zone” between screen and impeller
- Particles are size reduced (as fine as 150 micron) and instantly discharged through screen openings

Conical Milling



Underdriven Comil
(Invented 1990)

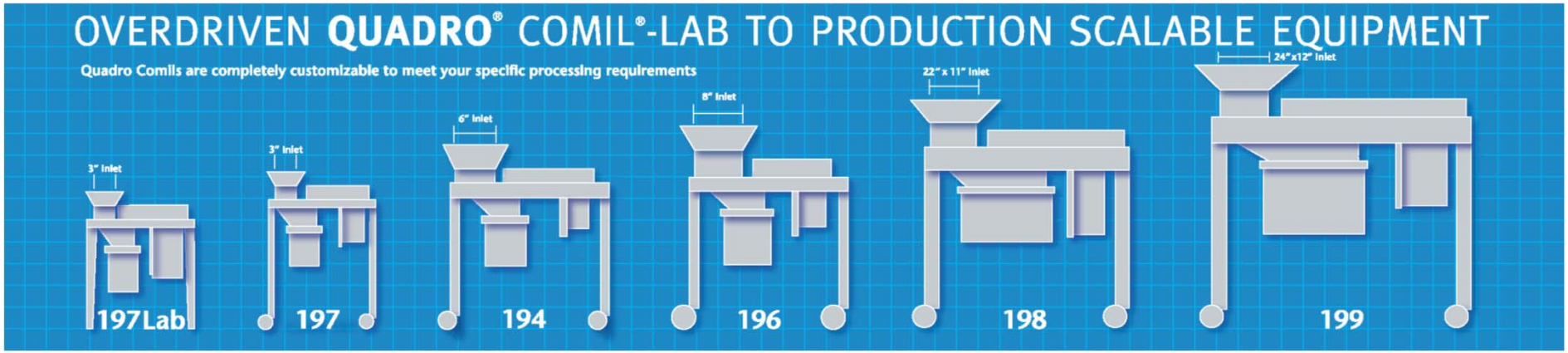


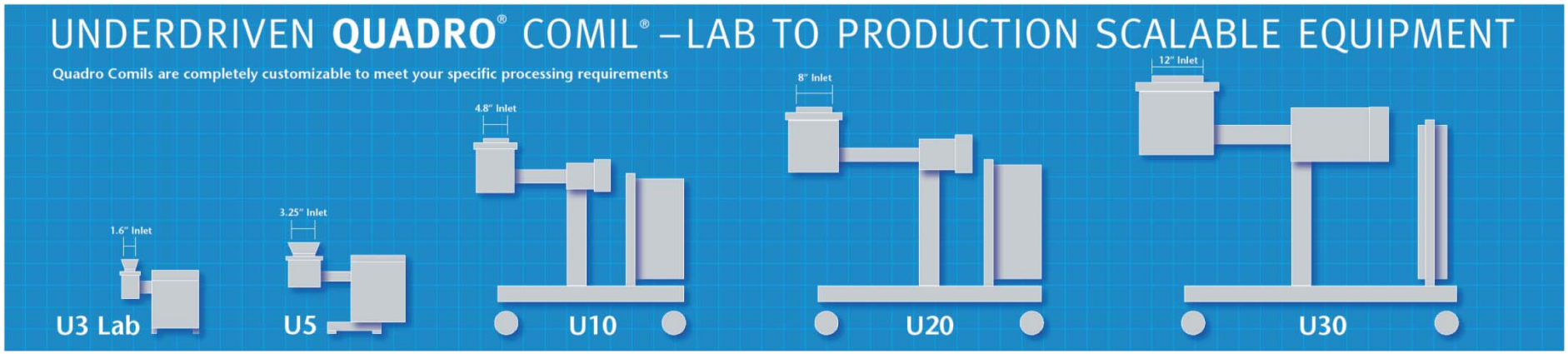
Overdriven Comil
(Invented 1976)

Conical Milling – Quadro COMIL

Scale	Quadro Comil Model		Power	Standard Impeller speed	Scale-Up Factor	Tip Speed M/sec (Ft/min)	Screen Diameter	Capacity Lb/hr (kg/hr)
	OVERDRIVEN	UNDERDRIVEN						
Lab		U3	0.246 KW (0.33 hp)	4500 RPM	0.25X	14.2 (2800)	2.55" (65mm)	From 3oz/100g to 220lb (100kg)
		U5	0.375 KW (0.5 hp)	3450 RPM	0.5X	14.2 (2800)	3.25" (83mm)	425 (195)
Pilot	197	U10	1.5 KW (2.0 hp)	2400 RPM	1 X	14.2 (2800)	4.84" (123mm)	800-850 (360-390)
Production	194	U20	4.0 KW (5.4 hp)	1400 RPM	5 X	14.2 (2800)	8.2" (208mm)	3900-4250 (1750-1950)
	196	U30	7.5 KW (10 hp)	900 RPM	10 X	14.2 (2800)	12.17" (309mm)	7800-8500 (3500-3900)
Large Production	198		15 KW (20 hp)	450 RPM	20 X	14.2 (2800)	24" (609mm)	15,600 (7000)
	199		22 KW (30 hp)	360 RPM	40 X	14.2 (2800)	30" (761mm)	20,000 (9000)

Conical Milling – Quadro COMIL

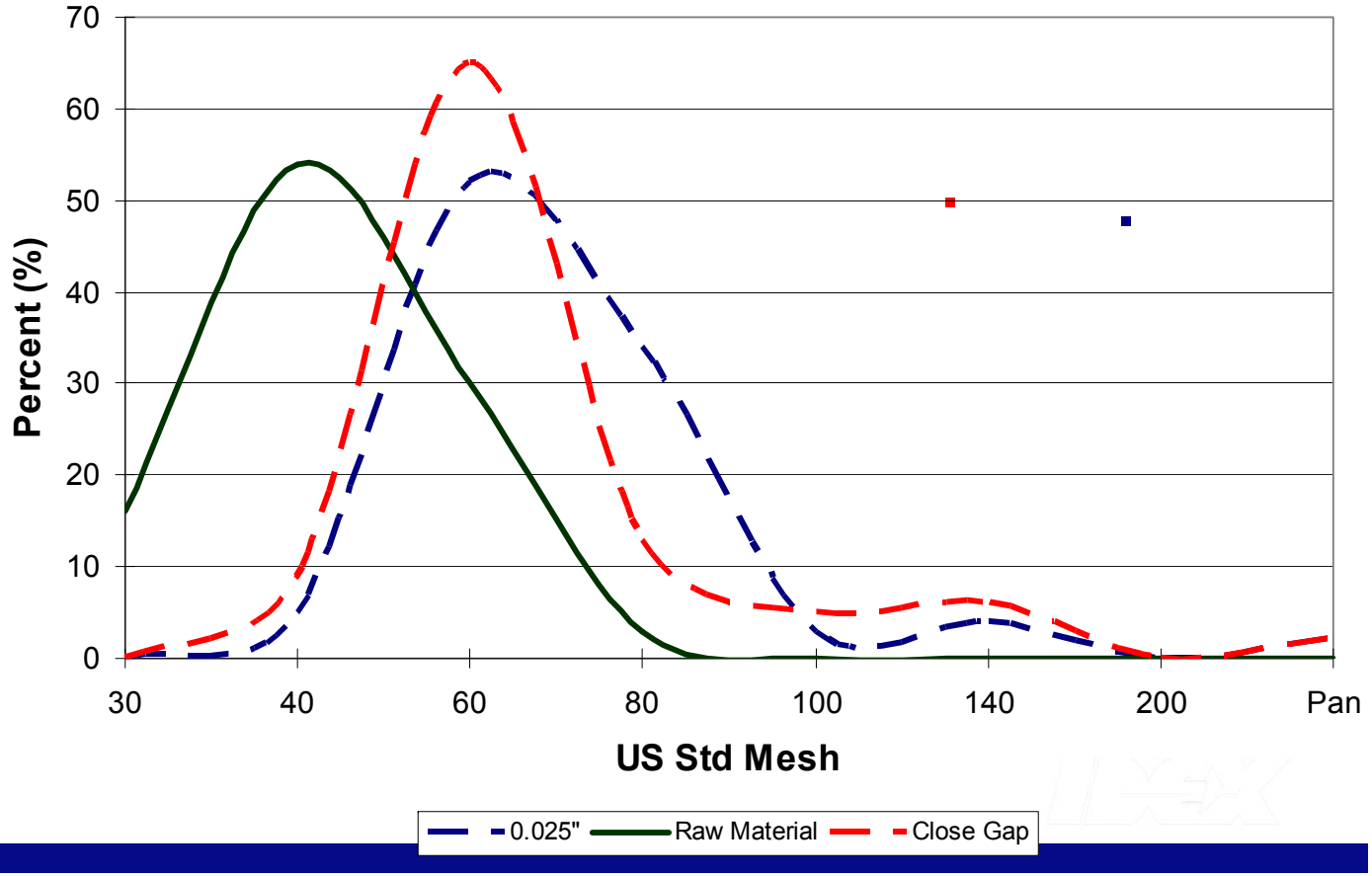




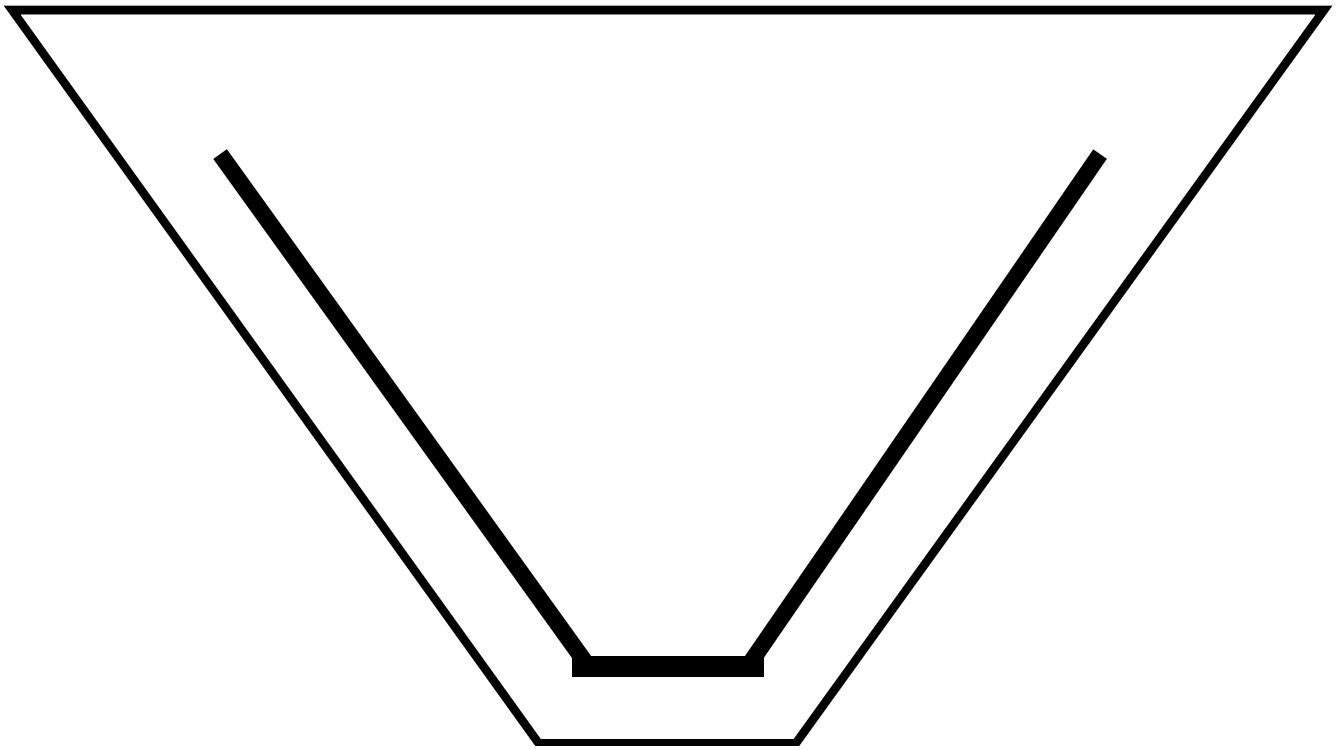
Critical Factors for Optimum Conical Milling Characteristics

Close impeller / Screen Gap

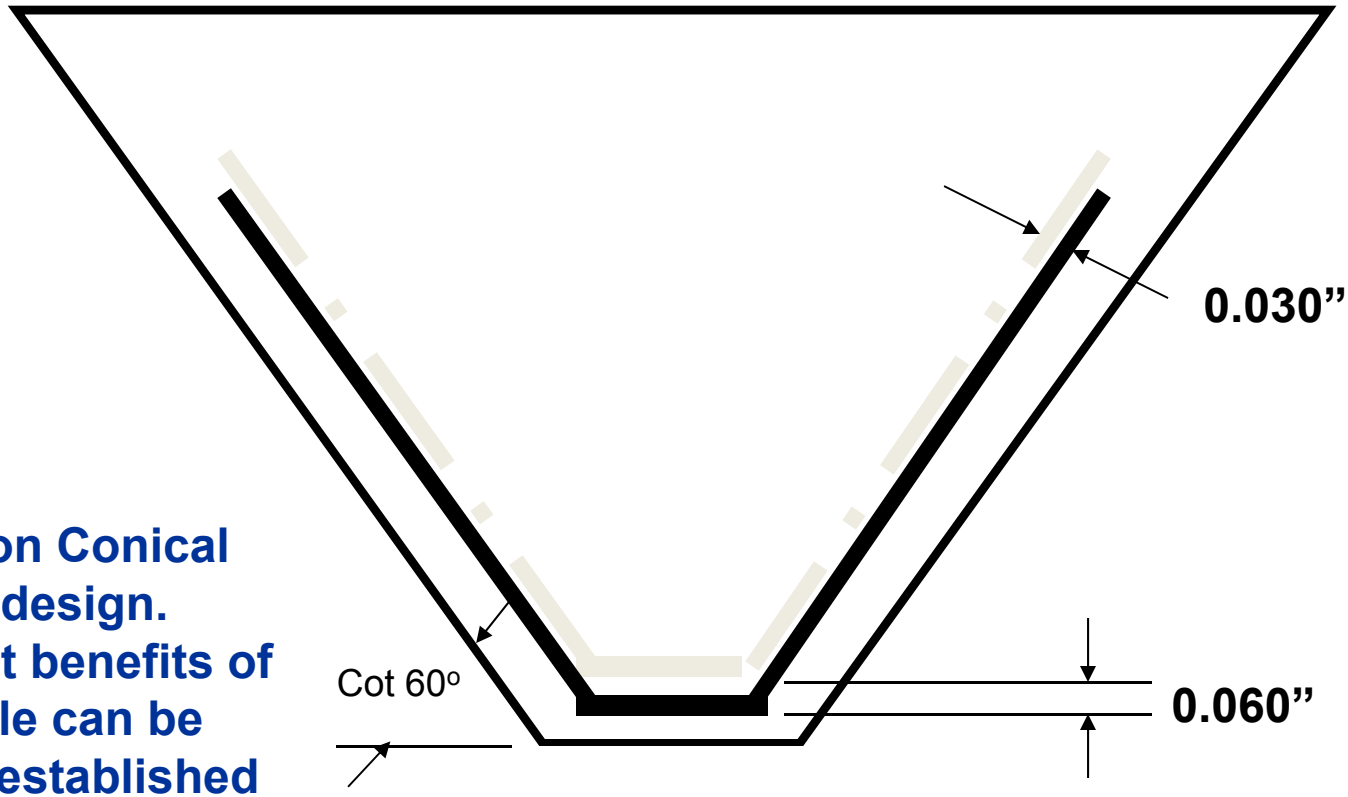
- Less fines
- High Yield



Critical Milling Factors:
Close Gap



Critical Milling Factors: Close Gap

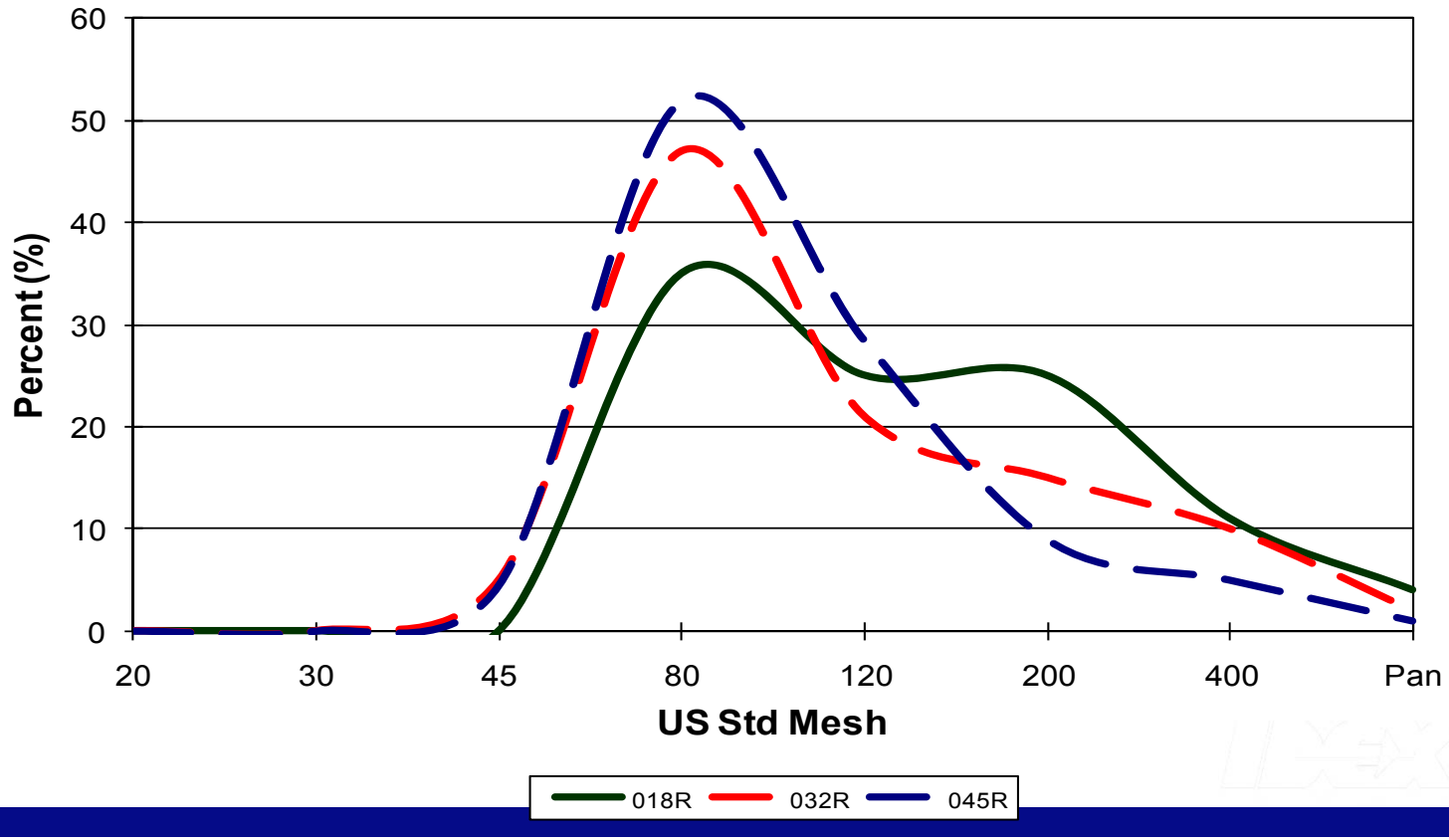


Based on Conical Screen design. Inherent benefits of the angle can be readily established as a 2:1 ratio.

Critical Factors for Optimum Conical Milling Characteristics

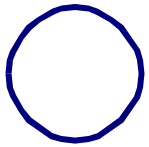
Proper Tooling Selection – Screens

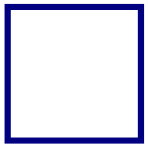
Effect of screen hole size on particle size distribution: generally a finer screen produces more fines and less overs.

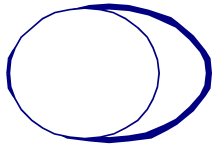


Conical Milling

Critical Milling Factors:
Proper Tooling Selection - Screens







R

Q

S

G

R – Round holes
(Dry Material)

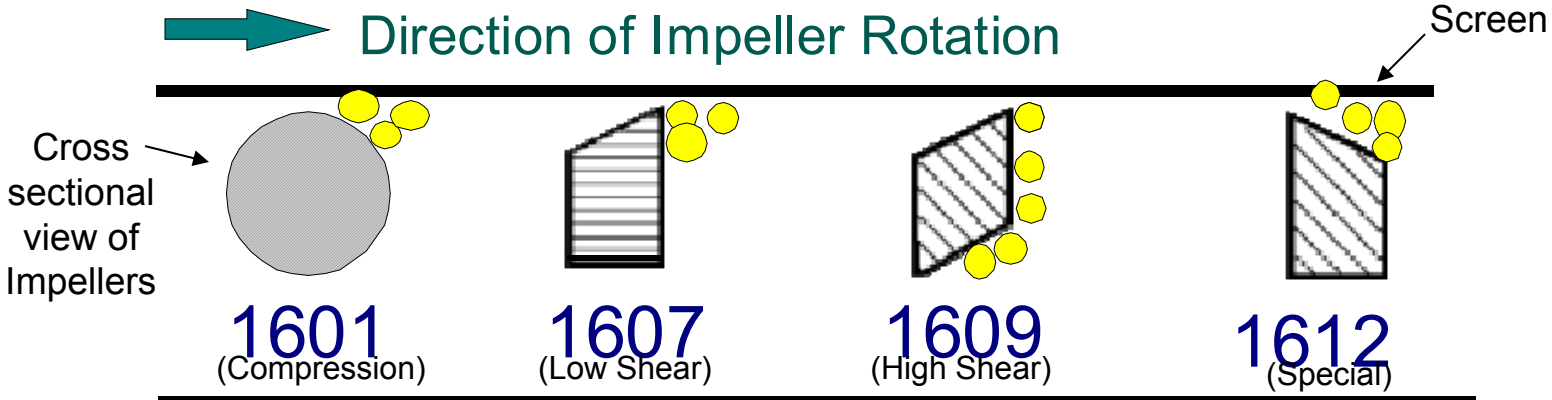
Q - Square holes
(Wet Material)

S – Slotted
(Pseudo Plastic)

G - Grater holes
(Hard & Dry)

Conical Milling

Critical Milling Factors:
Proper Tooling Selection - Impellers

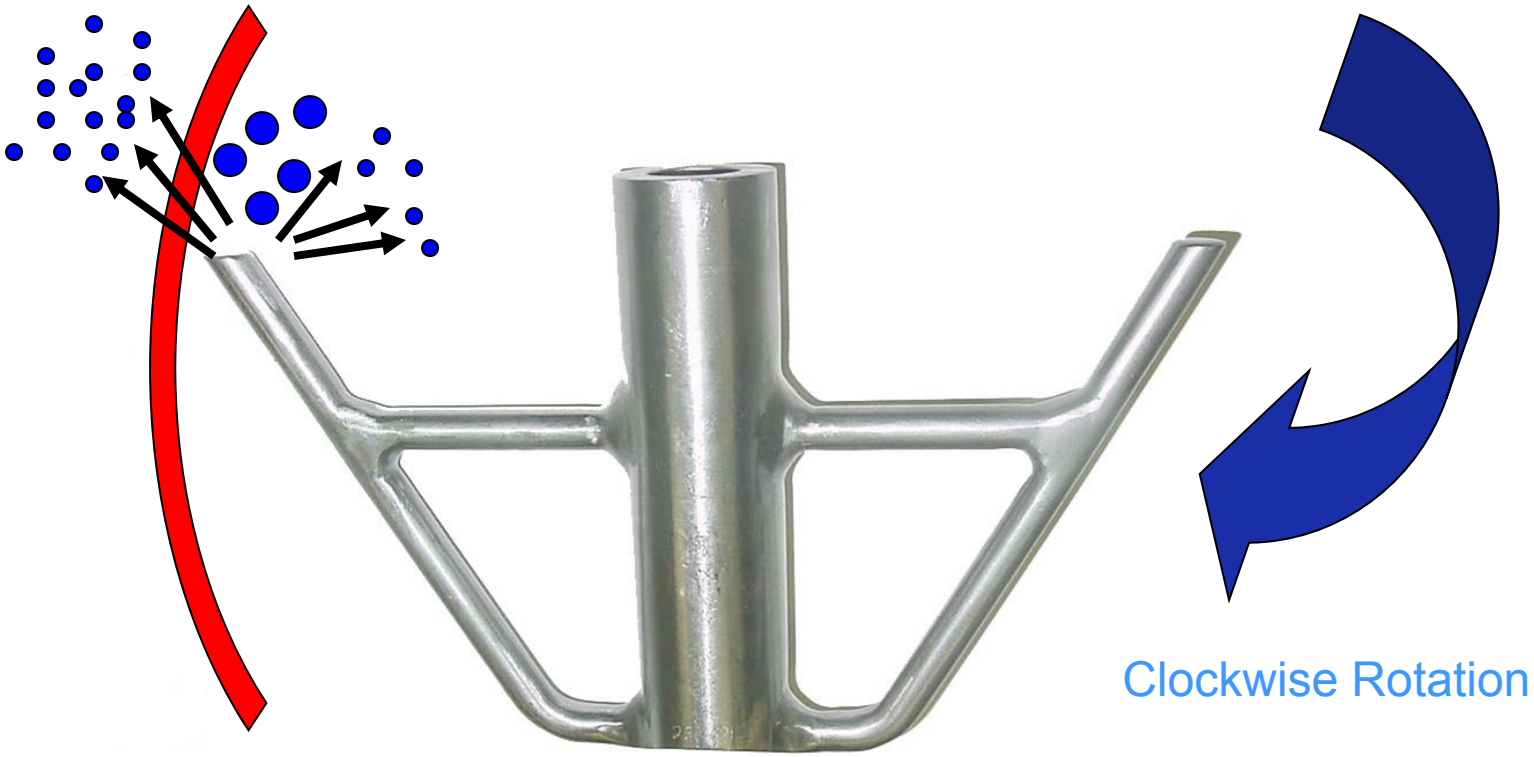


	1601 (Compression)	1607 (Low Shear)	1609 (High Shear)	1612 (Special)
Capacity	2	3	4	1
Fines	2	1	3	4
Screen Pressure	2	3	4	1
Amperage	2	3	4	1

1=Highest 4=Lowest

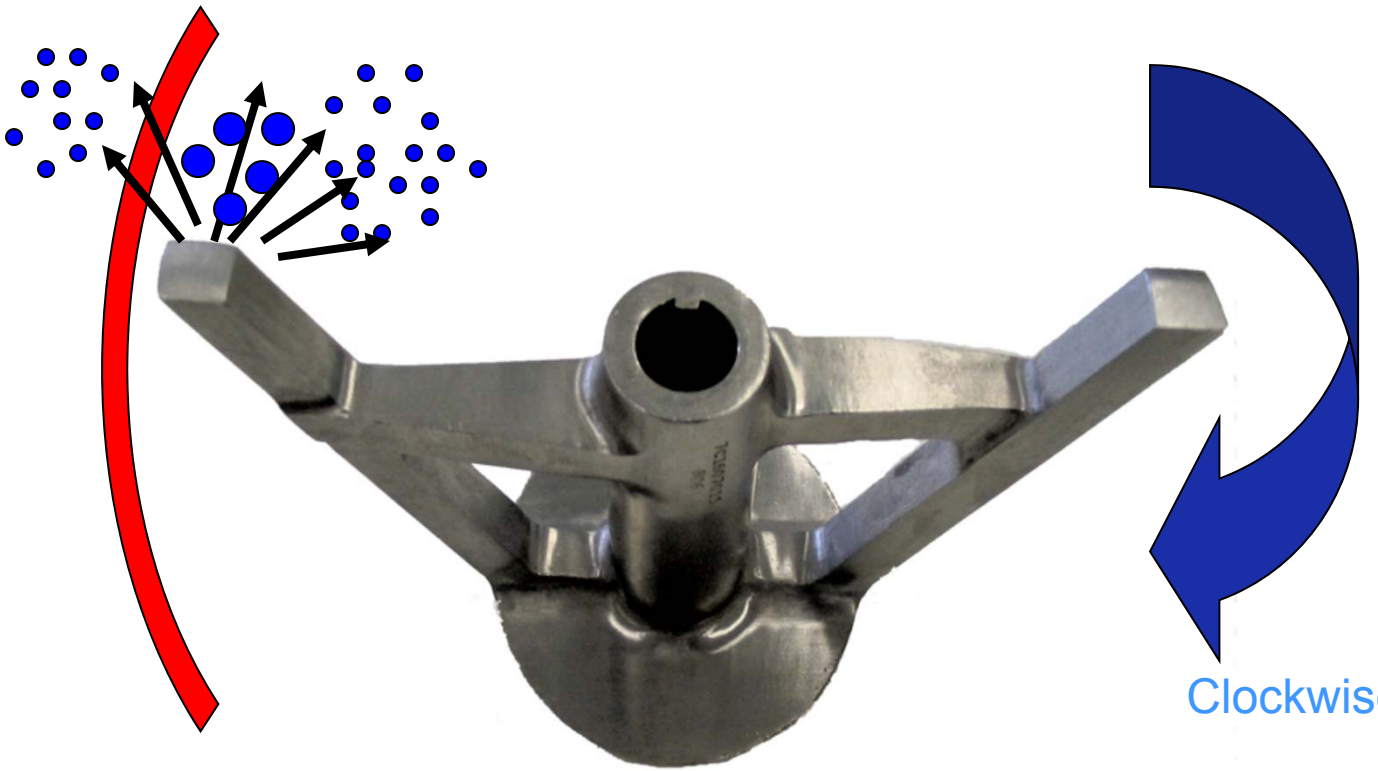
Conical Milling

Comil Impellers – Round Arms #1601



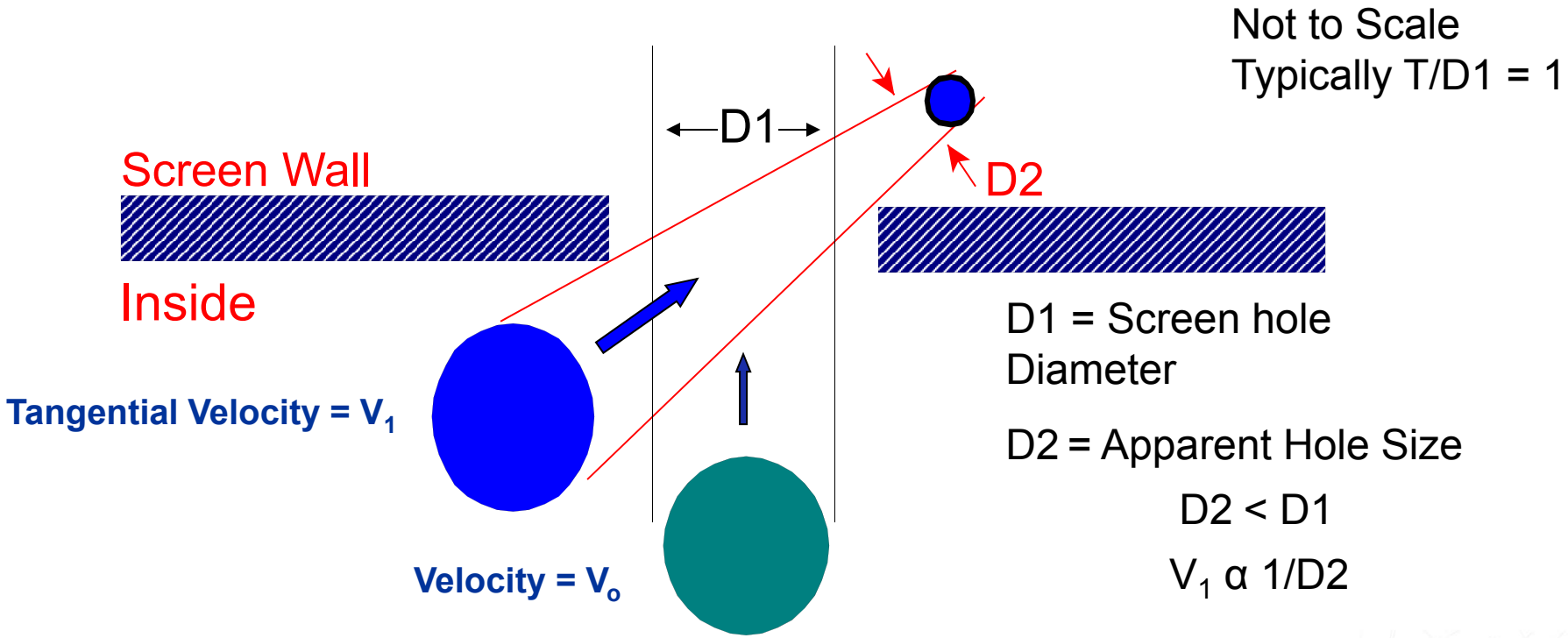
Round arms - primarily for dry sizing, some wet milling

Comil Impellers – Rectangular Arms Positive Leading Edge #1607



Square Arms – “Universal” for wet milling and dry sizing

Critical Milling Factors: Screens - Apparent Hole Size



Fine Milling

- Accepted definition of Fine Milling is **psd** between 5 - 100 Microns and for Micronization **psd** between 1 - 30 micron in diameter.

- It is possible to use some of the previously discussed equipment to reduce the particle size distribution of a product down to this range (Hammer Mill) however, distribution curve can be fairly wide spread and possibly even bimodal whereas a tight **psd** and unimodal curve is the goal of most processes.

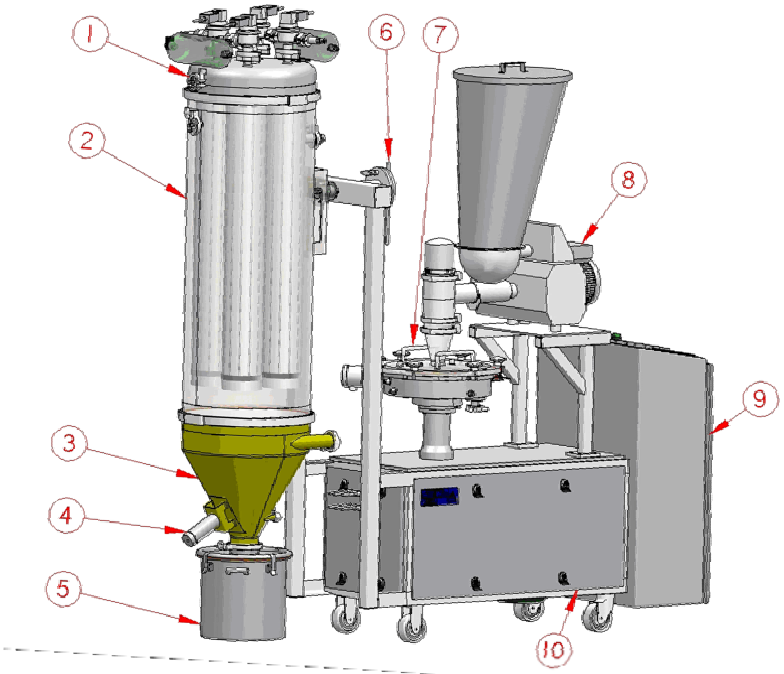
- Equipment commonly used for fine milling are: Pin Mills, Hammer Mills, Fine Grind, & Jet Mills

Fine Milling

SIZE REDUCTION CAPABILITY COMPARISON																	
Comil																	
F10 Fine Grind																	
Hammermill																	
Pin Mill																	
Jet Mill																	
Micron	-5	-2.5	1	5	10	25	38	45	75	125	150	180	250	300	425	600	1000
US Mesh	-	-	-	-	-	-	400	325	200	120	100	80	60	50	40	30	18

Fine Milling

Quadro Fine Grind F10

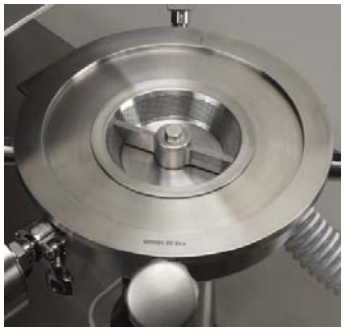


1. Collector Cover
2. Product Collector Body
3. Product Hopper
4. Pneumatic Vibrator
5. Outlet container
6. Rotation Hinge
7. Milling Head
8. Screw Feeder
9. Control Panel
10. Access Panel

Fine Milling

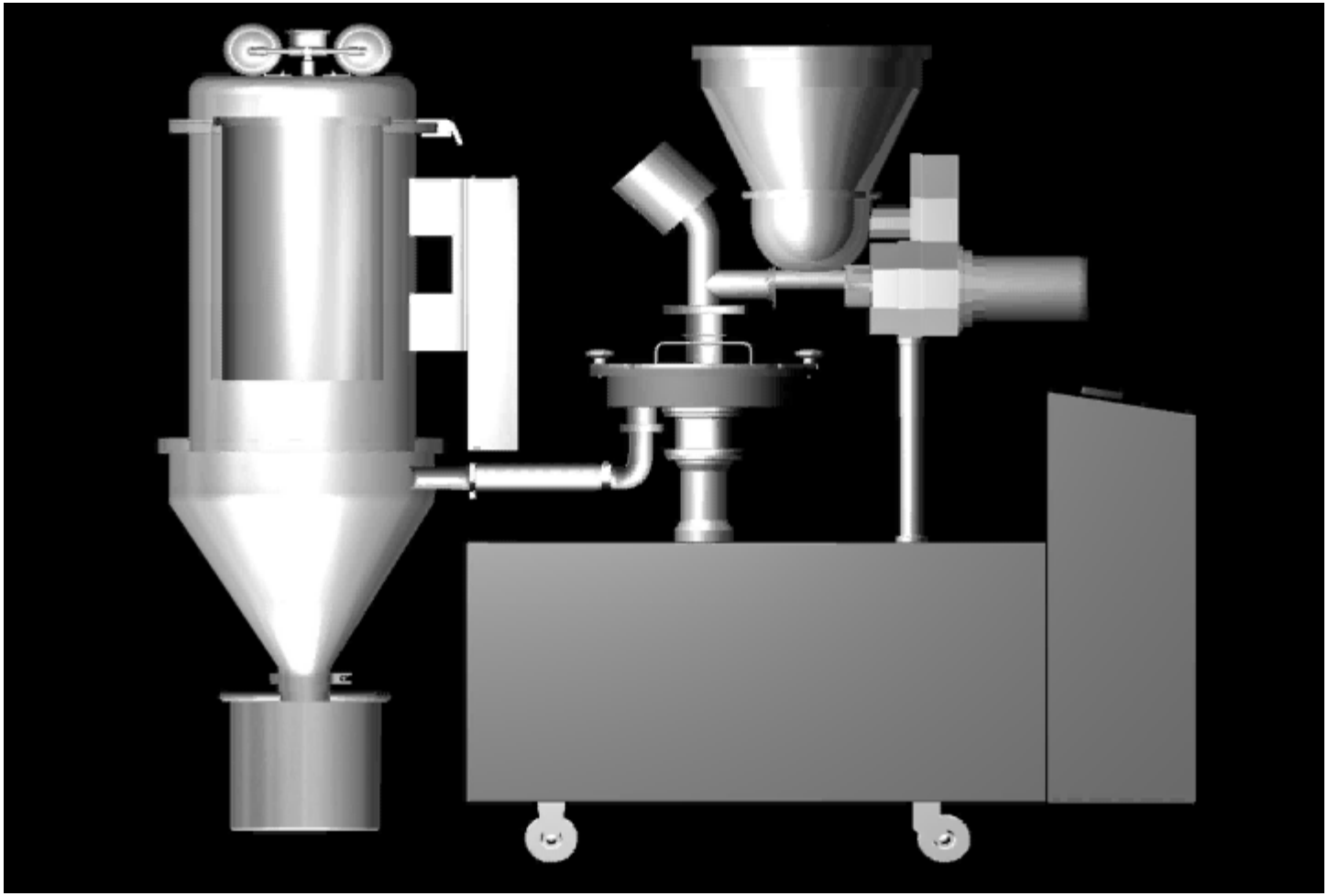
- Fine Grind F10 was developed to produce tailored **PSD** between 15 and 100 microns.
- Mobile, stand alone system (a complete plant) operates at low noise, dust heat and energy consumption.
- **The operating principle;**
  - control feed product into upper conical screen chamber.
  - a rotating impeller calibrates incoming material.
  - calibrated product then passes through to the lower chamber
  - a second intensifying impeller accelerates the particles.

Upper Chamber



Lower Chamber

Fine Milling



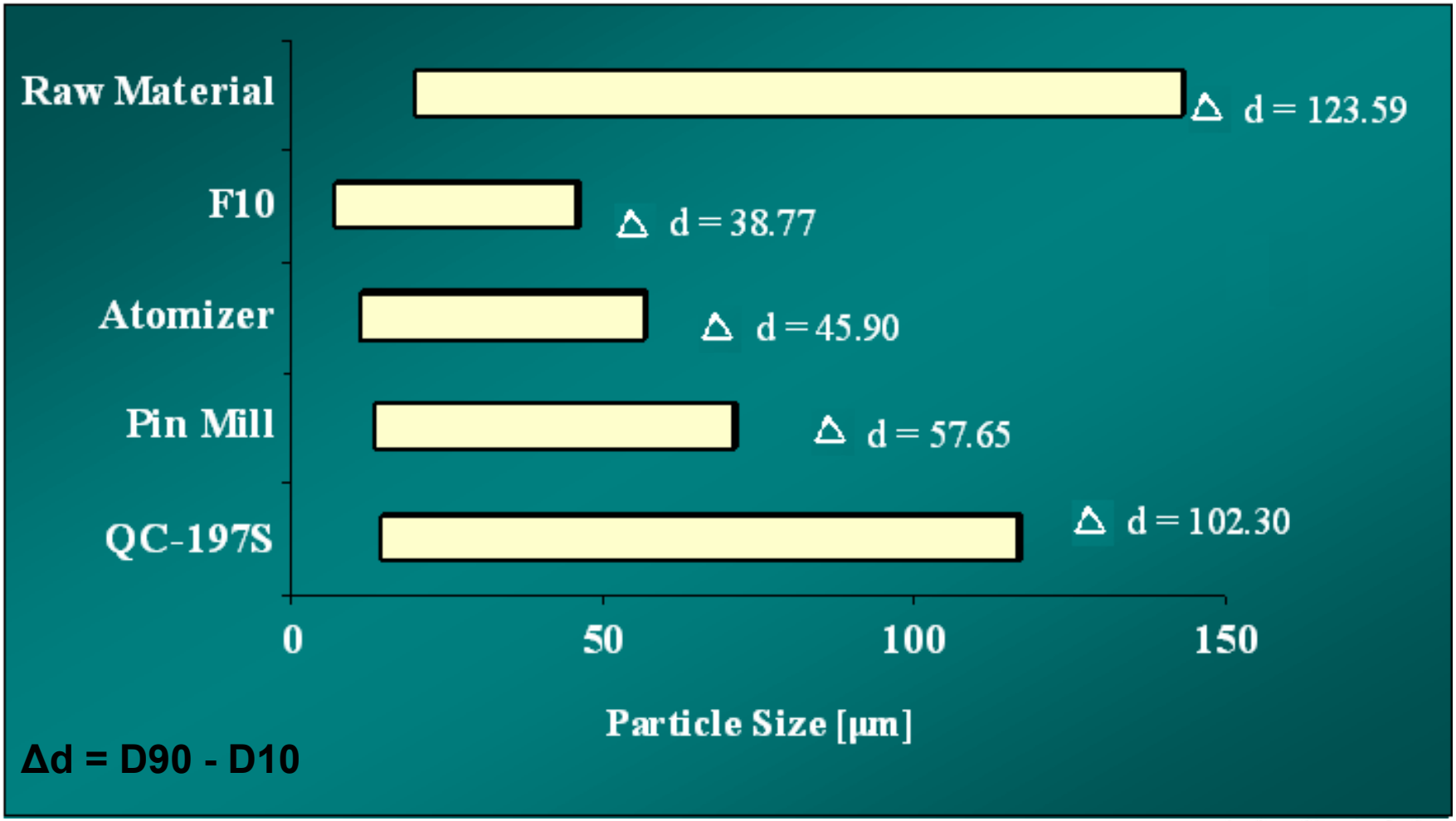
Fine Milling

F10 Breakthroughs

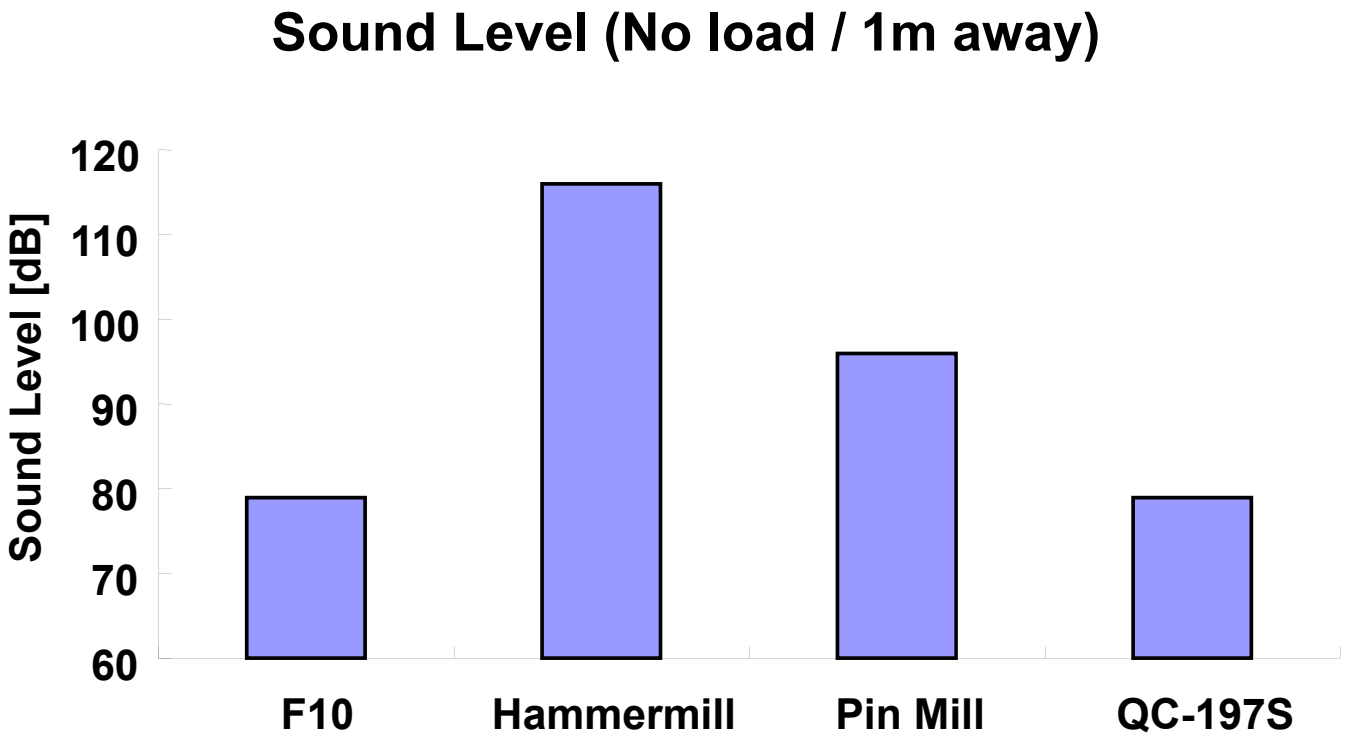
- Very tight Particle Size Distribution
- Very high Product Recovery rate (>99%)
- Dust-tight
- Mobile, All-In-One unit, no ancillaries required
- Operator-friendly: Easy to clean & Low-Noise Operation
- Sanitary, GMP design; Developed specifically for Pharmaceutical API Industry

Fine Milling

Technology Comparison – Lactose 200M



Technology Comparison – Noise



Case Study – Teva, Israel

MILLING EXPERIMENTS WITH PROTOTYPES OF THE QUADRO FINE-GRIND F-10 MILL

ABSTRACT

Quadro Fine grind (F-10) is a versatile mill which is effective in the range of 20-60 μm. Three Prototypes were received for experiments in Teva's API division. Different active pharmaceutical ingredients were tested to explore the mill's performance. Based on the conclusions, the final model was built. Improvements included enlargement of the milling chamber, Control over speed and vacuum, and introduction of water cooling. It was found that the milling range covers the particle size reduction range obtained today by either single or multiple milling in hammer-mills, and can provide comparable results to those of a pin-mill.

Case Study – Teva, Israel

INTRODUCTION

Teva's API division manufacturers over 200 molecules for various pharmaceutical clients. The physical properties of the products are tailor-made in order to meet various customer requests and optimize the formulation [1]. Because of the large number of products and different physical grades, it is required that mills will be versatile, i.e. capable to produce a wide spectrum of P.S.D by changing only the operating parameter.

The P.S.D range of ~20-40 microns is considered to be difficult to obtain. Larger particles can be controlled by Hammer-mills, Comils or other mechanical mills. Particles under 20 microns can be obtained by fluid-jet mills. However, only few mills can obtain narrow P.S.D in this range without having too many fines or oversized particles. One of these mills is the Pinmill [2]. Few main drawbacks of this mill are the heat generation and the very narrow gap that make it prone to blockages. Therefore, a great interest was found in the Quadro Fine grind (F-10). Two prototypes were tested, and based on Teva's findings, the final version was constructed and successfully applied in routine production.

Case Study – Teva, Israel

Teva Paper at CHoPS Conference Italy, Aug 2006
"Development of the F10 in Teva, API"

Paper Synopsis

Goal: PSD 20 to 40 µm range

Previous: Pin Mill. Heat changed product characteristics.
Narrow gap between pins prone to blockage
(9 hrs to clean vs. F10 at 1 hour)

Validation: 6+ API's validated with F10

Case Study – Teva, Israel

Customer Requirement	Observations & Discussion:			
F10 comparison versus Pin Mill and Hammermill	Material "A": F10 vs. Pin Mill / Hammermill			
	Material A	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)
	Unmilled	60	180	410
	Pin Mill	2	15	45
	Hammermill Double Pass	4	20	50
	F10 Single Pass	**1.6**	**11.9**	**49.4**

1. PSD Comparison between F10 versus Pin Mill and/or Hammermill results provided equal or better PSD distribution.
2. Material "A" is a proprietary pharmaceutical API

Fine Milling

Case Study – Teva, Israel

Customer Requirement	Observations & Discussion:			
F10 comparison versus Hammermill	Material "B": F10 vs. Hammermill			
	Material B	D_{10} µm	D_{50} µm	D_{90} µm
	Unmilled	12.73	66.33	211.83
	Hammermill	8	50	150
	F10	**3.44**	**18.69**	**63.33**

1. PSD Comparison between F10 versus Hammermill results provided better PSD distribution.
2. Comil was also tested: D90 180 µm, D50 70 µm, D10 10 µm
3. Material "B" is a proprietary pharmaceutical API

Fine Milling

Case Study – Teva, Israel

Customer Requirement	Observations & Discussion:

F10 comparison versus Hammermill

Material "C": F10 vs. Hammermill

Material C	D_{10} µm	D_{50} µm	D_{90} µm
Unmilled	24.33	118.91	339.14
Hammermill	7.96	57.34	157.62
F10	**7.59**	**30.84**	**85.04**

1. PSD Comparison between F10 versus Hammermill results provided equal or better PSD distribution.
2. Material "C" is a proprietary pharmaceutical API

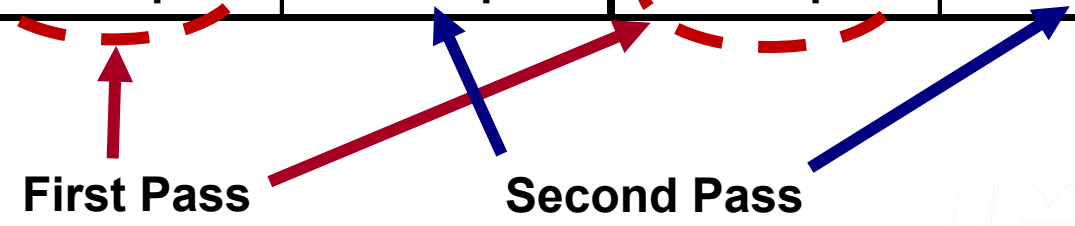
Fine Milling

Case Study – Apotex, Canada

Customer using Hammermill: 4-5 passes for d_{90} = 70 µm

F10: d_{90} = 53.6µm (single pass) 7200RPM and 20.4µm 8400RPM

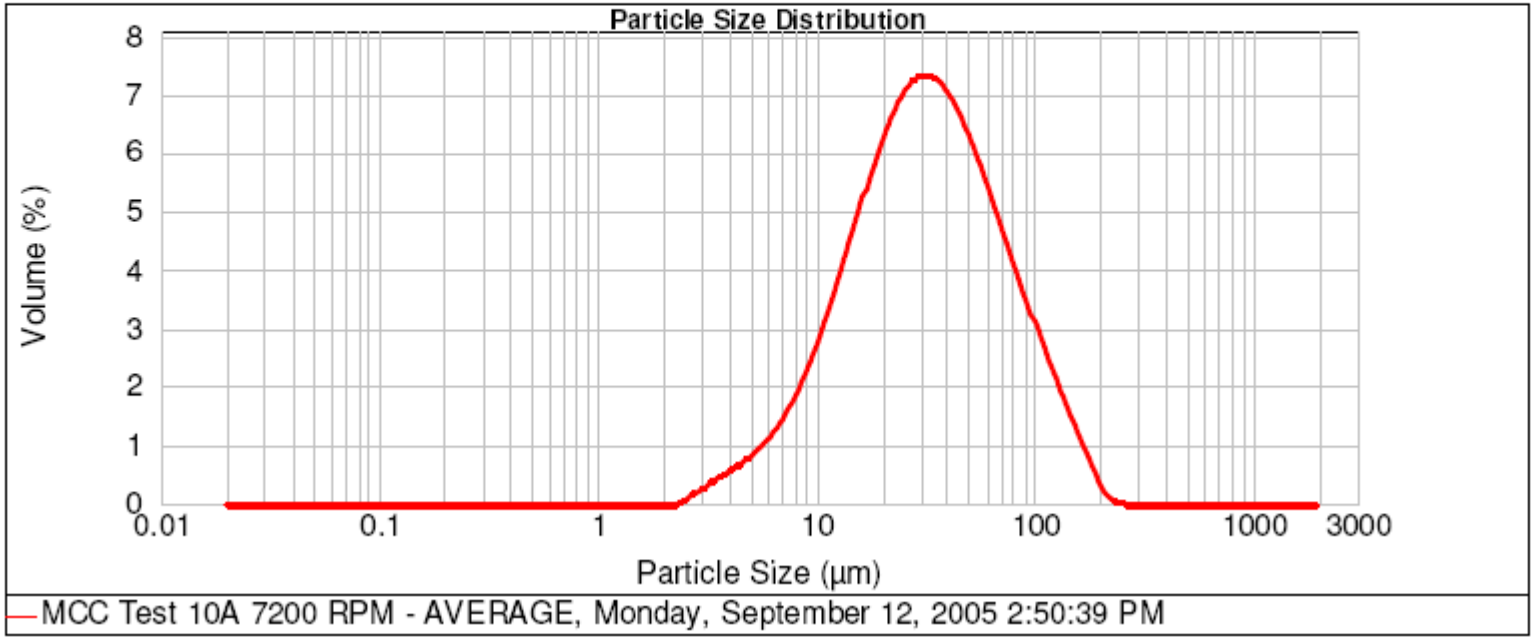
Alendronate Sodium Trihydrate		Impeller Speed = 7200 rpm		Impeller Speed=8400 rpm	
		Run 1	Run 1.1	Run 2	Run 2.1
PSD	Starting Material	PSD Run 1	PSD Run1.1	PSD Run 2	PSD Run 2.1
D(v,0.1)	8.847 µm	3.503 µm	2.523 µm	2.694 µm	2.876 µm
D(v,0.5)	49.214 µm	18.03 µm	7.408 µm	7.585 µm	7.05 µm
D(v,0.9)	262.787 µm	53.601 µm	19.442 µm	20.451 µm	14.805 µm



Typical F10 PSD Graph – MCC

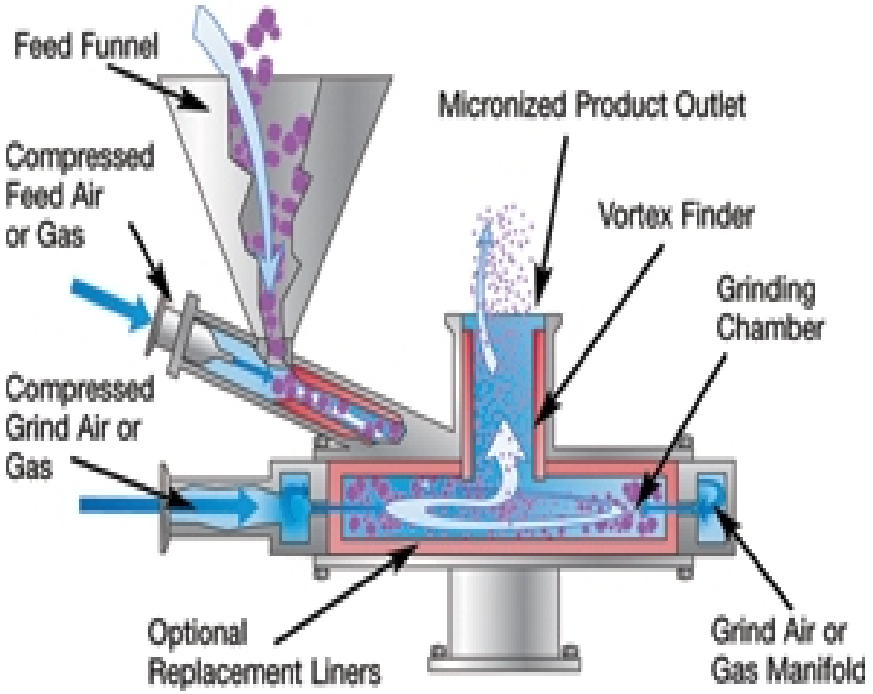
Specific Surface Area:	Surface Weighted Mean D[3,2]:	Vol. Weighted Mean D[4,3]:
0.275 m²/g	21.805 um	42.411 um

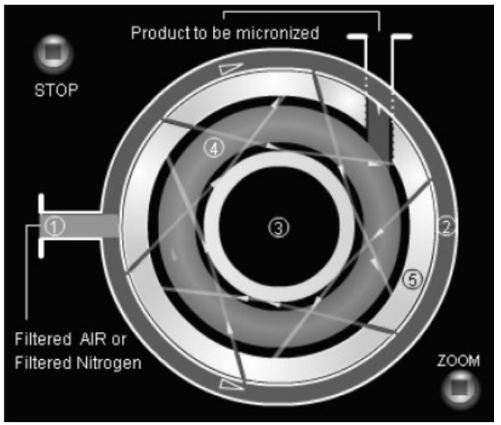
d(0.1):	d(0.5):	d(0.9):
10.560 um	31.714 um	89.907 um

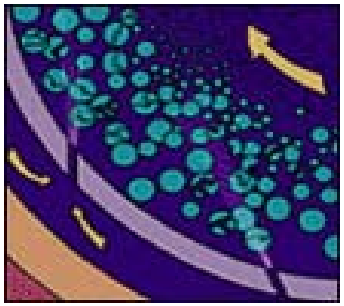


F10 was run at standard speed (7200RPM), 045R screen;
Malvern Mastersizer 2000 Results

Jet Mills & Micronizers







Jet Mills & Micronizers

- **The principle of micronizing fluid energy mills (also known as jet mills or spiral mills) is the size reduction of particles through inter-particulate collisions combined with surface collisions due to acceleration of product.**
- **These mills use accelerated fluid streams (normally compressed air, super heated steam or inert gas) to generate a high speed vortex which the particles are introduced into.**
- **The vacuum created by a venturi-nozzle propels the product throughout the milling chamber, forcing particles to collide with themselves as well as the chamber walls.**

Jet Mills & Micronizers

Key Components and attributes that affect micronization:

- **Nozzle design and direction of air jets**
- **Efficiency of air compressors**
- **Efficiency of filters and separators**

Mill Selection Criteria

Properties of Feed Material:	• Size • Shape • Moisture content • Physical and chemical properties • Temperature sensitivity • Grindability
Final Product Specification:	• Size • Particle size distribution • Shape
Versatility of Operation:	• Change of speed and screens • Safety features

Mill Selection Criteria

Scale-Up:	• Capacity of the mill • Production rate requirements
Dust Control:	• Loss of costly drugs • Health hazards • Contamination of plant • Safety
Sanitation:	• Ease of cleaning and sterilization • Design and material finish
Auxiliary Equipment:	• Cooling system • Dust collectors • Forced feeding

Mill Selection Criteria

Economical Factors:

- Equipment cost
- Power consumption
- Space occupied
- Labor cost

Mill Selection Criteria

Ability to handle dust explosions

General guidelines for inert milling:
Minimum Ignition Energy: (ref. BS5958 Part 1; 1991)

< 500 mJ Low sensitivity to ignition. Solution: **Earth plant**.
< 100 mJ Recommended at this point that customer seek expert advice. Common solution: **Earth personnel**.
< 25 mJ Majority of incidents occur when MIE is at or below this level. Solution: **Inert with nitrogen**.
< 10 mJ High sensitivity to ignition. Solution: **Inert with nitrogen and monitor allowable oxygen levels**.

Thank you

POWDER FLOW AND SEGREGATION PREDICTIONS BASED ON BENCH SCALE TESTING

James Prescott

Senior Consultant

Jenike & Johanson, Inc.

Tyngsborough, MA

Outline

- Flow patterns
- Flow properties and tests
- Segregation mechanisms and testers
- Assessment of uniformity

Common powder flow problems during manufacturing

- No flow: arching, ratholing
- Erratic flow: pulsing, variable bulk density, rate limitations, flooding; some batches work well, others don’t
- Limited production rates (press speeds, etc)
- Segregation: content uniformity problems
- Agglomeration
- Caking

Flowability

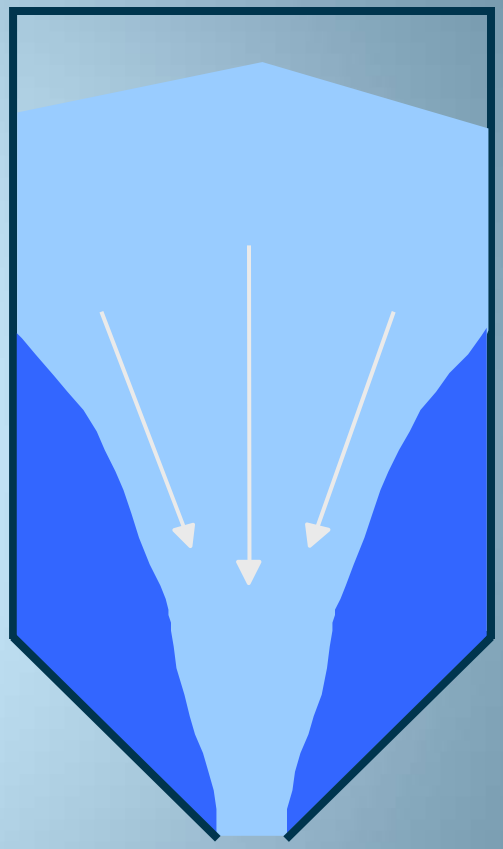
- Powder flowability is a function of:
  - The powder itself (Flow Properties)
    - Physical properties, e.g. particle size distribution, shape
    - Chemical properties, e.g. composition, moisture
  - The powder handling equipment
    - Geometry, e.g. angles, surface finish
    - Throughput, e.g. paddle speed

Flow patterns in hoppers, bins

- Funnel flow
  - Some material is in motion while the remainder is stagnant
- Mass flow
  - All material is in motion whenever any is discharged

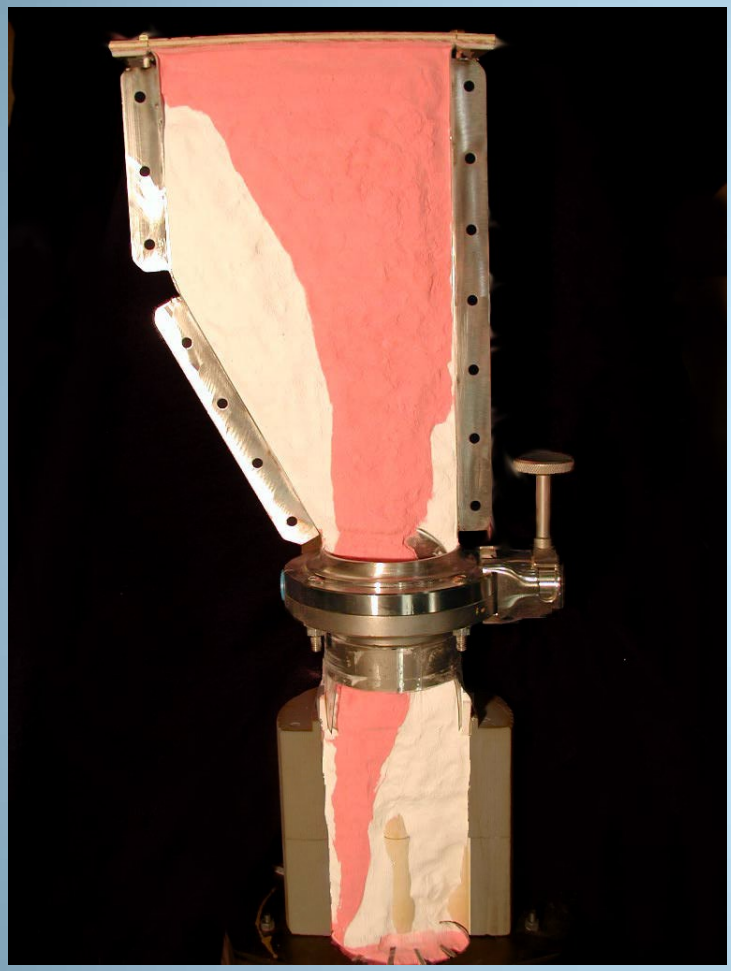
Funnel flow

- Features
  - *First-in, last-out* flow sequence: material at walls discharges last
  - Segregation often made worse
  - More likely to yield flow problems



Funnel flow containers

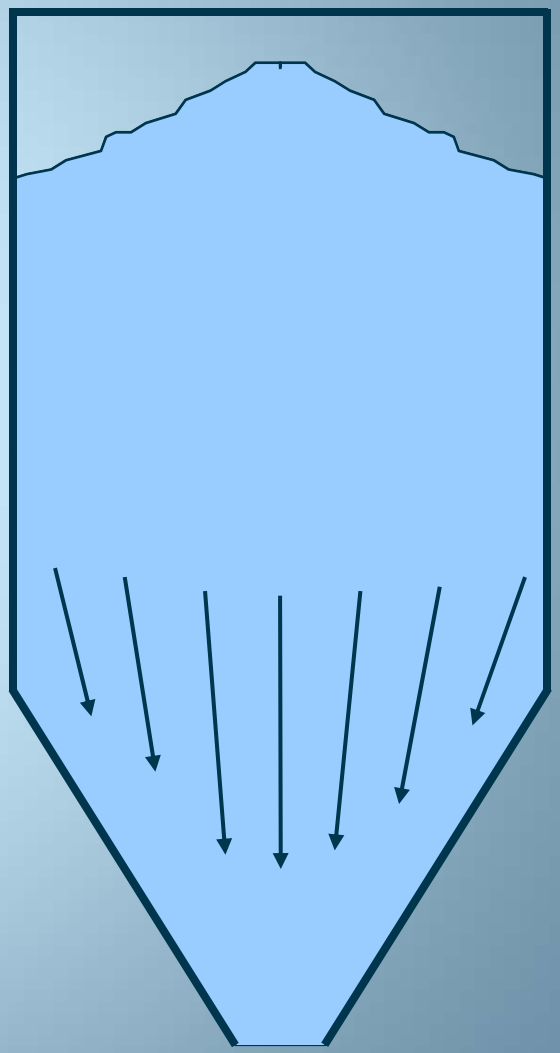
Funnel flow press hopper



Erratic flow of granulation

Mass flow

- Features
  - *First-in, first-out* flow sequence: material moves as a mass
  - Segregation *generally* minimized
- Hopper angle & outlet size determined *a priori* by ASTM D 6128



Mass flow containers

Quantify flowability

- Use lab-scale tests to predict what will happen at the manufacturing scale
- Quantified, absolute dimensions/angles
- ASTM Standards:
  - D6128 Direct Shear (Jenike)
  - D6682 Rotational Shear Cell (Peschel)
  - D6773 Ring (Annular) Shear Cell (Schulze)

Measuring Powder Flow

- Non-predictive:
  - Angle of repose
  - Flow funnel
  - Minimum orifice diameter
  - Bulk density (e.g. Hausner ratio)
- Def. *Non-predictive*:

  Test results cannot be used conclude whether the material will or will not flow reliably in a given process, absent of substantial empirical data.

USP <1174> Powder Flow

- Angle of repose
  - “Angle of repose is not an intrinsic property of the powder; i.e., it is very much dependent upon the method used to form the cone of powder”
- Compressibility
  - “Compressibility index and Hausner ratio are not intrinsic properties of the powder; i.e., they depend on the methodology used”

USP <1174> Powder Flow

- Flow through an orifice
  - "General Scale of Flowability for Flow Through an Orifice
    - No general scale is available because flow rate is critically dependent on the method used to measure it. Comparison between published results is difficult.
  - Experimental Considerations for Flow Through an Orifice
    - Flow rate through an orifice is not an intrinsic property of the powder. It very much depends on the methodology used."

What Can Be Predicted?

- Flow pattern
- Angles required to achieve flow along walls (press hoppers, IBCs, transfer chutes)
- Outlet size needed to overcome arching and/or ratholing
- Maximum flow rate and flow rate stability

Measuring Powder Flow

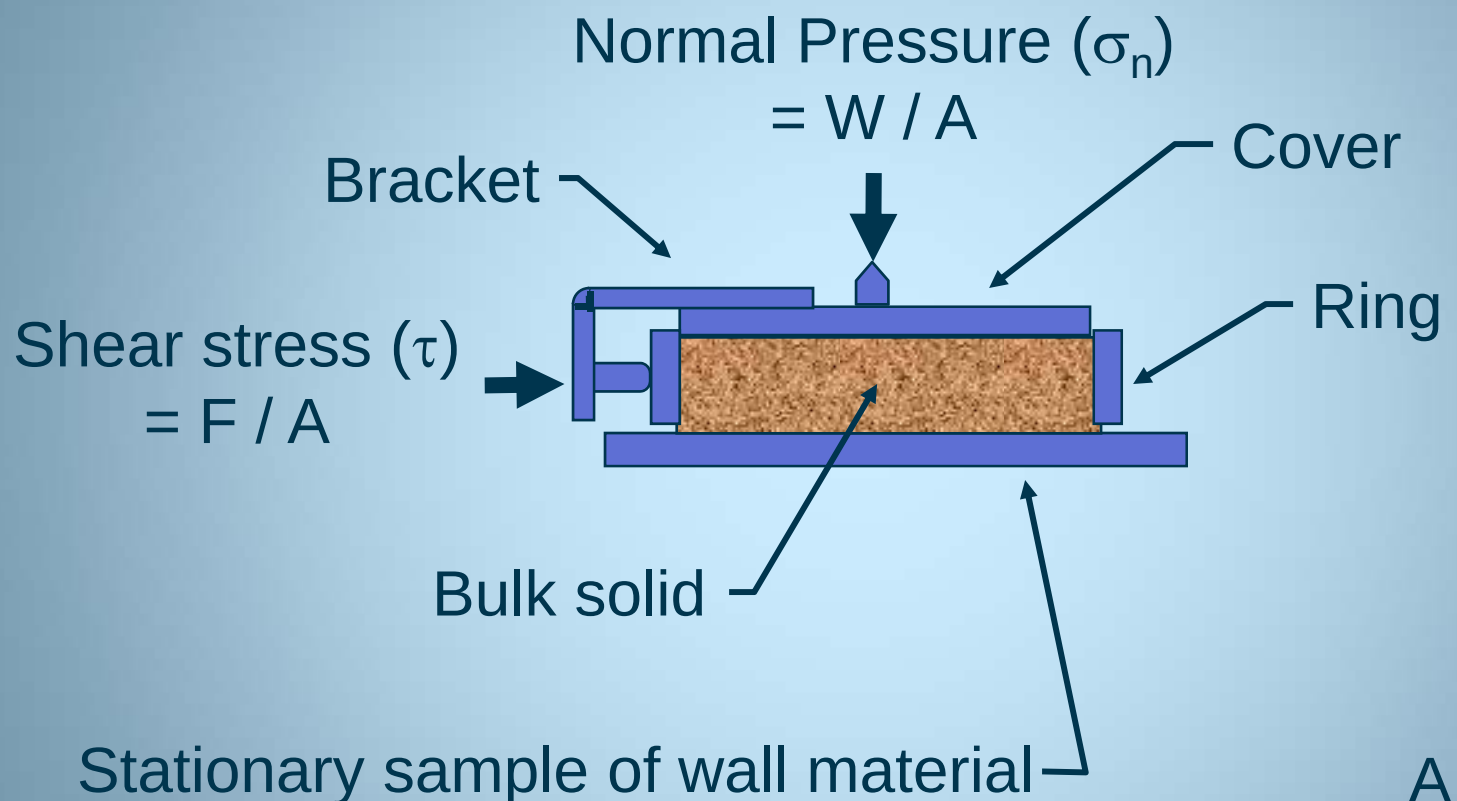
- Shear cells are a predictive technique
- The basics have been known for many years
  - Jenike, University of Utah “Bulletin 123”, 1964, http://www.utah.edu/uees/bulletin123.html

Flow Properties Tests

- Wall Friction
  - Achieve flow along the walls
- Cohesive Strength
  - Prevent arching

Jenike Direct Shear tester

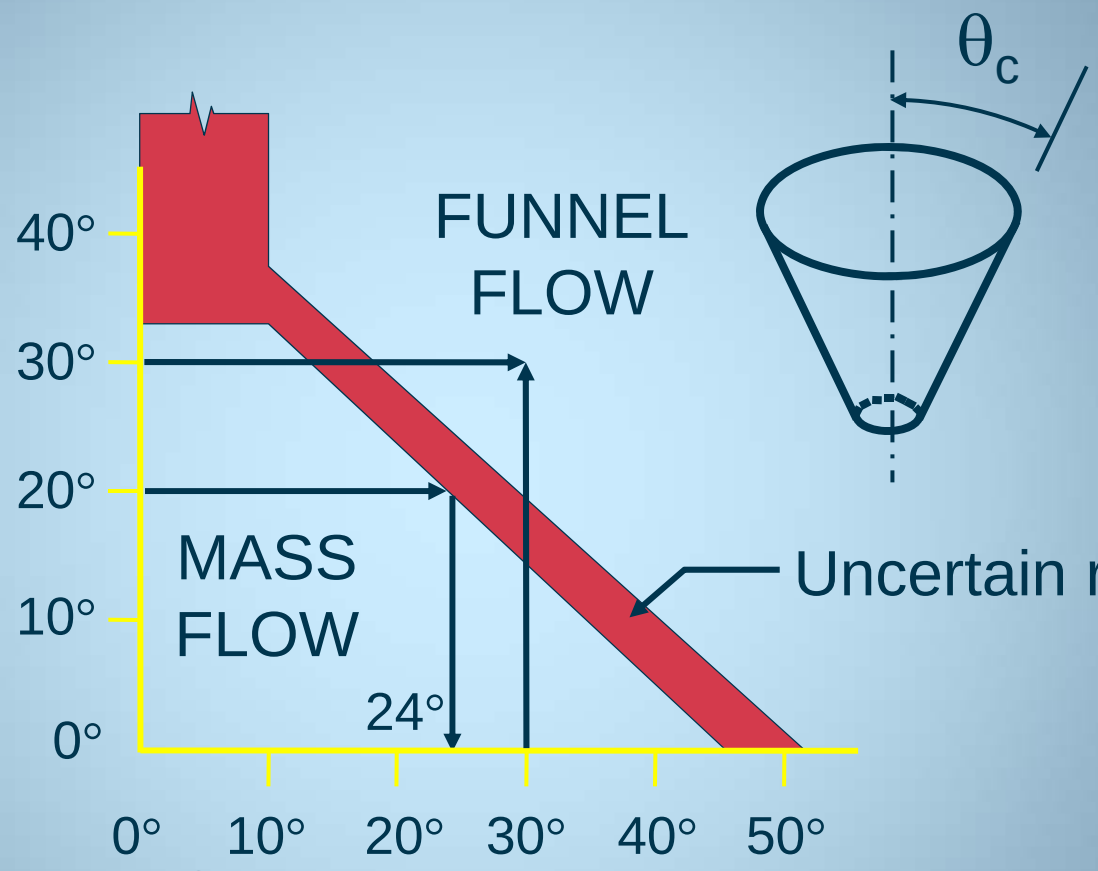
Wall friction test



A = Area
W = Weight
F = Force

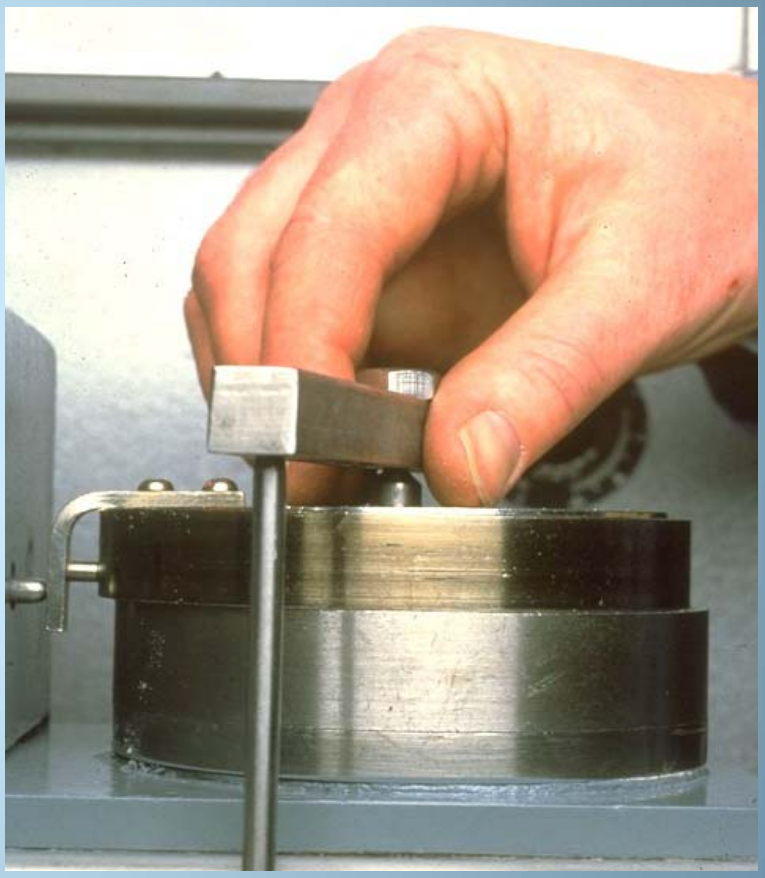
Conical hopper design chart

(Example - refer to Bulletin 123 for actual charts)

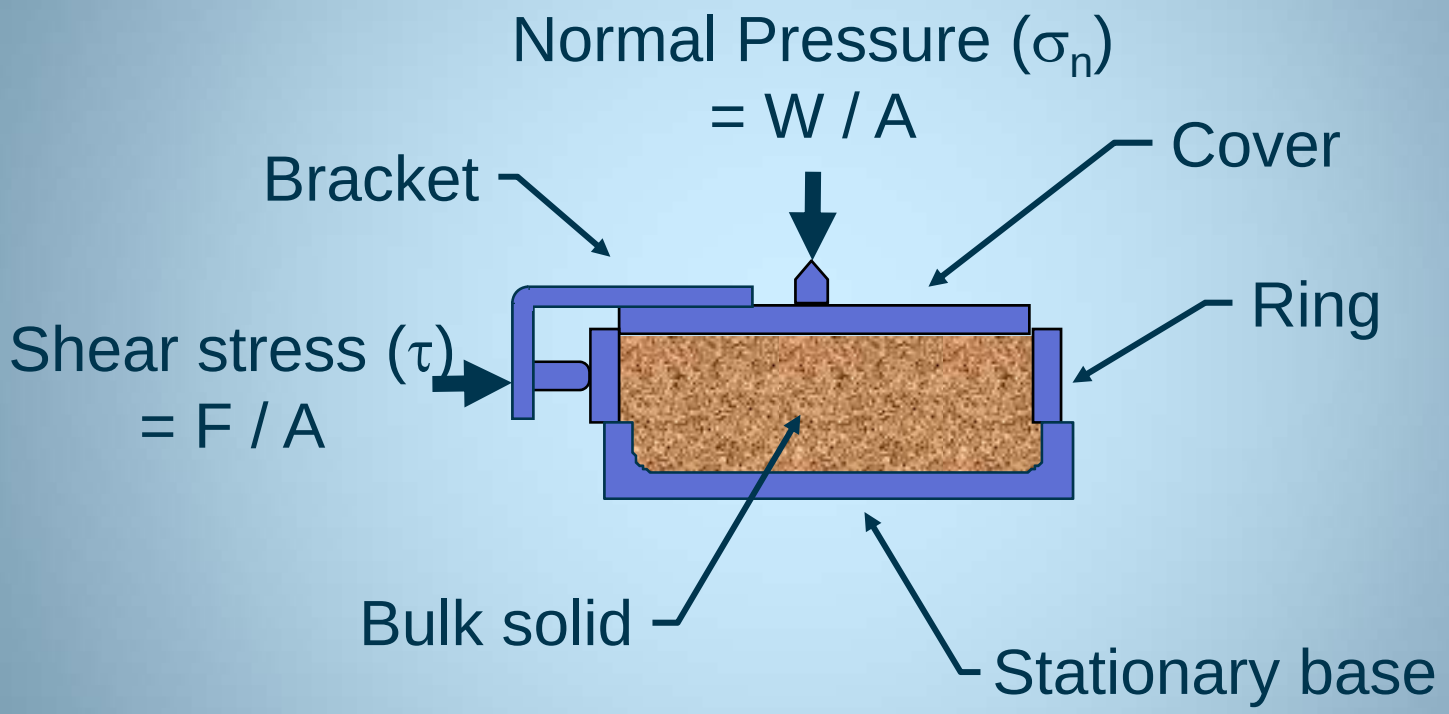


ϕ': Wall friction angle

Jenike Direct Shear tester



Direct Shear tester



Translational, Direct Shear Cells

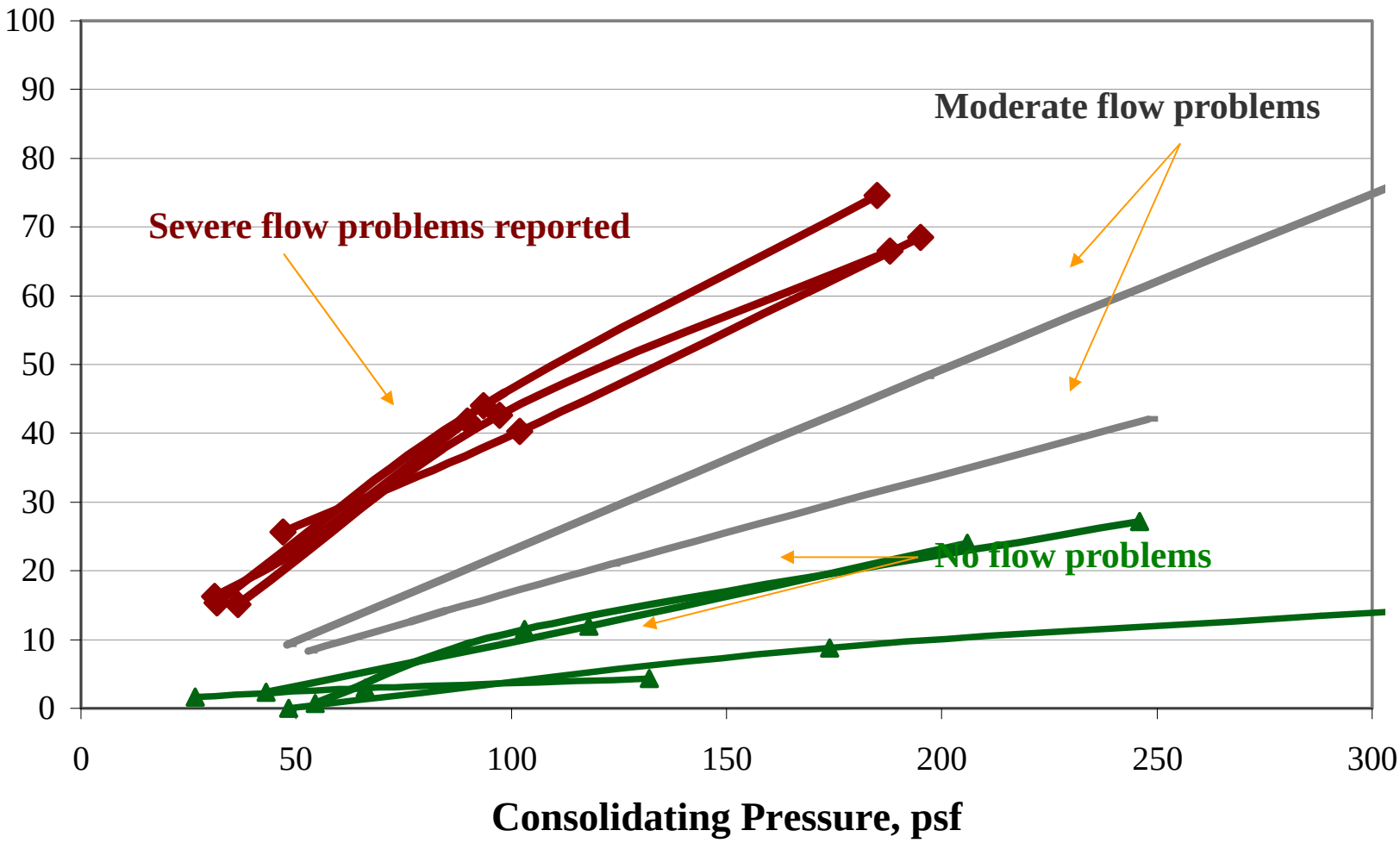
- Widely accepted in bulk solids handling circles
  - ASTM D6128 Direct Shear (Jenike), SSST EFCE
- …but not always adopted
  - Operator dependence (skill in conducting test)
  - Dead weights needed
  - Long time to conduct tests, labor-intensive
  - Limited travel to develop shear plane
  - Complexity of analysis, interpretation
  - Skill set: mechanical engineering; seldom found in an analytical lab in a pharmaceutical company
  - Low demand for equipment = limited commercial availability

Ring Shear Testers

- Automation
  - Faster, fewer cells needed, less skill/subjectivity, no weights required
- Analysis built into software
- Material sparing (<30 ml); compact tester
- Unlimited travel
- Standards:
  - D6773 Ring (Annular) Shear Cell (Schulze)
  - D6682 Rotational Shear Cell (Peschel)
- Several commercially available units

Jenike-Schulze RST-XS

Flow Functions for Various Materials



USP <1174> Powder Flow

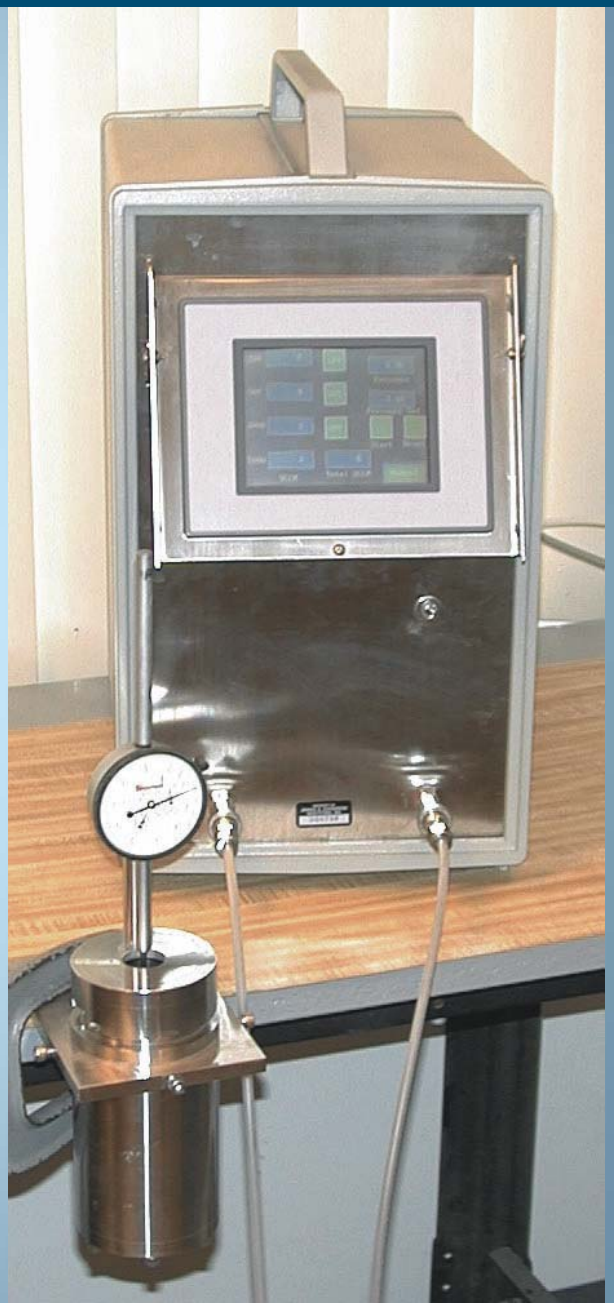
- "Shear cell methodology has been used extensively in the study of pharmaceutical materials. From these methods, a wide variety of parameters can be obtained, including the yield loci representing the shear stress-shear strain relationship, the angle of internal friction, the unconfined yield strength, the tensile strength, and a variety of derived parameters such as the flow factor and other flowability indices. Because of the ability to more precisely control experimental parameters, flow properties can also be determined as a function of consolidation load, time, and other environmental conditions. The methods have been successfully used to determine critical hopper and bin parameters."
- *Note*: the yield locus does not provide a stress/strain relationship. It provides a shear stress / normal stress relationship, specifically demarcating the point at which the powder bed yields (flows).

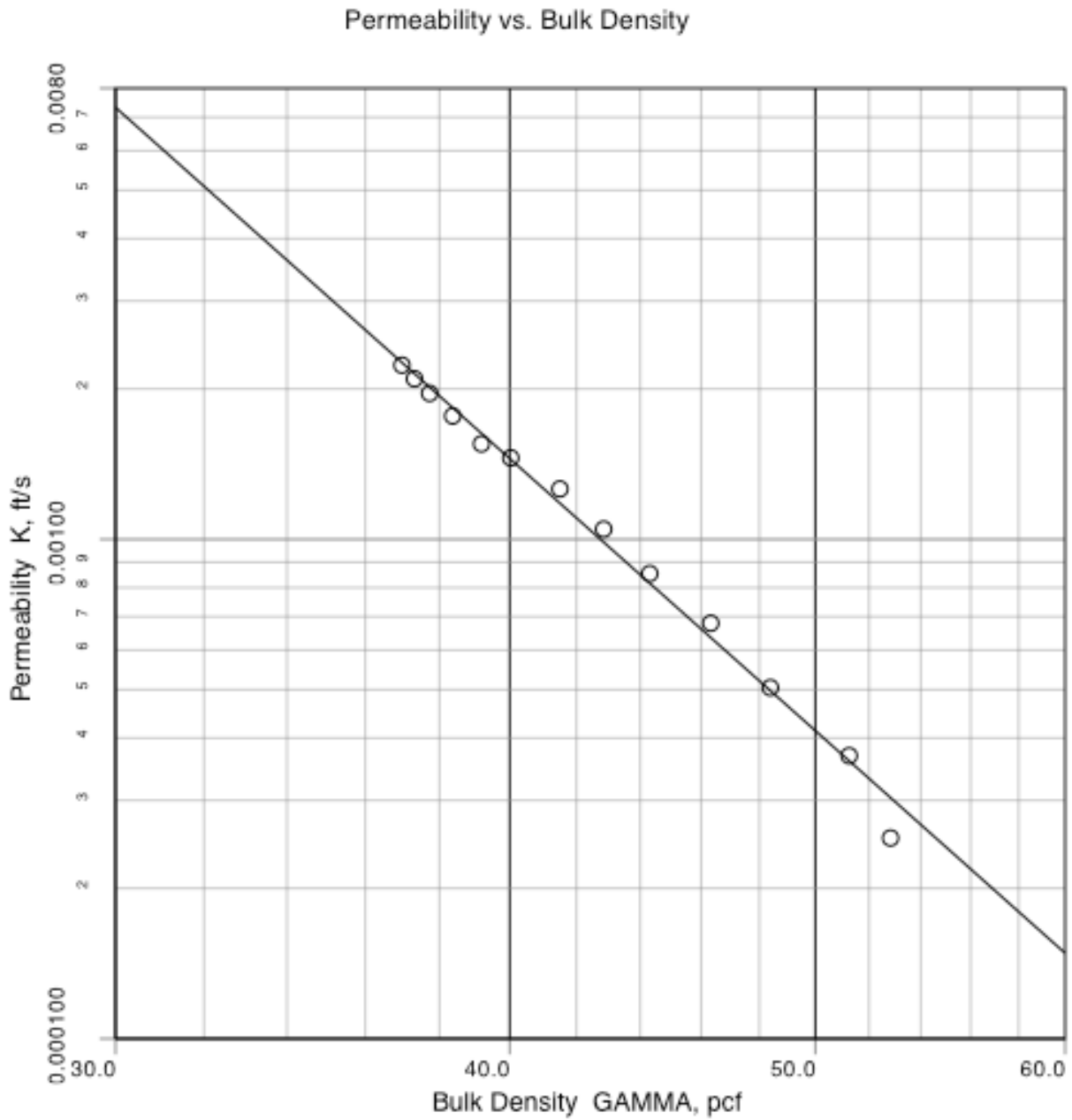
How about Flow *Rate*?

- Permeability and compressibility (bulk density) used for:
  - Maximum rate
  - Stability of flow
  - Settlement/deaeration time

Permeability Tester

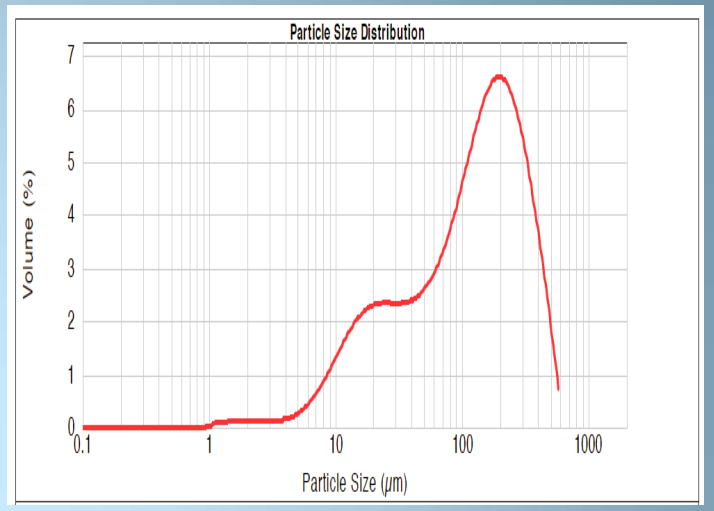
- Measures resistance to airflow through a contact bed of powder
- Permeability is a function of bulk density
- K0 is one of the constants that result from the test; Higher K0 means more permeable



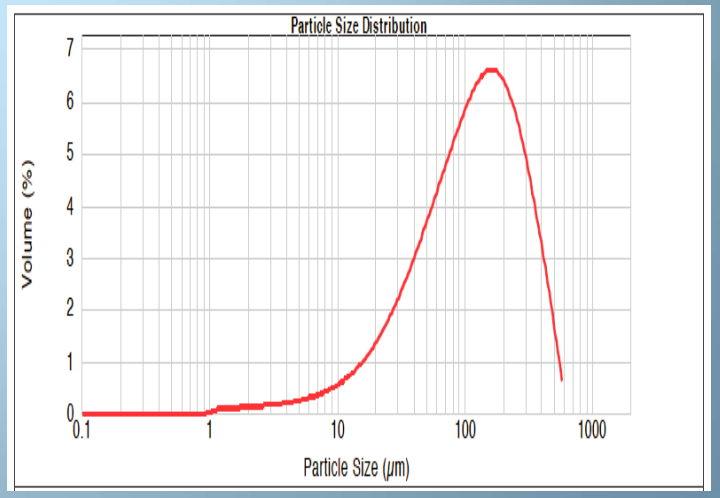

Permeability vs. Bulk Density
Permeability K, ft/s
0.0080
0.00100
0.000100
30.0
40.0
50.0
60.0
Bulk Density GAMMA, pcf

Case Study in Rate Limitation

- Before
  - d10: 16μ, d50: 125μ
  - K0: 0.0017 fps
  - Critical flow
    - Calculated: 60% of target
    - Actual: 75% of target



- After
  - d10: 26μ, d50: 119μ
  - K0: 0.0032 fps
  - Critical flow
    - Calculated: >110% of target
    - Actual: 100% of target (max)



Such a thing as *too* free-flowing?

- Extremely free flowing materials can:
  - Flow through small openings, including small gaps in equipment
  - Be very dusty
  - Be highly segregating
  - Flood, flush and have variable bulk density (if fine)
- … but they seem good at the lab scale

Define "segregation"

A powder segregates as a result of:

- Variations of properties of the particles
  - Physical/chemical properties, *e.g.* particle size distribution, shape, charge, cohesion
- Forces induced on the particles cause interparticle motion
  - Air flow, vibration, gravity, impact
- Fill & flow sequence (equipment specific)

Segregation mechanisms

- Particle entrainment
- Air entrainment
- Sifting
- Sliding on a surface
- Dynamic effects

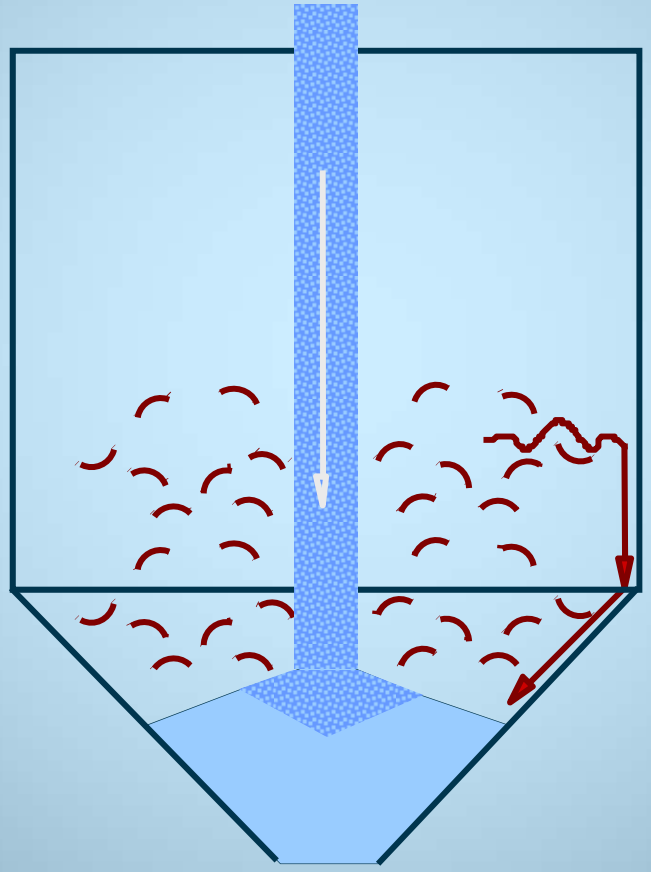
Segregation mechanisms

- Particle entrainment (dusting)

Segregation mechanisms

- Particle entrainment (dusting)
  - Particle entrainment requires:
    - Airborne particles
    - Differences in settling velocities
    - Air currents
  - Results in thin layer at walls, significantly different than bulk

Particle entrainment filling a bin

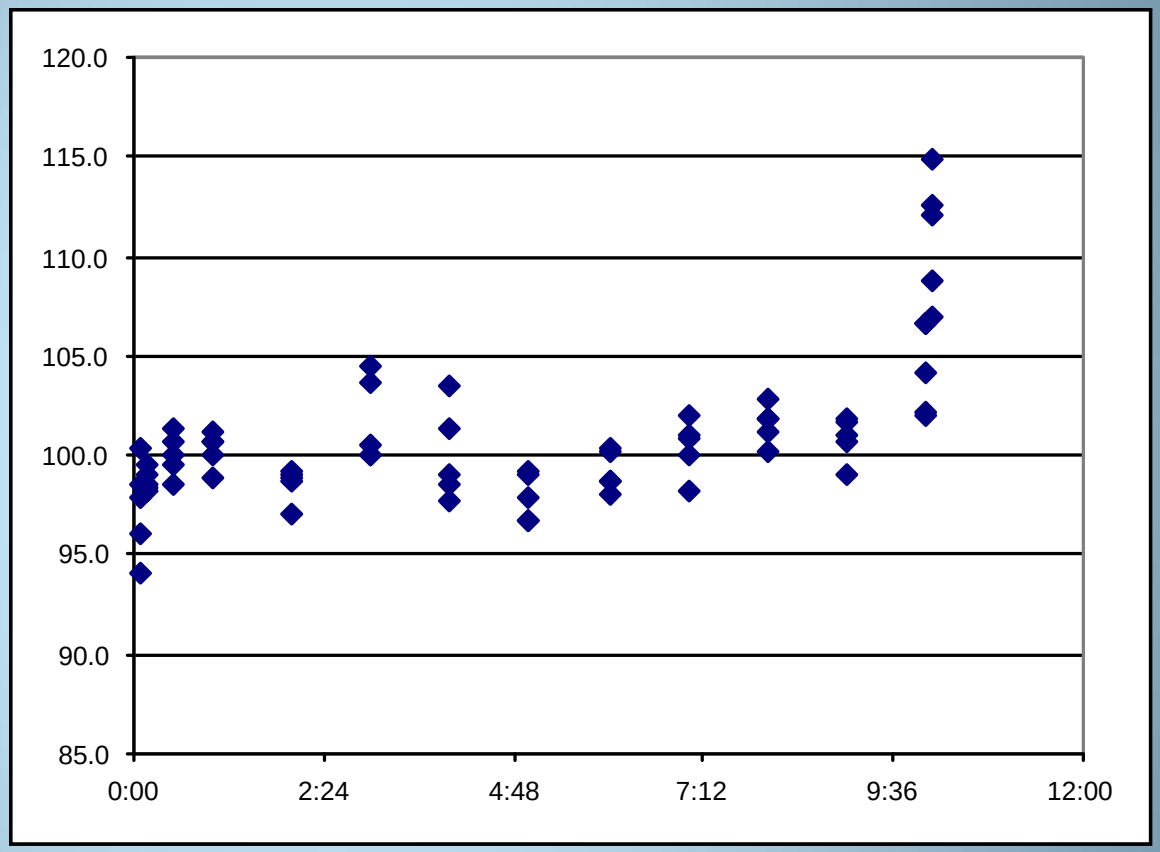


Particle entrainment filling a bin

Particle entrainment filling a bin

Dusting segregation results

Assay, % label



mean = 100.9, %RSD = 3.63

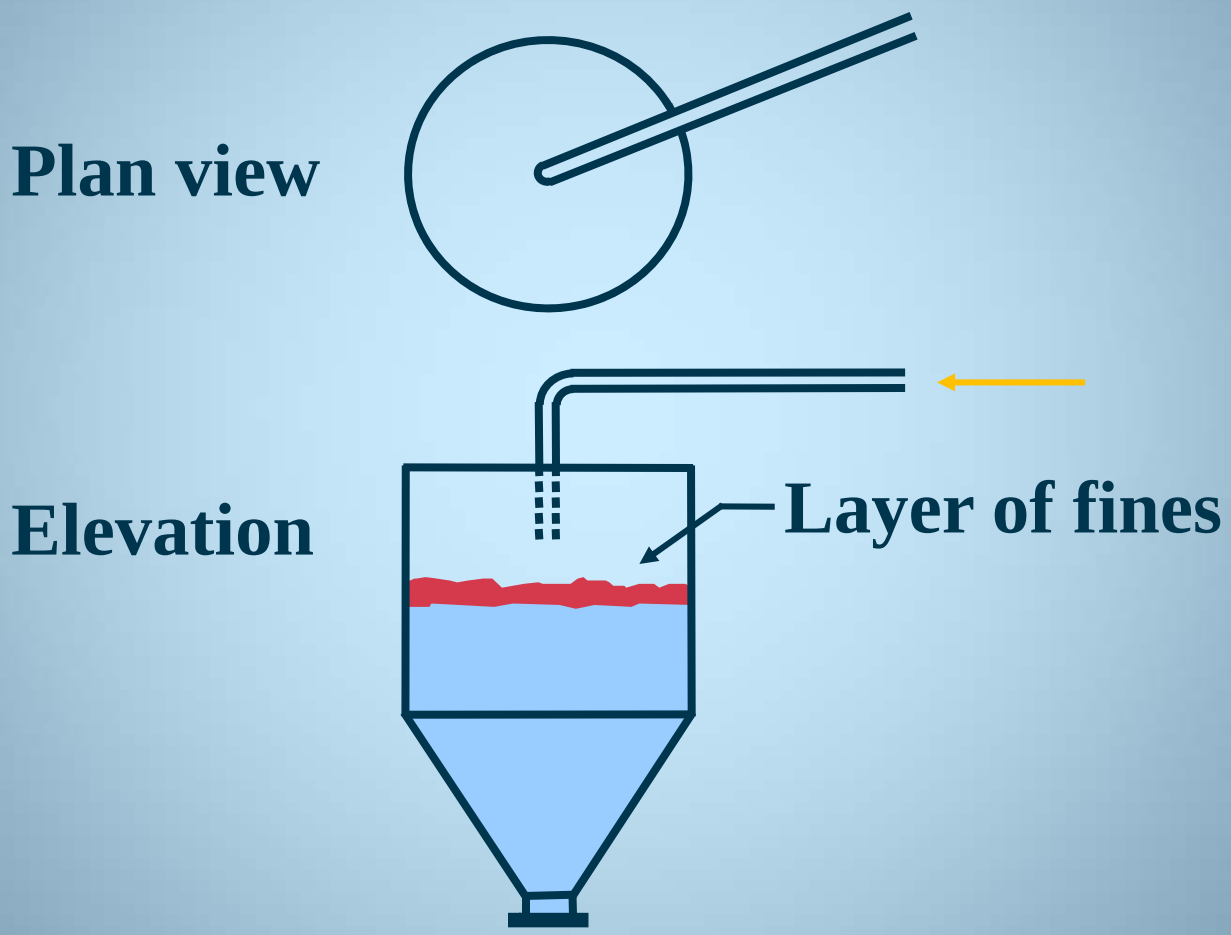
Segregation mechanisms

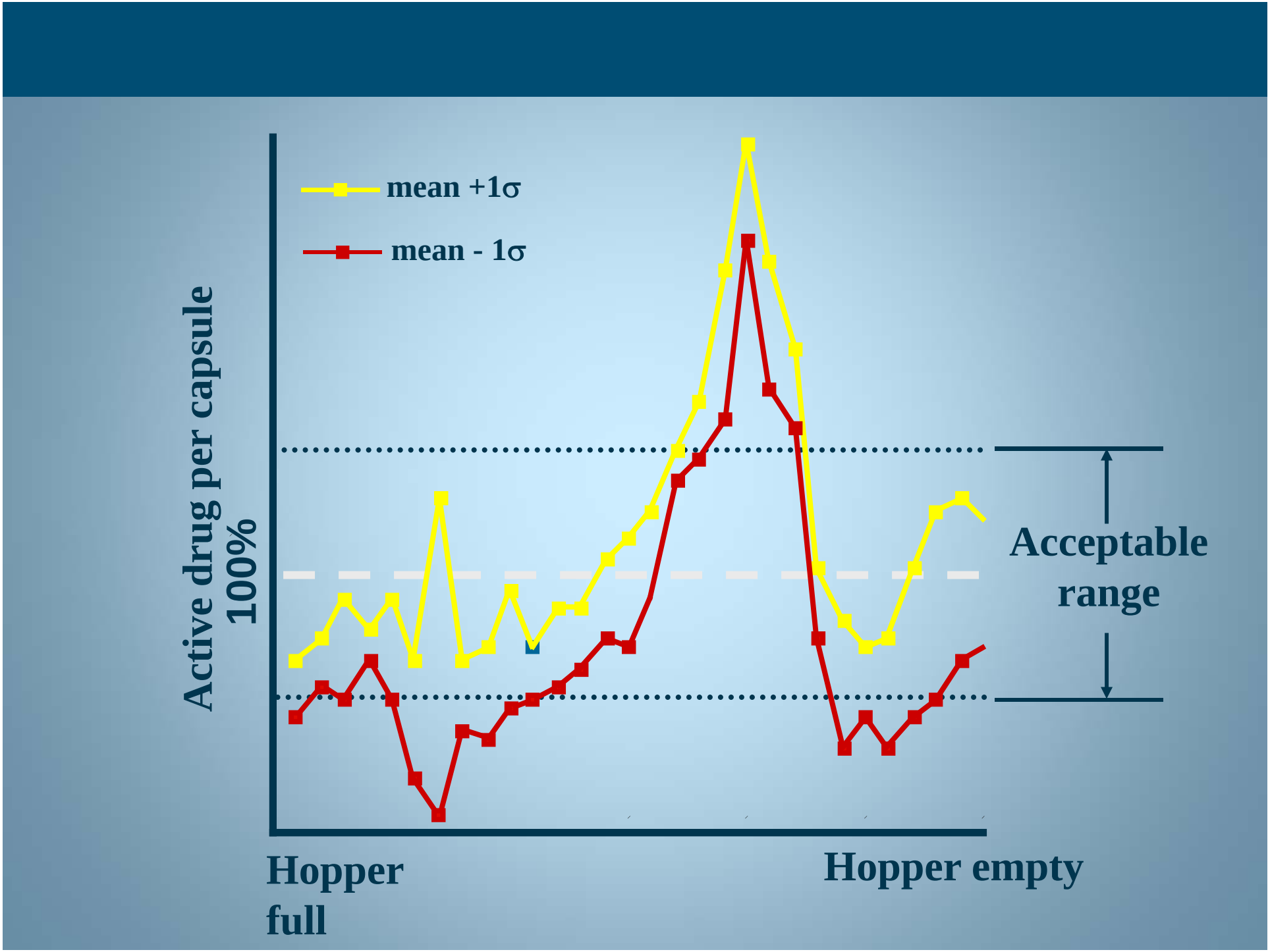
- Particle entrainment (dusting)
- Air entrainment (fluidization)

Segregation mechanisms

- Air entrainment (fluidization)
  - Air entrainment requires:
    - Fine particles
    - Excess air between particles
    - Air counterflow
  - Results in top-to-bottom differences; can also occur during pile formation resulting in side-to-side differences

Fluidization segregation during deaeration

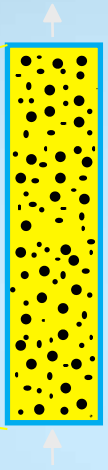


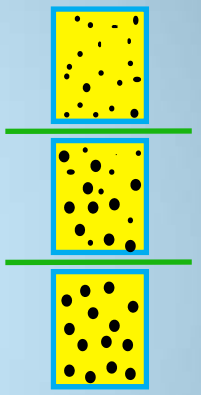

mean +1σ
mean - 1σ
Active drug per capsule
100%
Acceptable
range
Hopper
full
Hopper empty

Identifying potential problems

- No *first principle* predictors
- Segregation testers:
  - Are an empirical approach
  - Must isolate and reproduce the mechanism
  - Give, at best, a qualitative indication of the tendency to segregate
  - Can rank different formulations

Fluidization segregation test





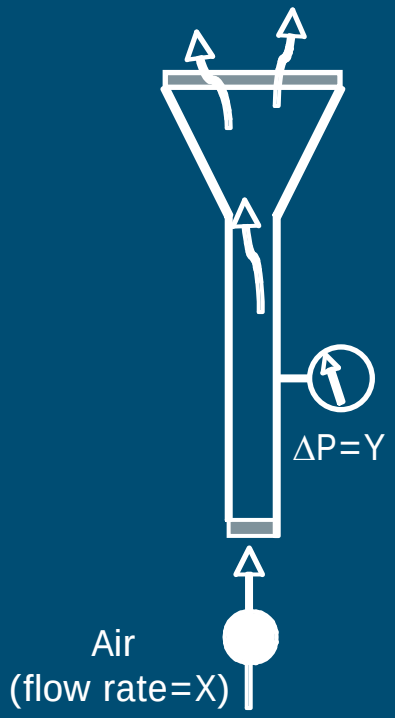
Column of material is fluidized

Column is split and each section is measured for segregation

ASTM Standard D 6941 – 03

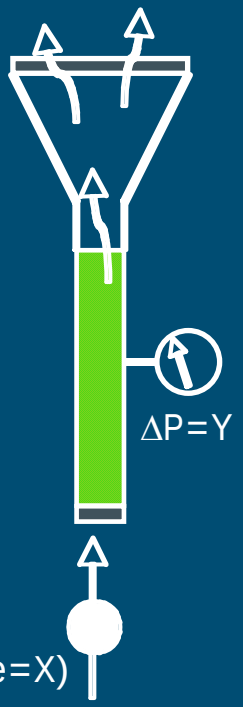
“FMSST”

Baseline readings

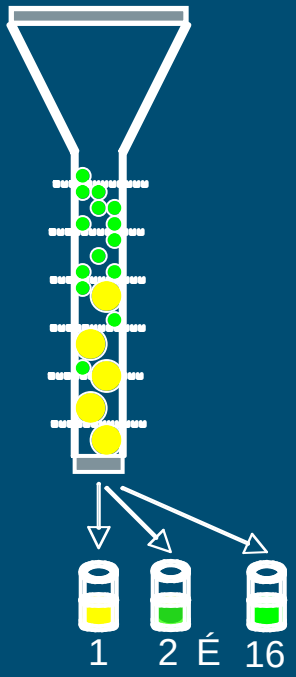


Filling

Test



Sample retrieval



<u>Instrumentation</u>
- air flow rate
- pressure drop across column

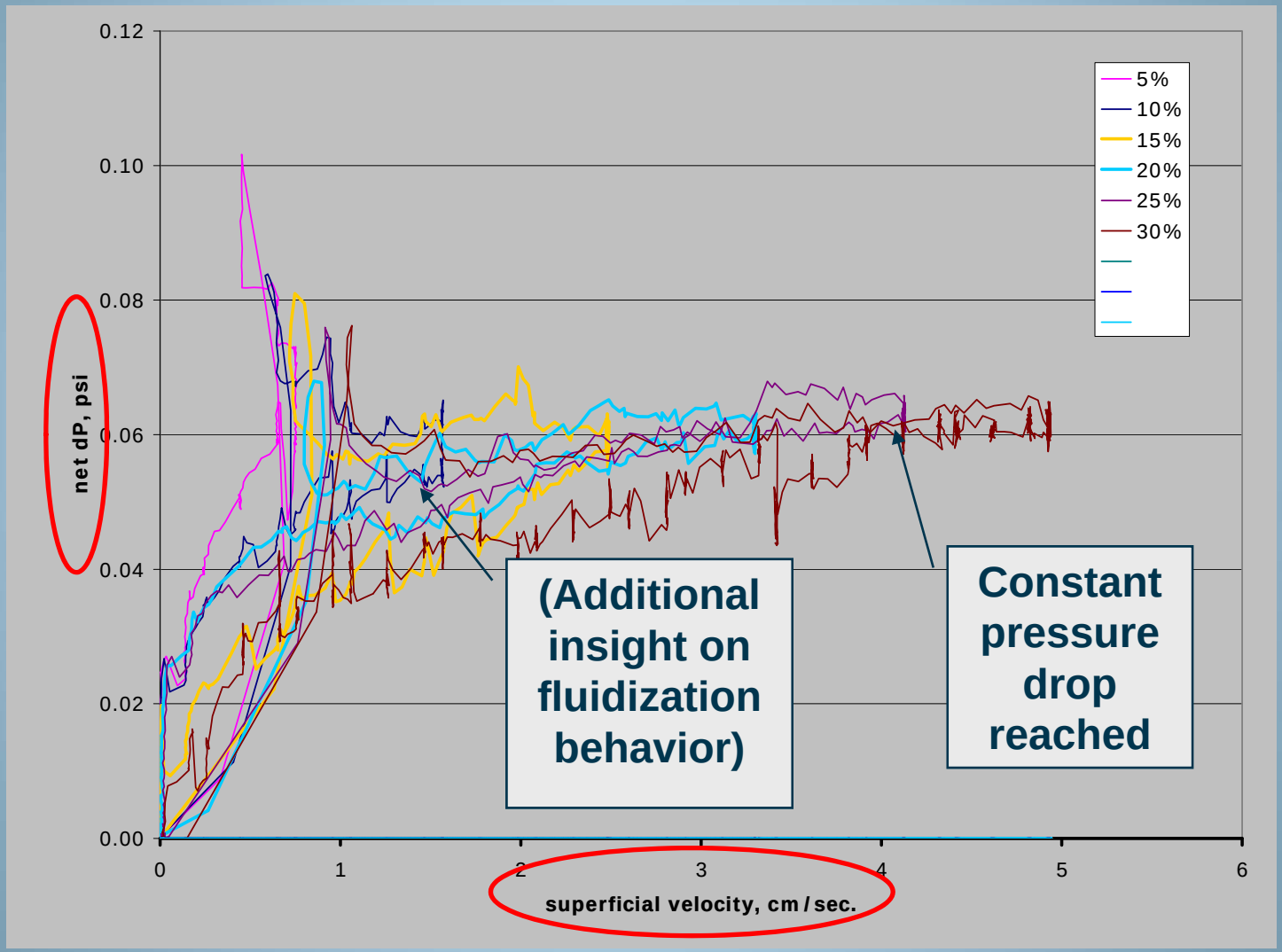
<u>Sample</u>
- ~15g
- loaded from above

<u>Fluidization</u>
- sample is fluidized (mixed) ($X>>U_{mf}$), and then allowed to settle slowly

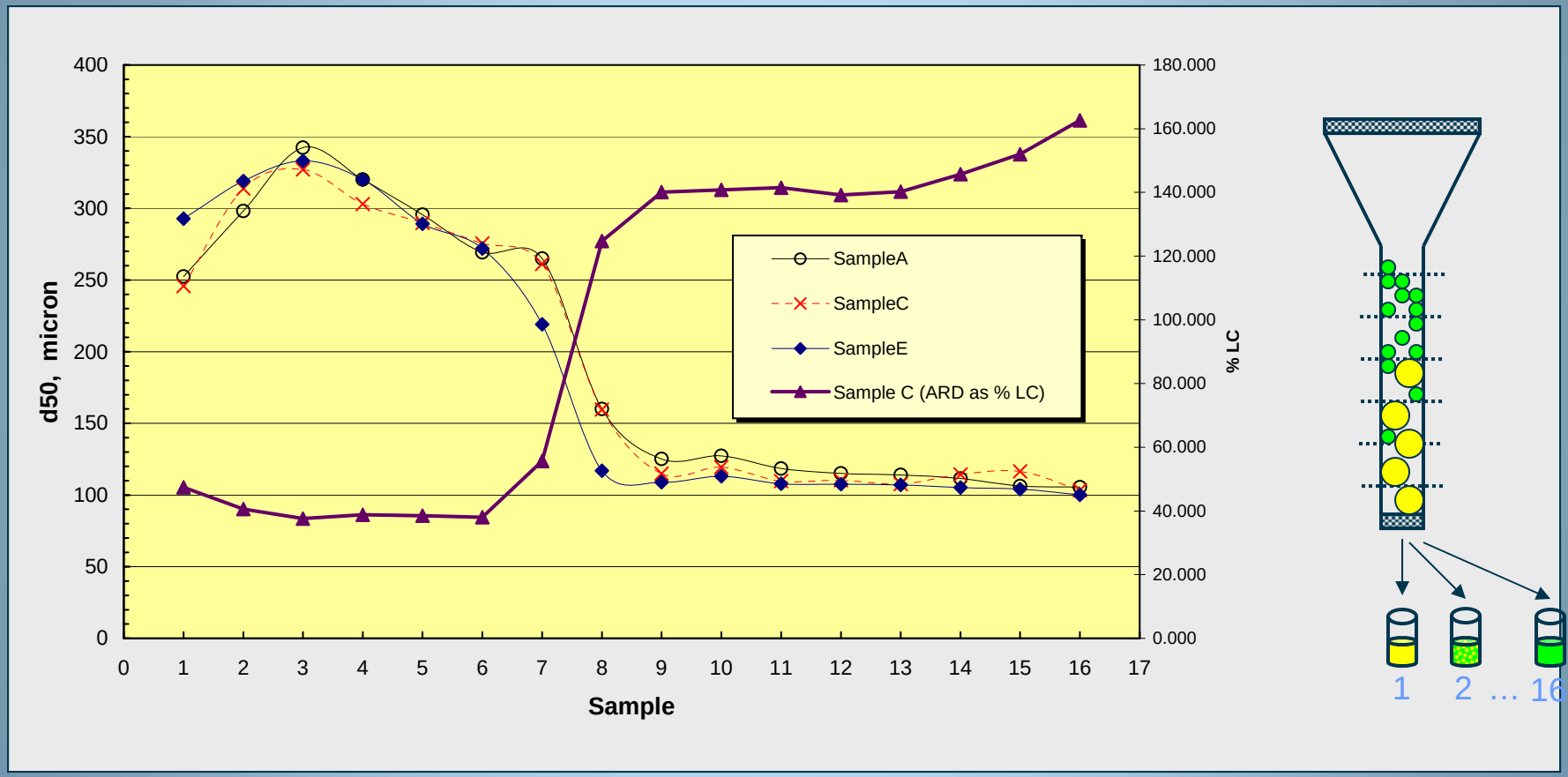
<u>Sample retrieval</u>
- unit dose samples (~500mg)
- from bottom of column
- ~16 horizontal layers (1=bottom, 16=top)


COMPAQ

Instrumentation & Controls



Typical Results



Segregation mechanisms

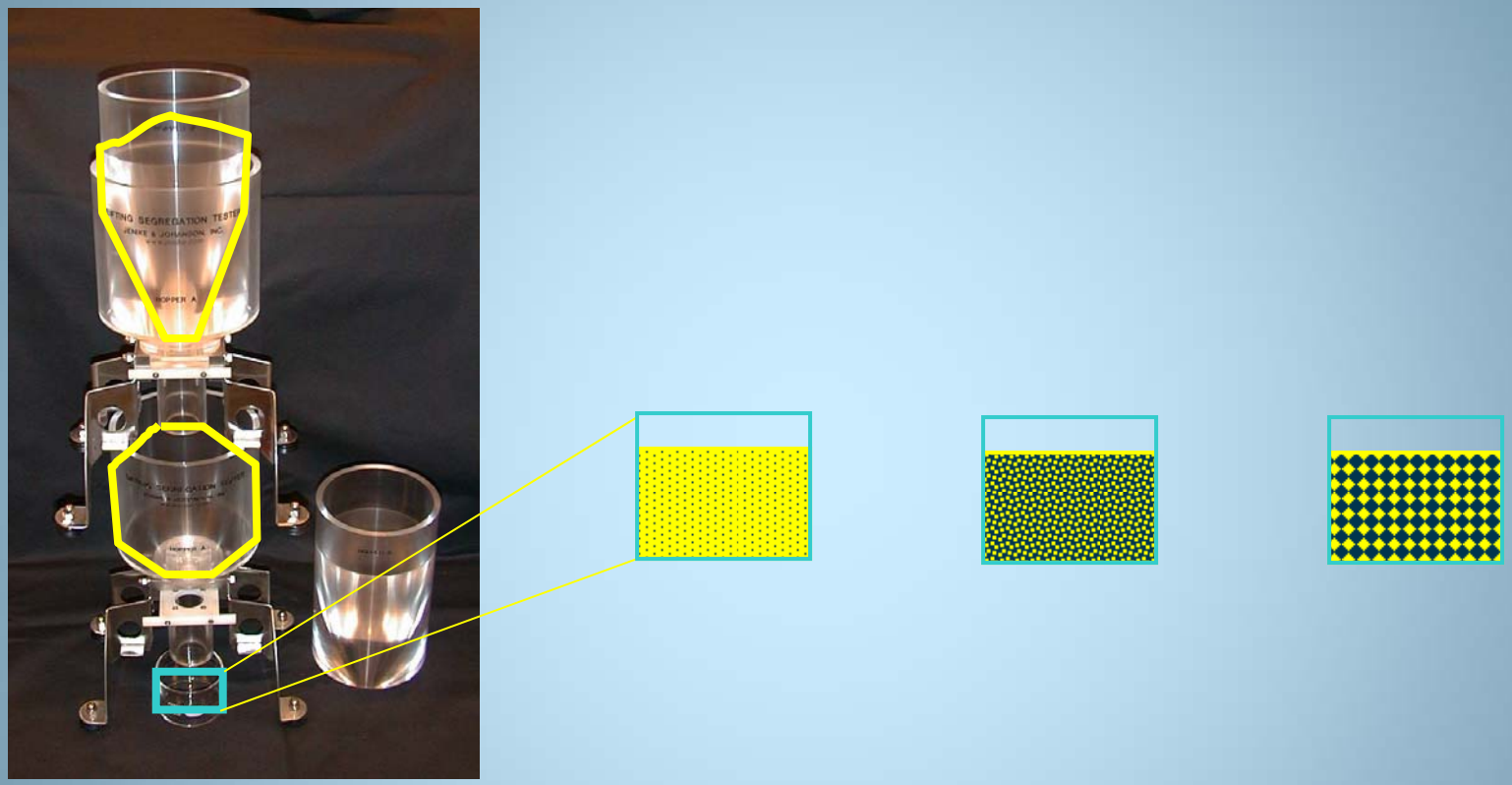
- Particle entrainment (dusting)
- Air entrainment (fluidization)
- Sifting

Sifting segregation

Segregation mechanisms

- Sifting
  - Sifting requires:
    - Particle size differences (little as 1.3:1)
    - “Large” particles (above 50 μ)
    - Free-flowing material
    - Interparticle motion
  - Results in center-to-perimeter (of pile) differences
  - Driven by geometric differences between particles (friction, density, momentum also play a role)

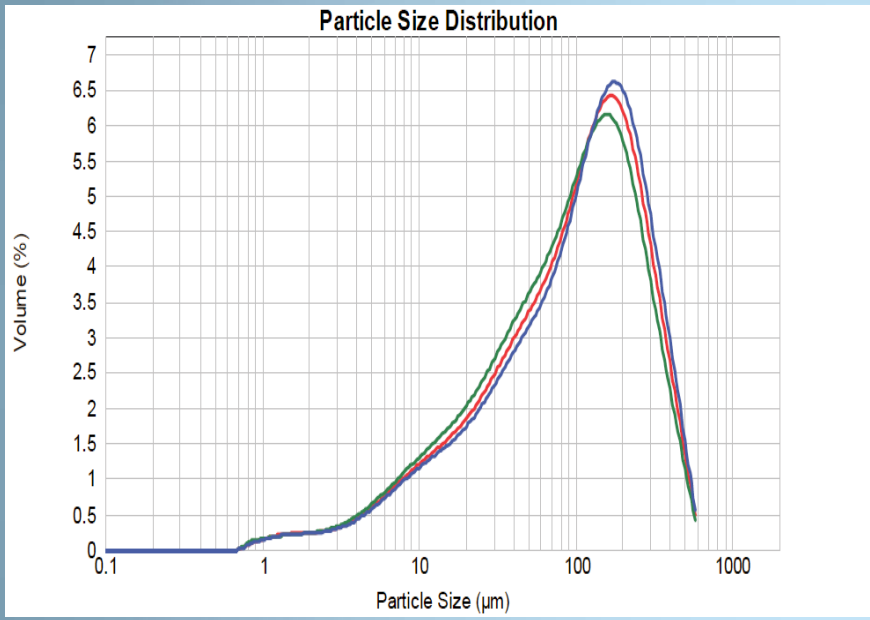
Sifting segregation test



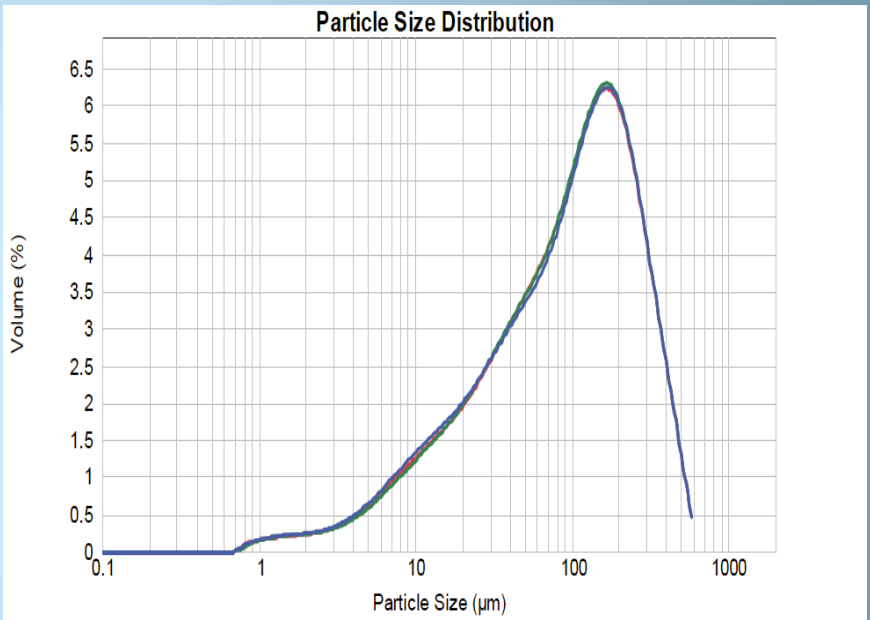
ASTM Standard D 6940 – 03

Low Fluidization/Low Sifting Potential

“Product B”



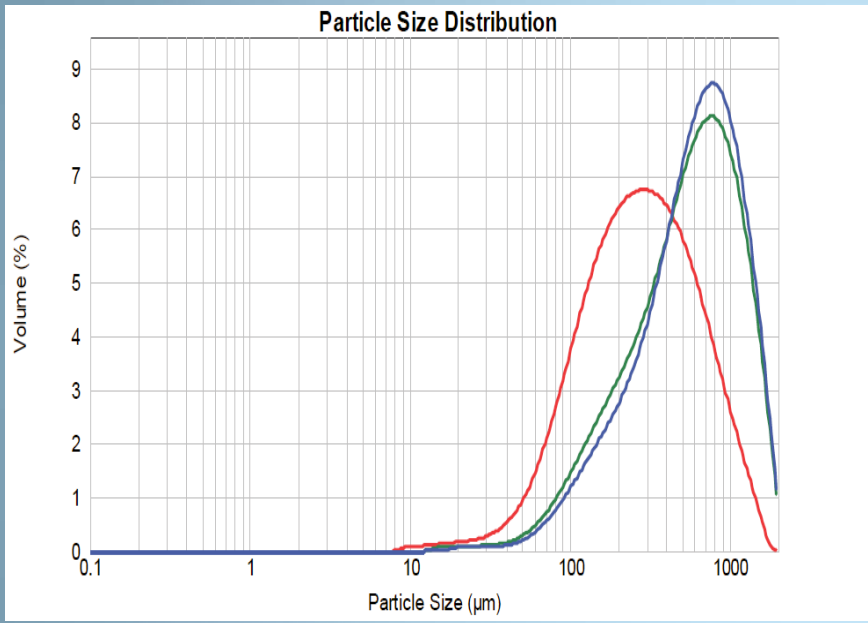
Fluidization segregation test
top=red, center=green, bottom=blue

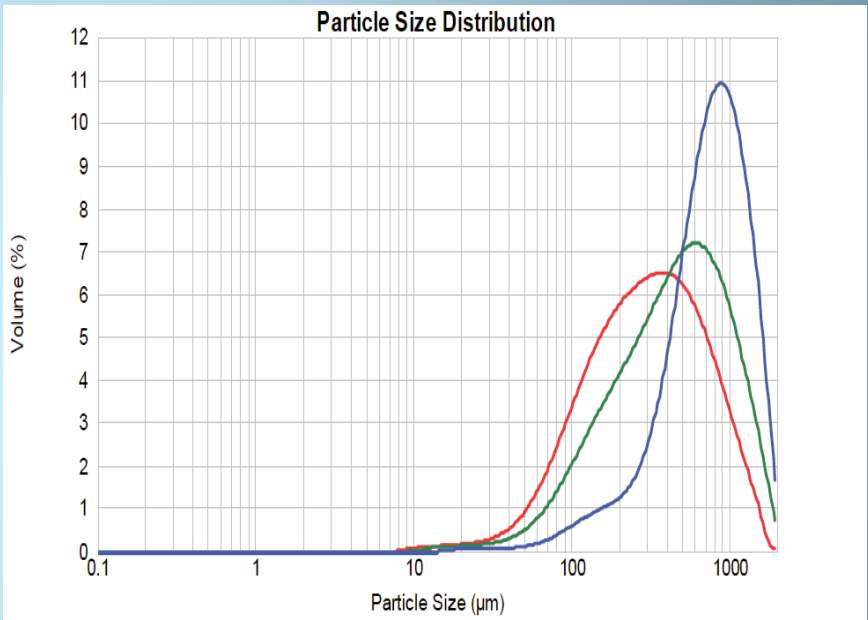


Sifting segregation test
first=red, middle=green, end=blue

High Fluidization/High Sifting Potential

“Product C”



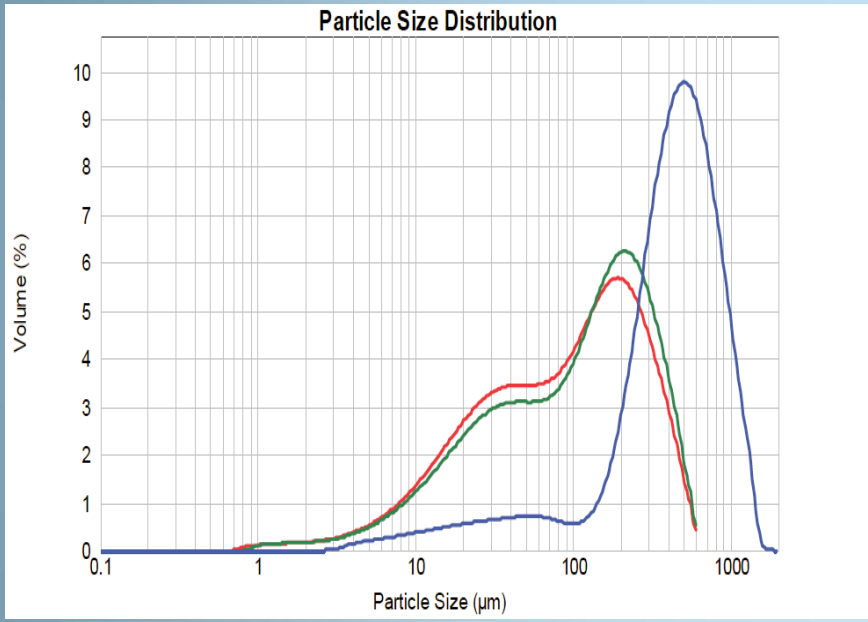


Fluidization segregation test
top=red, center=green, bottom=blue

Sifting segregation test
first=red, middle=green, end=blue

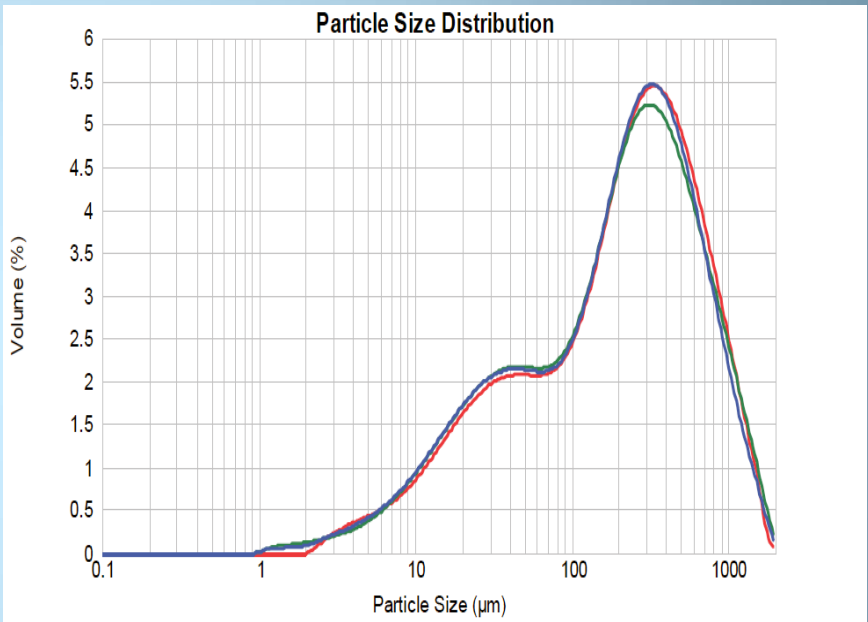
High Fluidization/Low Sifting Potential

“Product D”



Fluidization segregation test

top=red, center=green, bottom=blue



Sifting segregation test

first=red, middle=green, end=blue

What to do about segregation

- Change the blend to reduce segregation potential
  - Increase cohesion
  - Change particle size distribution or shape: active(s) and/or excipient(s)
  - Granulate material (wet/dry)
  - Ordered (structured, adhesive) blend

What to do about segregation

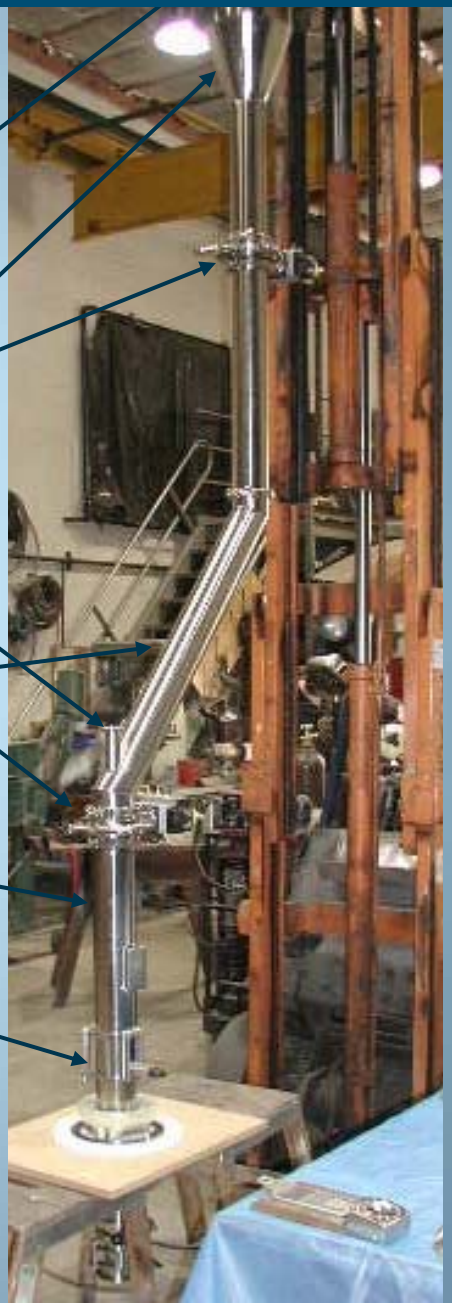
- Minimize the initial occurrence of segregation
  - Mix when needed (minimize transfer)
  - Prevent air flow through the material
  - Transfer “quietly”
  - Use a distributor
  - Proper chute and hopper design
  - Maintain symmetry

What to do about segregation

- Allow segregation, but provide remixing
  - Use mass flow
  - Use an insert
  - Control velocity profiles
  - Remix in-line

Chute Design to Reduce Segregation

- Vents for air escape
- Valves for step-down
- Mass flow hopper
- Proper chute angle
- Minimized diameter
- No protruding sensors
- Proper interior polish



Before and After:
Using Wall Friction Data

Left; original bin with rathole forming.
Right; replacement bin flowing in mass flow.

Other sources of variability

- Segregation often shows up as between location variation
- Within location variations:
  - sampler error
  - analytical error
  - weight variations
  - *“micro” non-uniformity of blend*

Characterization of data

Blend or ***Product***:

- Satisfactory
- High within-location variability
- High between-location variability
- Stray value
- Trending or hot spot
- Assay shift

Also consider:

- Prior history with this and similar products and processes; what is unique about this
- Recent changes
- Specifications
- Repeatability
- Observations and malfunctions
- RSD of blend vs. product vs. theory

Possible root causes

- Non-optimum blending
- Thief sampling error
- Segregation after discharge
- Product weight control
- Wrong mass/loss of component
- Analytical error- product/blend
- Insufficient particle distribution

Troubleshooting diagram

Solid Dosage and Blend Content Uniformity
Troubleshooting Diagram

This is not a stand-alone document; refer to "A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram" by J.K. Prescott and T.P. Garcia, *Pharmaceutical Technology* , March 2001






Steps 1 & 2: Describe the Product (dose) and Blend Data

(assumes nested sampling of product and blender)

1. First, describe the PRODUCT (see "Product and Blend Data Definitions " and Figs 1-6)

Product Trends	Mean of product	RSD of product within-loc.	RSD of product between-loc.
Satisfactory (1)	about 100%	low	low
Wide variability (2)	about 100%	HIGH	low
Wandering (3)	about 100%	low	HIGH
Stray value (4)	about 100%	HIGH locally	low
Trending (5)	about 100%	low	HIGH locally
Assay shift (6)	SHIFTED	low	low
No product data available yet (0)			

2. Next, describe the BLEND SAMPLES (see "Product and Blend Data Definitions " and Figs 1-6)

Blend Samples	Mean of blend	RSD of blend within-loc.	RSD of blend between-loc.	Probability of a single deterministic cause
Satisfactory (.1)	about 100%	low	low	ideal outcome
High within-location RSD (.2)	about 100%	HIGH	low	high
High between-location RSD (.3)	about 100%	low	HIGH	low
Stray value (.4)	about 100%	HIGH locally	low	medium
Hot spot (.5)	about 100%	low	HIGH locally	medium
Assay shift (.6)	SHIFTED	low	low	high
No blend data available (.0)	-	-	-	(is blend data needed?)
Satisfactory	about 100%	low	low	medium
High within-location RSD	about 100%	HIGH	low	high
High between-location RSD	about 100%	low	HIGH	medium
Stray value	about 100%	HIGH locally	low	low
Hot spot	about 100%	low	HIGH locally	low
Assay shift	SHIFTED	low	low	low
No blend data available	-	-	-	-
Satisfactory	about 100%	low	low	medium
High within-location RSD	about 100%	HIGH	low	low
High between-location RSD	about 100%	low	HIGH	high
Stray value	about 100%	HIGH locally	low	low
Hot spot	about 100%	low	HIGH locally	medium
Assay shift	SHIFTED	low	low	low
No blend data available	-	-	-	-
Satisfactory	about 100%	low	low	medium
High within-location RSD	about 100%	HIGH	low	medium
High between-location RSD	about 100%	low	HIGH	medium
Stray value	about 100%	HIGH locally	low	medium
Hot spot	about 100%	low	HIGH locally	medium
Assay shift	SHIFTED	low	low	low
No blend data available	-	-	-	-
Satisfactory	about 100%	low	low	high
High within-location RSD	about 100%	HIGH	low	low
High between-location RSD	about 100%	low	HIGH	low
Stray value	about 100%	HIGH locally	low	low
Hot spot	about 100%	low	HIGH locally	low
Assay shift	SHIFTED	low	low	high
No blend data available	-	-	-	-
Satisfactory	about 100%	low	low	-
High within-location RSD	about 100%	HIGH	low	-
High between-location RSD	about 100%	low	HIGH	-
Stray value	about 100%	HIGH locally	low	-
Hot spot	about 100%	low	HIGH locally	-
Assay shift	SHIFTED	low	low	-

Step 3: Reference Number

Step 4: Correlate the Data with Possible Root Causes ; continue with Steps 5 and 6 below

Probability is given on a scale of 0 - 4 (see Key)

Non-optimum blending	Thief sampling error (can only explain the blend)	Segregation after discharge (can only explain the product)	Product weight control	Wrong mass/loss of component	Analytical error (product/blend) Product / Blend	Insufficient particle distribution
0	0	0 if adequate product sampling	0	0	0 0	0
2 poor blend w/ reblending during handling	4 sampling error	0 if adequate product sampling	0	0	0 2 poor powder sample handling	1
3 poor blend w/ reblending during handling	1	0 if adequate product sampling	0	0	0 0	0
1	2	0 if adequate product sampling	0	0	0 3 single error	3 agglomerated active (esp. if spike>150%)
2 poor blend w/ reblending during handling	3 biased location	0 if adequate product sampling	0	0	0 0	0
0	4 biased sampling	0 if adequate product sampling	0	0	0 2 poor powder sample handling	0
-	-	0 if adequate product sampling	0	0	0 -	1
2 poor microblending w/ false blend data	2 counterfeiter- false satisfactory	3 segregation close to press	3 poor fill due to flow	0	1 0 esp. if different analytical methods	1
3 poor microblending	2	1	1	0	1 0 poor powder sample handling	4 large PS active w/ low dose
3 macro non-uniformity	0	2	2 poor fill due to flow	0	0 0	1 large PS active w/ low dose
2 possible dead spot	2	2	2 poor fill due to flow	0	0 2 explains blend, not product	3 agglom or large PS active w/ low dose
3 dead spot	0	2	2 poor fill due to flow	0	0 0	1
1	2 biased sampling	3	2 poor fill due to flow	0	0 1	1
3 poor microblending	-	2 investigate blend, particle distribution first	2 poor fill due to flow	1	0 -	3 agglom or large PS active w/ low dose
1 macro non-uniformity w/ false blend data	1 sampling error	4 seg. transfer, esp. if repeatable	2 poor control or overcontrol	0	0 0	0
2	3 sampling error	2 investigate blend first	2 poor control or overcontrol	0	0 1 poor powder sample handling	1 agglom or large PS active w/ low dose
4 macro non-uniformity	0	1 investigate blend first	1	0	0 0	0
2	1	2 investigate blend first	2	0	0 2 explains blend, not product	2 agglomerated active
2 macro non-uniformity	0	2 investigate blend first	1	0	0 0	0
1	3 biased sampling	3 seg. transfer, esp. if repeatable	2 poor control or overcontrol	2	0 1 explains blend, not product	0
4 macro non-uniformity	-	3 seg. transfer, esp. if repeatable	2 poor control or overcontrol	1	0 -	1
2 dead spot w/ false blend data	2 error-missed spot	3 accum. of one component; esp. at tails	1 problem w/ single punch or head	0	3 0 esp. if single dose	4 agglomerated active (esp. if spike>150%)
2 poor microblending	3 sampling error	1	1	0	2 1 multiple problems	4 agglomerated active (esp. if spike>150%)
3 dead spot(s)	0	1	1	0	1 0 esp. if single dose	2 agglomerated active (esp. if spike>150%)
3 dead spot	1	1	1	0	0 0 too coincidental	4 agglomerated active (esp. if spike>150%)
4 dead spot	0	1	1	0	0 0 too coincidental	2 agglomerated active (esp. if spike>150%)
2 dead spot	3 biased sampling	3 esp. if at tails	1	1	1 1 multiple problems	3 agglomerated active (esp. if spike>150%)
3 dead spot	-	2 investigate blend, analytical error first	1	0	0 - esp. if single dose	3 agglomerated active (esp. if spike>150%)
2 poor blend w/ false blend data	2 error-missed spot	4 segregation during transfer/ filling	2 weight varies due to segregation	0	0 0	0
1	3 sampling error	3 investigate blend first	1	0	0 1 poor powder sample handling	1
3 macro non-uniformity	0	2 investigate blend first	1	0	0 0	0
3 possible dead spot	1	3 investigate blend first	1	0	0 2 single error	1
4 macro non-uniformity	0	3 investigate blend first	1	0	0 0	0
1	3 biased sampling	4 segregation during transfer	2 weight varies due to segregation	1	0 1	0
3	-	4 segregation during transfer	2 weight varies due to segregation	0	0 -	1
0	0	0 if adequate product sampling	3 wrong setting	3 loss of active after blending	2 0	0
1	3 sampling error	0 if adequate product sampling	2 wrong setting	3 loss or low potency of active	2 1 poor powder sample handling	1
2	0	0 if adequate product sampling	2	3 loss or low potency of active	2 0 esp. if different analytical methods	0
2 possible dead spot	2	0 if adequate product sampling	2	3 loss or low potency of active	2 2	3 agglomerated active
2 macro non-uniformity	0	0 if adequate product sampling	2	3 loss or low potency of active	2 0	0
0	1 biased sampling	0 if adequate product sampling	1	4 dispensing error or potency	2 2 calibration, or bad standard	0
0	-	0 if adequate product sampling	2 wrong setting	4 dispensing error, or loss/potency	2 - calibration, or bad standard	1
1	1	- need dosage form data	- need dosage form data	1	- 0	1
3 poor microblending	4 sampling error	- need dosage form data	- need dosage form data	1	- 2 poor powder sample handling	3 agglom or large PS active w/ low dose
4 macro non-uniformity	0	- need dosage form data	- need dosage form data	0	- 0	0
2 possible dead spot	2 adhesion to thief	- need dosage form data	- need dosage form data	0	- 3 single error	3 agglomerated active
3 likely dead spot	1 biased location	- need dosage form data	- need dosage form data	0	- 0	2 agglomerated active
1	4 biased sampling	- need dosage form data	- need dosage form data	2 dispensing error	- 2 calibration or powder handling	1

Step 5. With Possible Root Causes Identified, Continue with Further Investigation

Non-optimum blending	Thief sampling error	Segregation after discharge	Product weight control	Wrong mass of component	Analytical error (product/blend)	Insufficient particle distribution
Review temporal data (see Figs. 7-10)	Use PDA "Technical Report No. 25"	Conduct segregation tests	Normalize data to weight	Sample dust collector	Perform OOS investigation	Review PSD of active(s)
Review scale-up techniques	Collect larger samples	Conduct flow properties tests	Investigate powder flow of components	Collect and assay dust in room	Review sample preparation, handling	Review active concentration (# particles/dose)
Review loading of blender	Use a different thief	Analyze fill and discharge sequence	Conduct flow properties tests	Measure adhesion to surfaces	Conduct a methods comparison	Obtain photomicrographs/SEM's
Review blender operation	Conduct segregation tests	Sample likely hot spots	Investigate powder flow of blend	Investigate stability of active	Test duplicate samples	Consider active potency
Use PDA "Technical Report No. 25"	Consider static electricity	Review equipment design	Is data cyclical?	Challenge suitability of method	Review reference standards	Seek agglomerates
Use a different thief	Aggressive in-process product testing	Consider discharge rates	Check each station or head	Perform reconciliation studies		Statistically analyze particle distribution
Collect larger samples		Consider material observations		Review weigh-out procedures		Consider environmental factors
Perform intensified sampling		Consider static electricity		Check potency of drug substance		
Consider order of addition		Evaluate environmental factors				

Step 6: With Additional Data to Support Root Cause, Consider Possible Solutions

Non-optimum blending	Thief sampling error	Segregation after discharge	Product weight control	Wrong mass of component	Analytical error (product/blend)	Insufficient particle distribution
Use a different blender type	Collect larger samples	Redesign handling equipment	Improve powder flow	Modify dust collection / containment	Conduct training	Mill one or more components of the blend
Change the blend cycle	Use a different thief	Reformulate	Different paddles/feed frame	Change active (increase stability)	Use different lab equipment	Screen and remove large particles
Consider an intensifier bar	Reformulate	Consider particle size changes	Modify feeder/hopper	Change environment	Use improved sample handling methods	Increase particle count
Change the fill method	Intensified in-process product testing	Conduct training	Change feed rates	Modify surfaces	Use a spinning riffler to divide powder samples	Increase active loading
Reformulate	Conduct training		Consider flow aid devices	Granulate the material		Reformulate
Change loading (% fill) of blender	Define sampling procedures		Process changes (larger particle size)	Conduct training		Increase shear in blender
Consider prelending			Reformulate			
Consider baffles			Glidant addition			

Key to Probabilities of Possible Root Causes

- **4** Highly likely root cause. Start here first.
- **3** Likely, seek supporting data.
- **2** Good chance, but keep your eyes open for other possibilities.
- **1** Not likely, rule out other reasons first; multiple root causes may be present.
- **0** Very unlikely, seek other reasons; multiple root causes may be present.

Some additional considerations:

- Is this a new product or an existing one with a significant body of data?
- Has this problem been seen with this product or one similar to it?
- What is unique or different about this product or process?
- Have materials, processes, operators, equipment or environmental control changed recently?
- How do the physical characteristics of materials used for this batch compare to what was intended?
- Is the problem repeatable among multiple batches or was this an isolated incidence?
- Did the operators observe any anomalies during the manufacture of the batch?
- Were any equipment malfunctions encountered?
- Compare the mean of product to the mean of blend
- Compare the RSD of product to the RSD of blend

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Pharmaceutical Technology

www.pharmaportal.com

V-blender and thief photos courtesy Dr. Fernando Muzzio

Additional references for each root cause are given in " **A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram** " by J.K. Prescott and T.P. Garcia in the March 2001 *Pharmaceutical Technology*)

Any Questions?

James Prescott

Senior Consultant

Jenike & Johanson, Inc.

Tyngsborough, MA

Use of Artificial Intelligence Tools in Pharmaceutical Applications

"EXPERT SYSTEMS"

Metin Çelik, Ph.D.

PTI, Inc

Metin.Celik@pt-int.com

www.pt-int.com

What is an expert system?

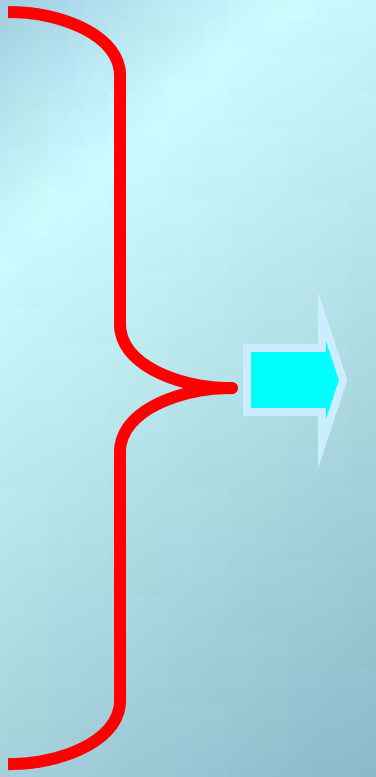
An expert system is a computer program capable of making recommendations or decisions based on knowledge gathered from experts in the field.

Why build an expert system?

- Replacement of an expert
  - Make expertise available anywhere/anytime
  - Automate a routine task requiring an expert
  - Expert is retiring or leaving or expensive
  - Expertise is needed in a hostile environment
- Assisting an expert
  - to improve productivity in some routine tasks
  - to manage the complex projects effectively
  - to access information that is difficult to recall
- Reduce cost of product development
- Use as a training tool

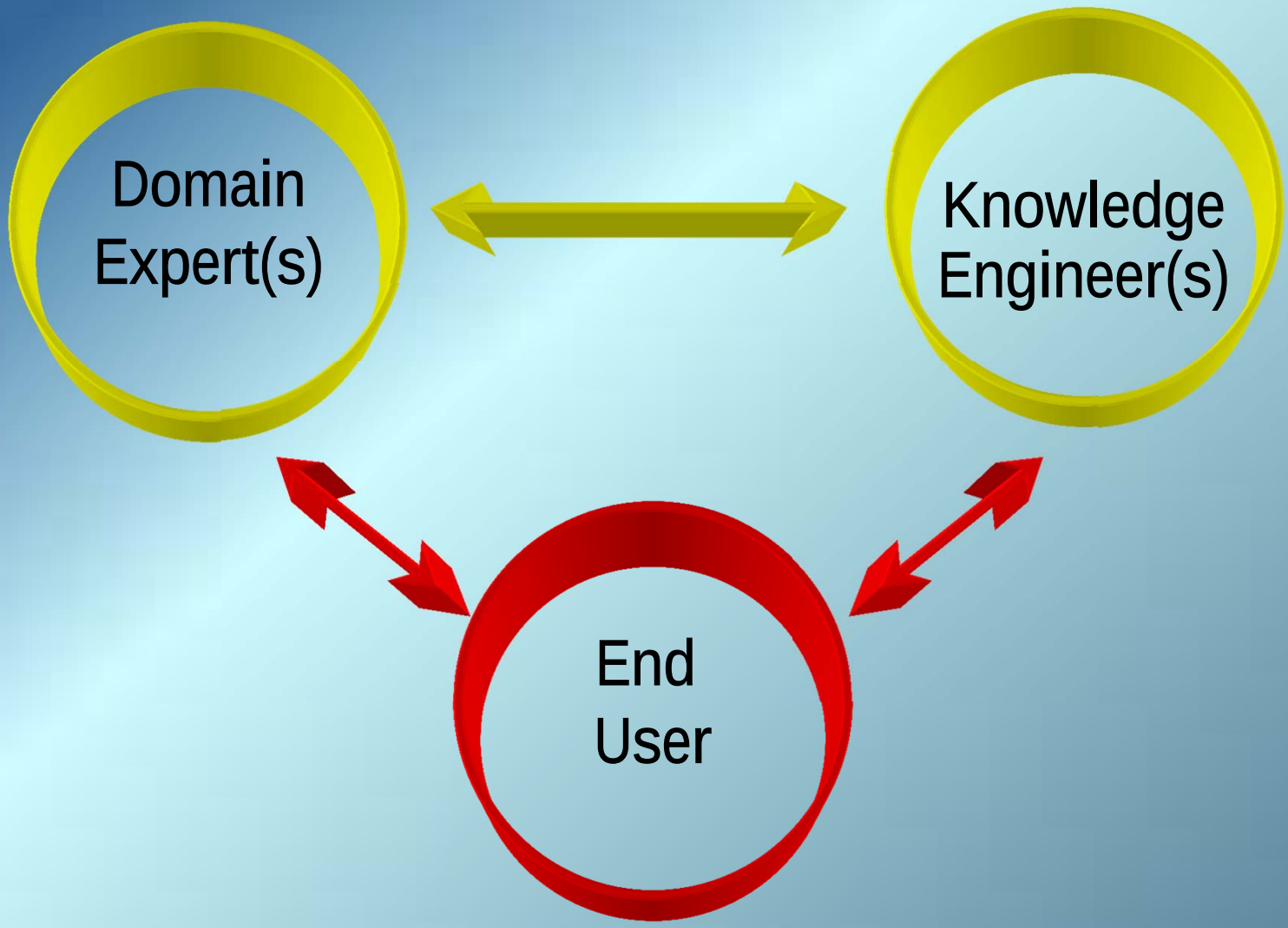
Why built an expert system?

- Documentation
- Organization
- Project Planning
- Training
- Linking
  - Cross Functional
  - External



Corporate Memory

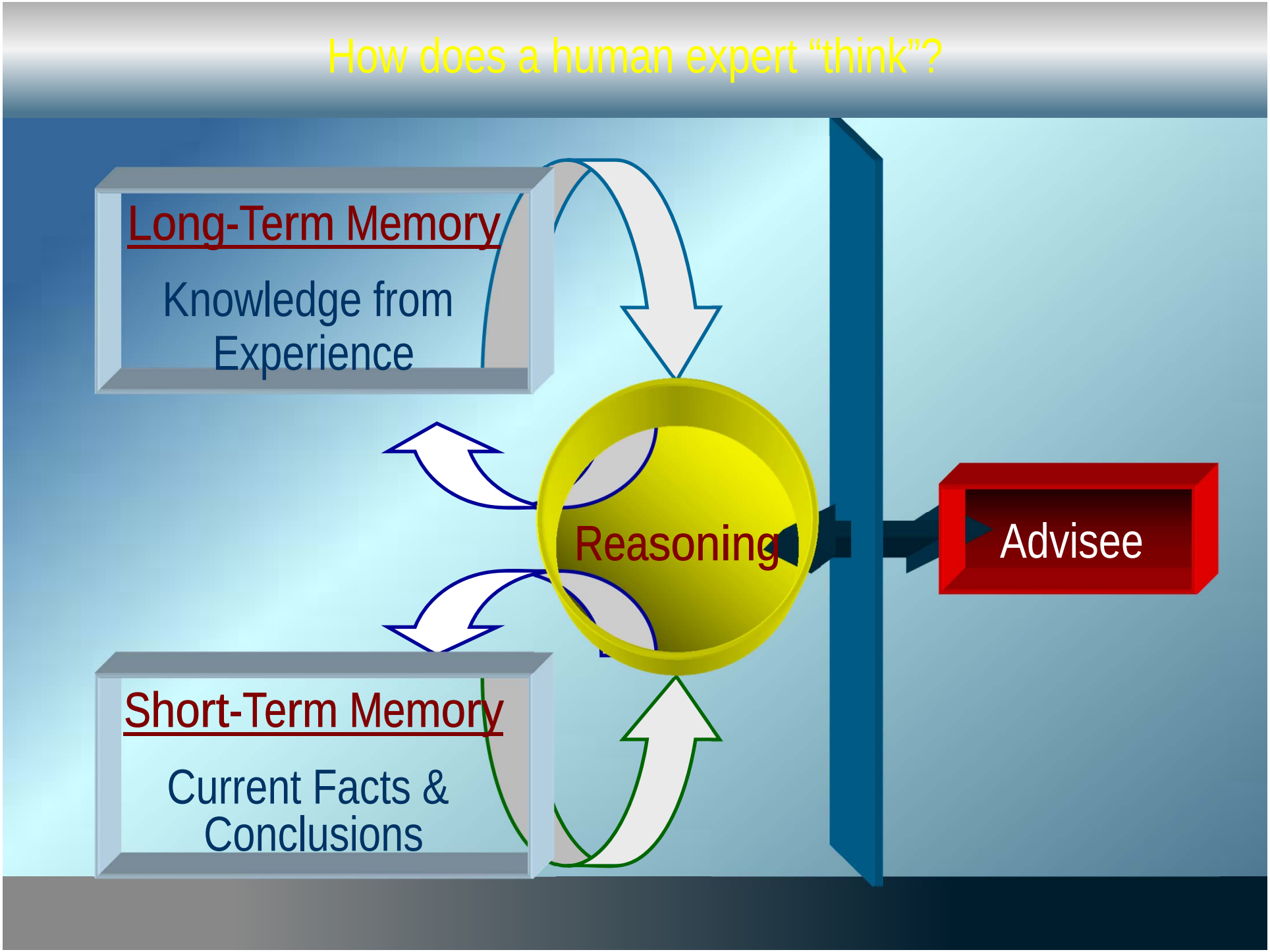
Building an expert system:



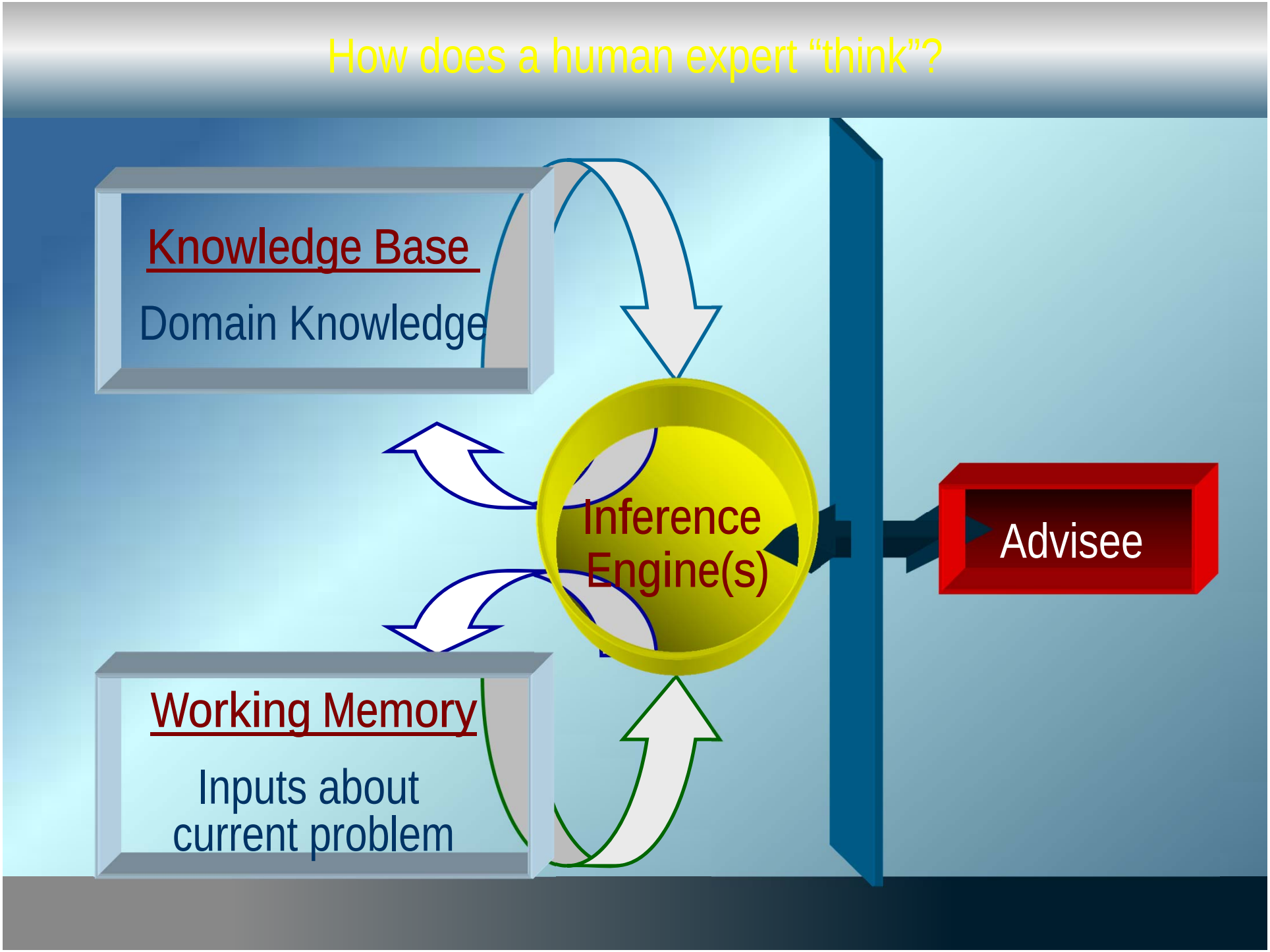
What is a domain expert?

Domain Expert is a person who possesses the skill and knowledge to solve a specific problem in a manner superior to others.

How does a human expert “think”?



How does a human expert “think”?

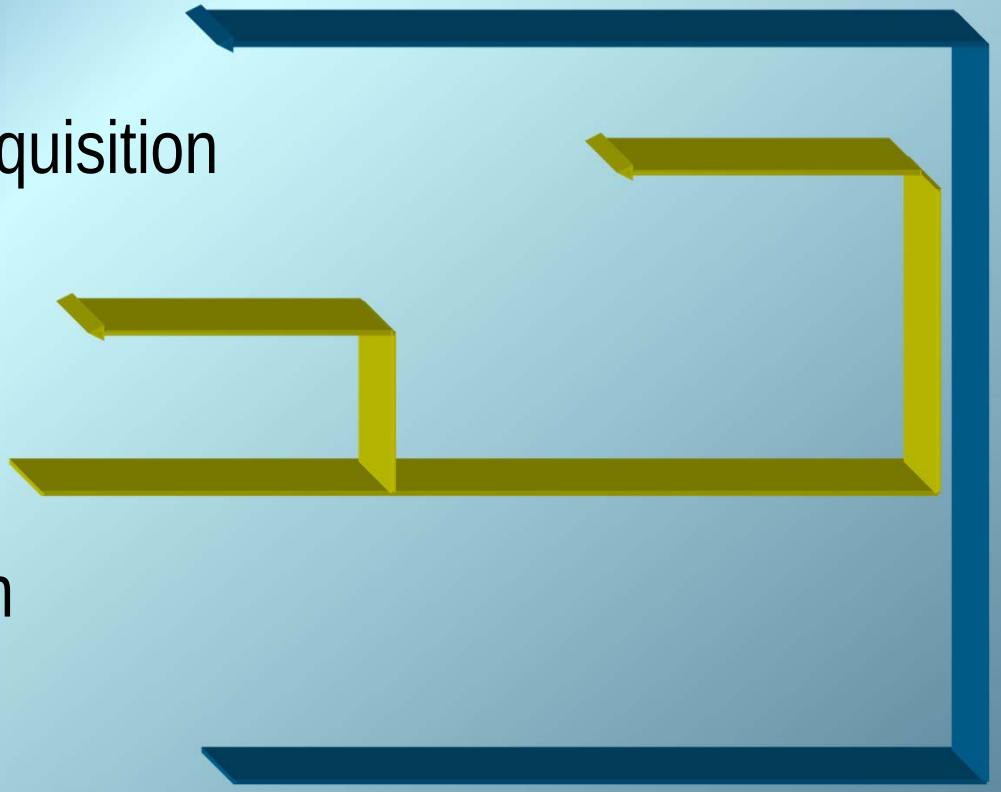


Explanation Facility:

- explains HOW
- explains WHY

Knowledge Engineering

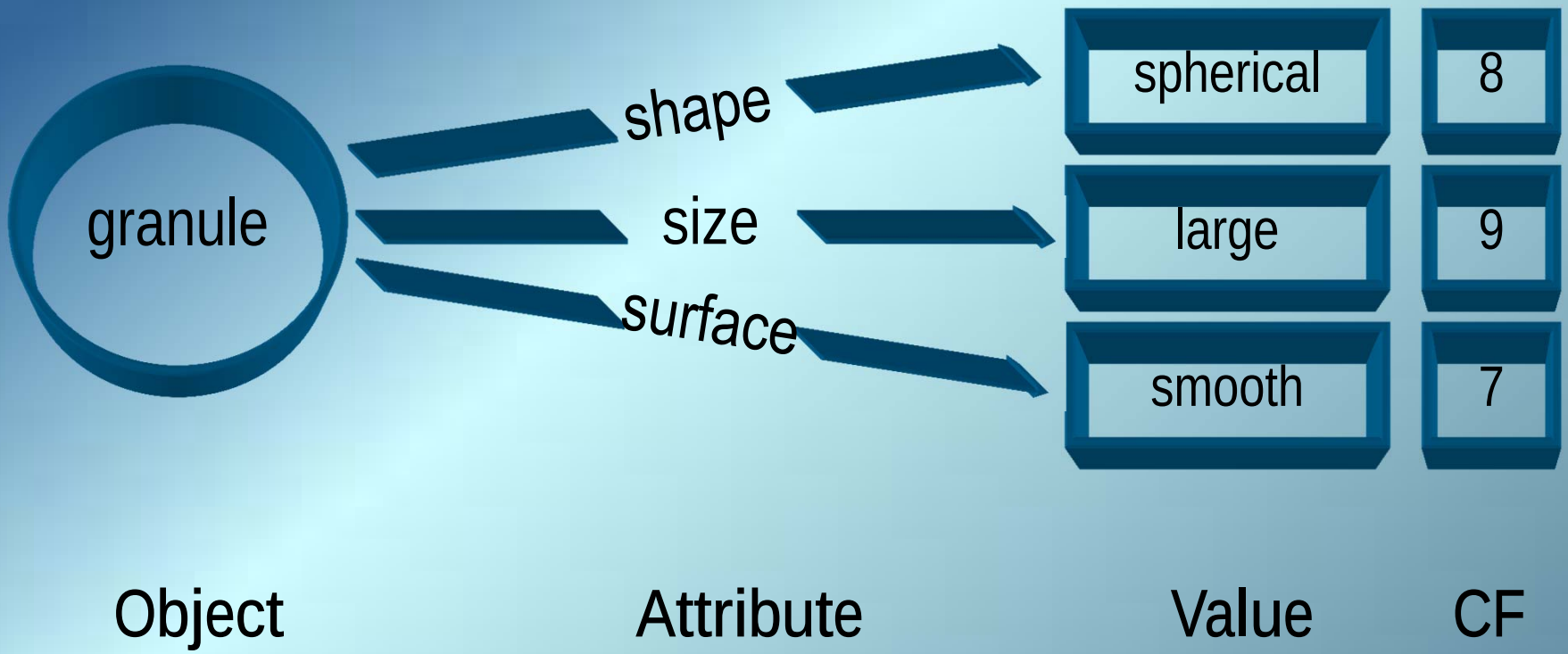
- Phase 1: Assessment
  Requirements
- Phase 2: Knowledge Acquisition
  Knowledge
- Phase 3: Design
  Structure
- Phase 4: Test
  Evaluation
- Phase 5: Documentation
  Product
- Phase 6: Maintenance



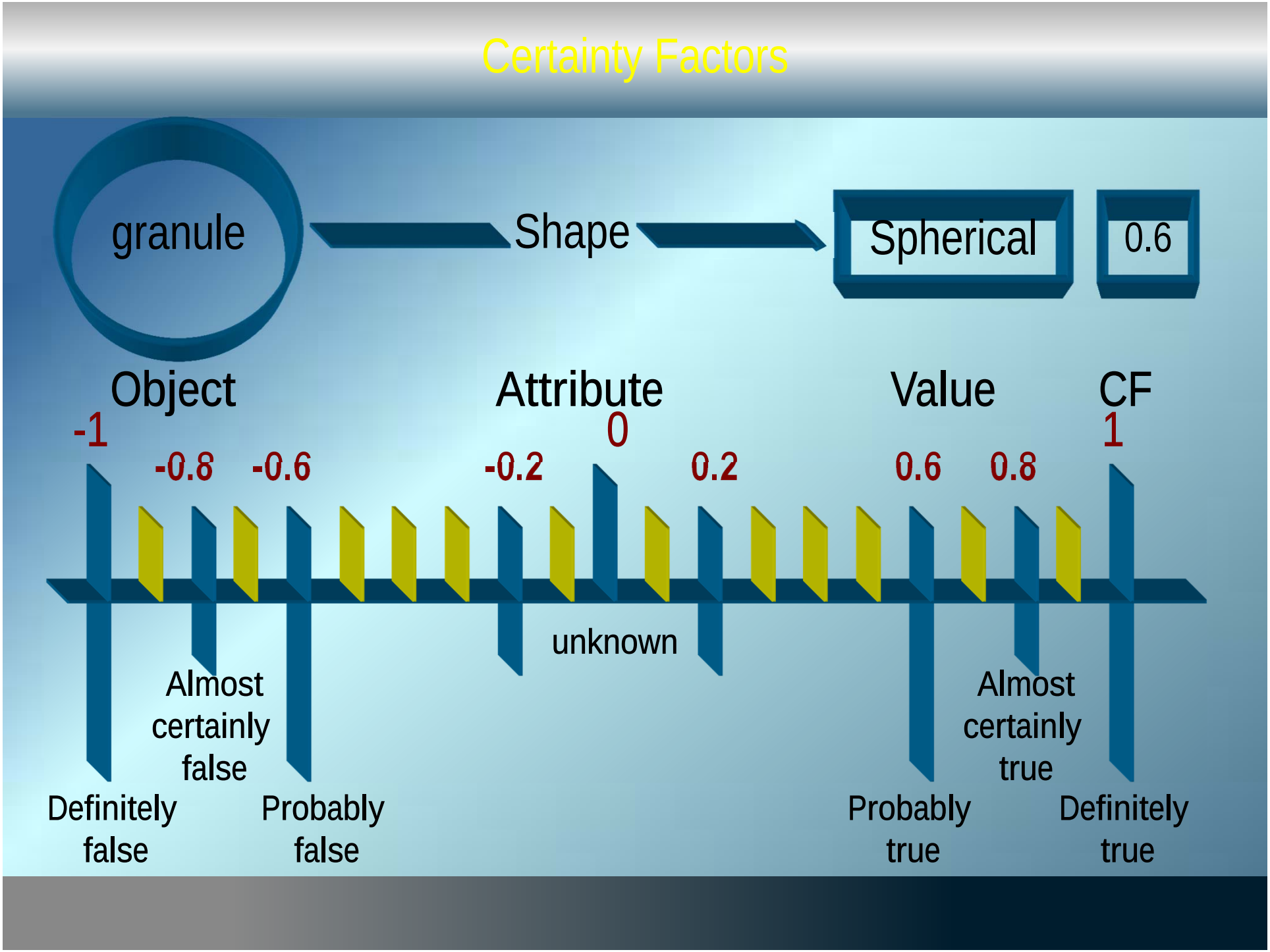
Knowledge Representation Techniques:

- Object-Attribute-Value Triplets
- Rules
- Others:
  - fuzzy logic
  - genetic algorithm
  - case based reasoning
  - ANNs
  - Simulation Tools (Arena, etc)

Object-Attribute-Value

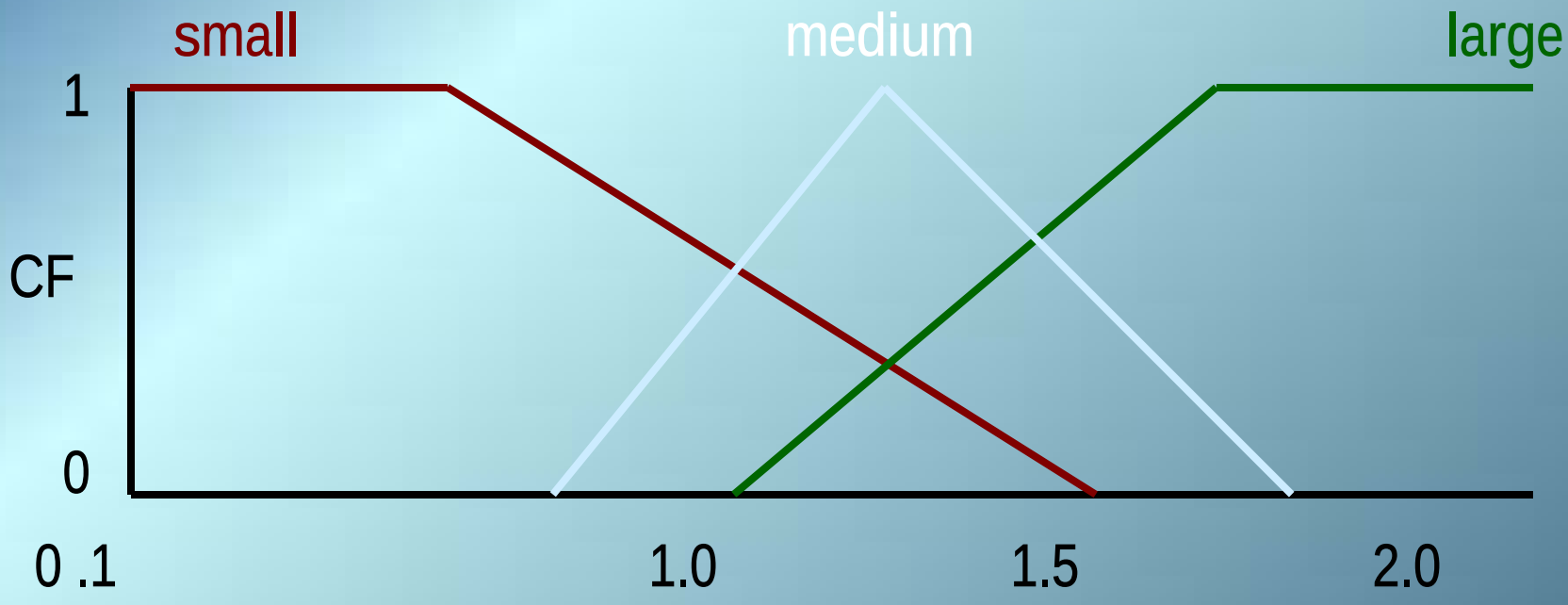


Certainty Factors



Fuzzy Facts


granule
Shape
Spherical
0.6
Object
Attribute
Value
CF


small
medium
large
1
CF
0
0 .1
1.0
1.5
2.0

Rule-Based Expert Systems:

Rules and Decision Trees

- Rule 22.
  IF The weather is hot
  THEN Go to beach

- Rule 112.
  IF It is summer and it is sunny
  THEN The weather is hot

- Rule 10.
  IF The month is August
  THEN It is summer

Rule-Based expert systems:

Rules and Decision Trees

IF

The selected polymer is HPMC only

AND

There is no regulatory restrictions for the use of PEG 400 in that country

THEN

Recommend PEG 400

ELSE

Check for compatibility (from the database) with the selected polymer

BECAUSE

PEG 400 is compatible with HPMC and it is efficient in its functionality.

Case-Based Reasoning

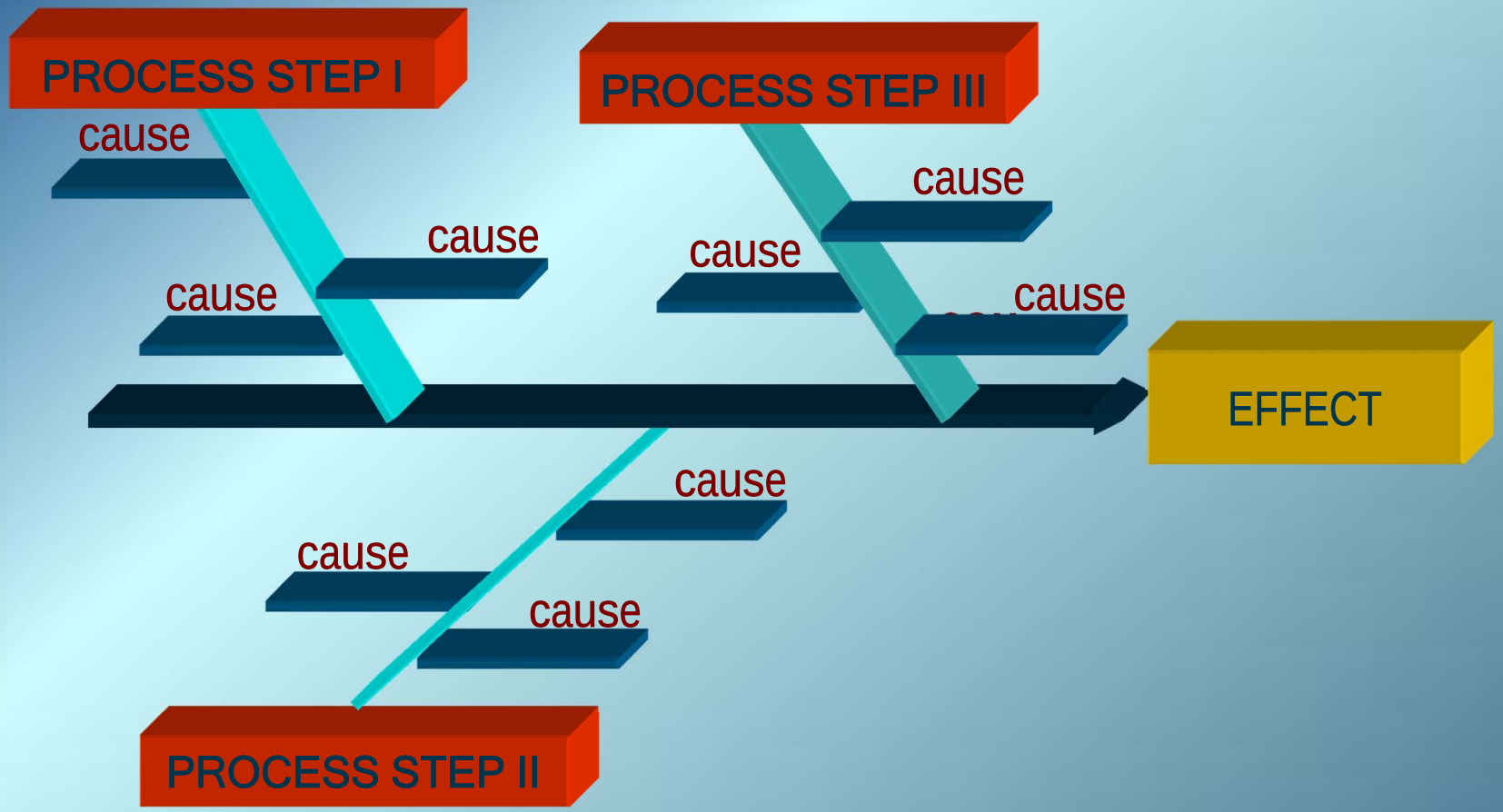
- Utilizes knowledge base (long-term memory)
- Finds a similar problem that was solved in the past
- Adapts the old solution to solve the new problem

Genetic Algorithms:

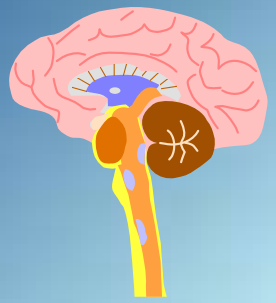
Genetic Algorithms:

- Mathematically relates initial condition to desired outcome by establishing a “desirability function” (optimized algorithm)
- Initial algorithm is iteratively revised by minimizing the differences between the initial condition and the desired outcome
- As in real evolution, only the best solutions survive and are carried forward.
- Extremely effective optimization technique.

Cause-Effect Diagrams
(Ishikawa Diagrams, Fishbone Diagrams)



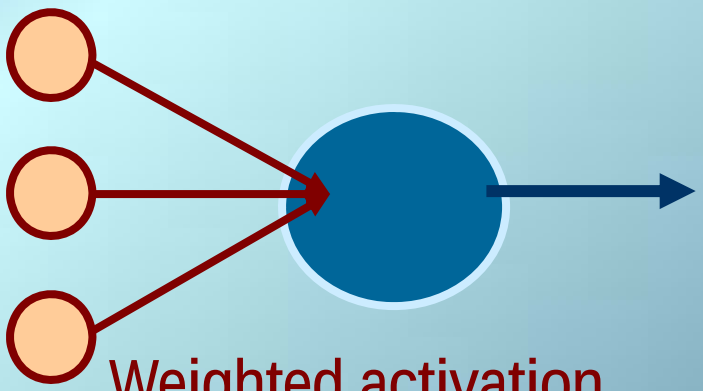
Artificial Neural Networks:



Brain

Neuron

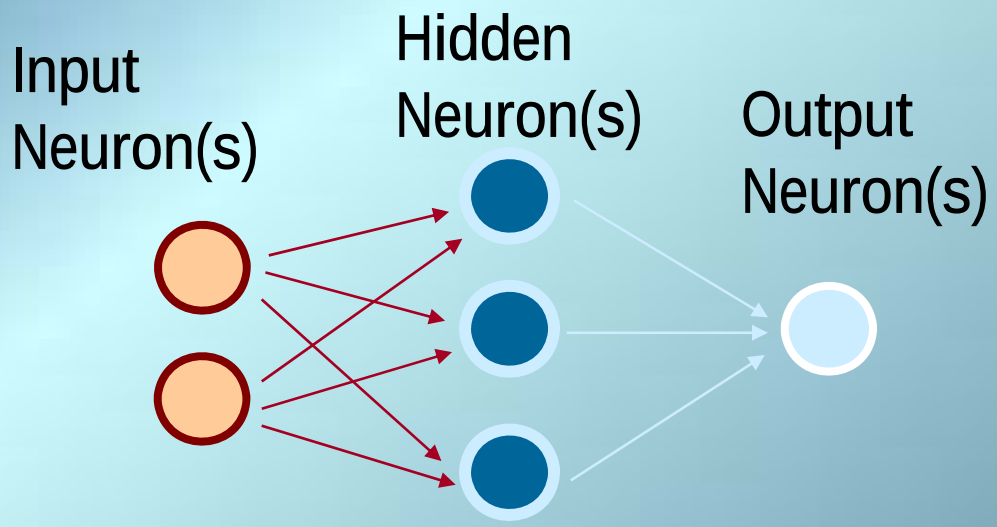
Simulated Neuron



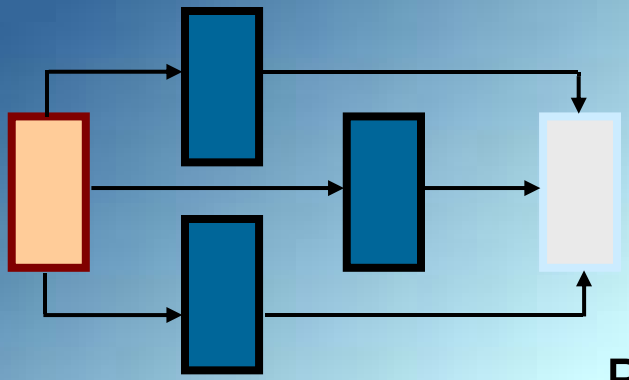
Activation from left is multiplied by the value on the weight it travels along.
It then enters a unit, is summed and squashed, and passed out to the next layer.

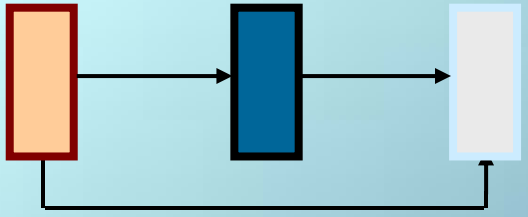
Artificial Neural Networks:

Neuron Model

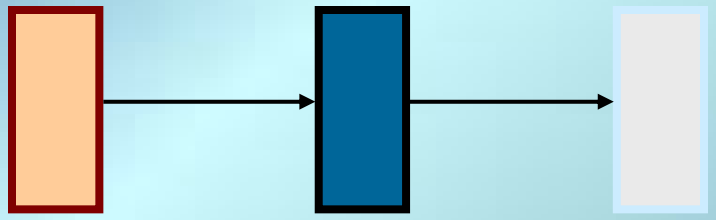


Artificial Neural Networks: Sample Architectures

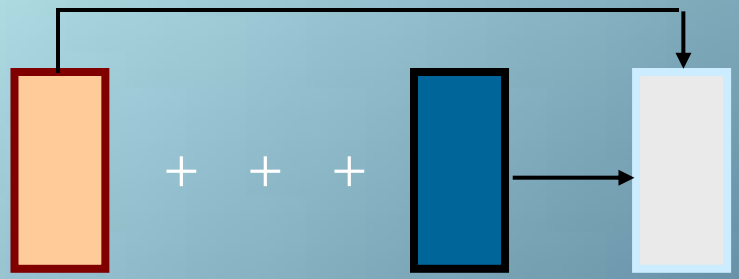




Backpropagation



General Regression (GRNN)



Polynomial (GMDH)

Integration:

Advantages of combining neural networks with other methods of knowledge representation:

Rule-Based System provides heuristic reasoning but they are not best at automated learning or recognizing patterns in large amounts of data. This gap in expert systems is filled by neural networks.

SCIENTIFIC DATA INTERACTION PREFORMULATION (DATABASE)

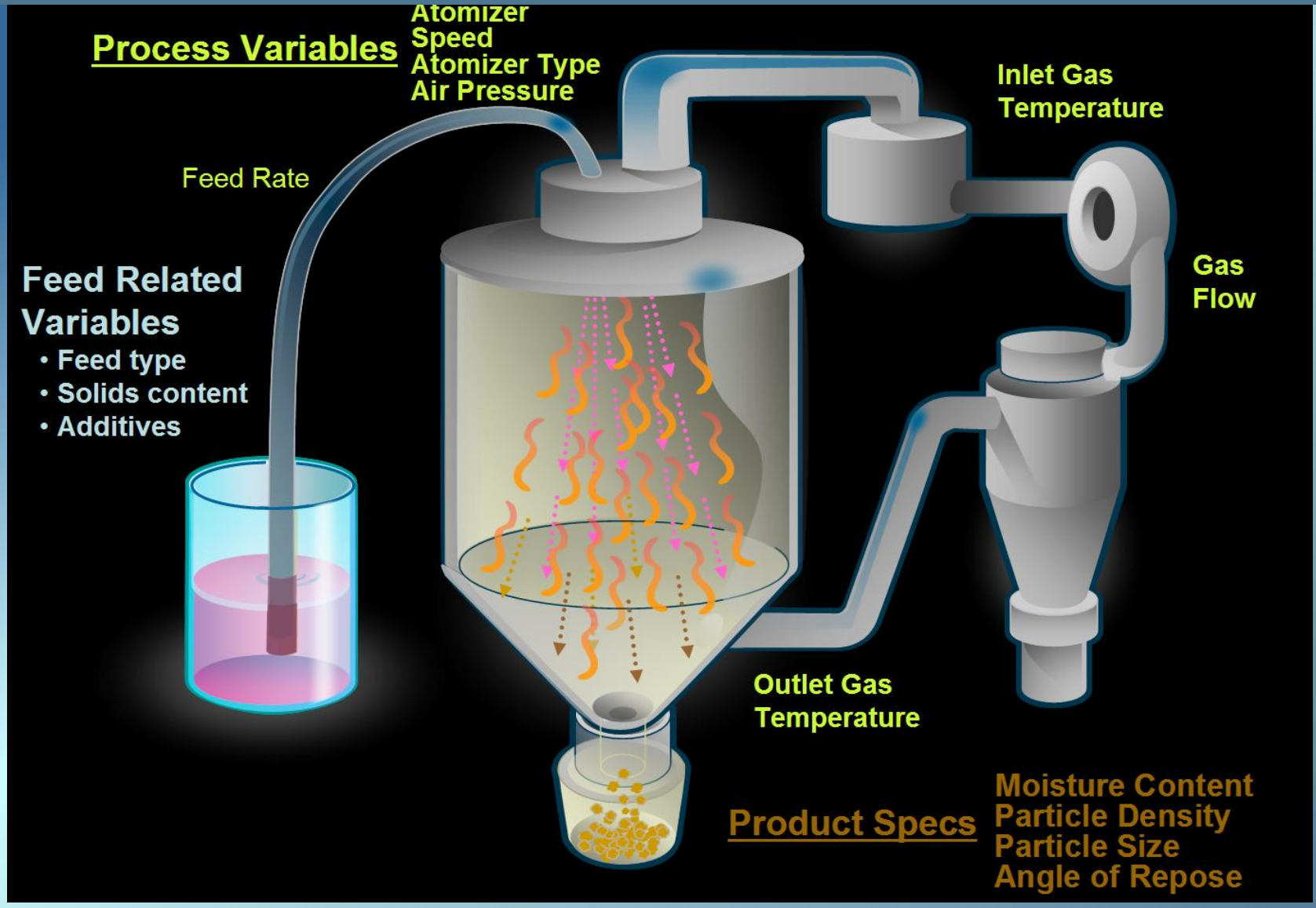
CASE STUDIES

PROCESS PREDICTION/TRAINING

Spray Drying

"Transformation of liquid feed into dry particles using a one-step, continuous drying process"

Spray Drying Process



- Material Characteristics
  - Feed Density
  - Solids Content
  - Surface Tension
  - Viscosity
  - Desorption Differential
  - Sorption/Desorption Hysteresis Area

  For moisture content only
  - Feed Density

  For bulk density and mean particle size only
  - % of solids undissolved

- Process Parameters
  - Chamber Collection Point
  - Outlet Temperature
  - Temperature Differential
  - Cyclone Differential Pressure
  - Air mass to feed mass ratio

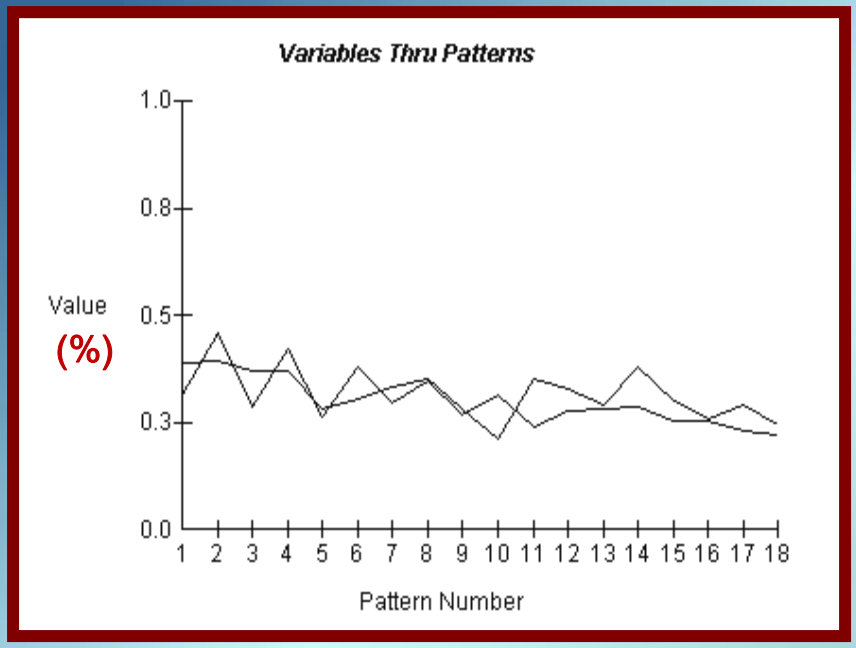
  or

  - Atomizer speed to feed rate ratio
  - Nozzle size for 2 fluid config

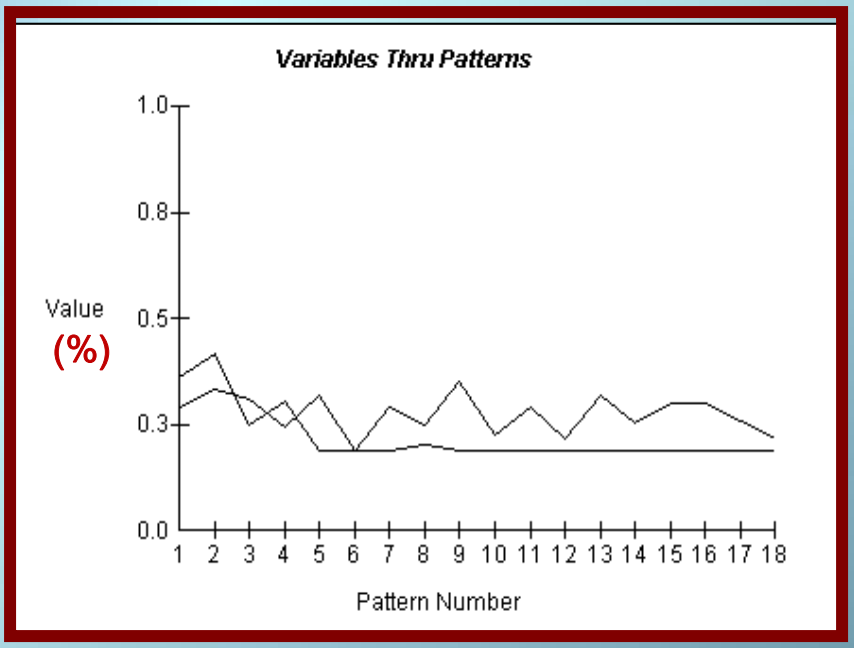
Outputs

- Moisture Content
- Bulk Density
- Mean Particle Size

Moisture Content ANN Models

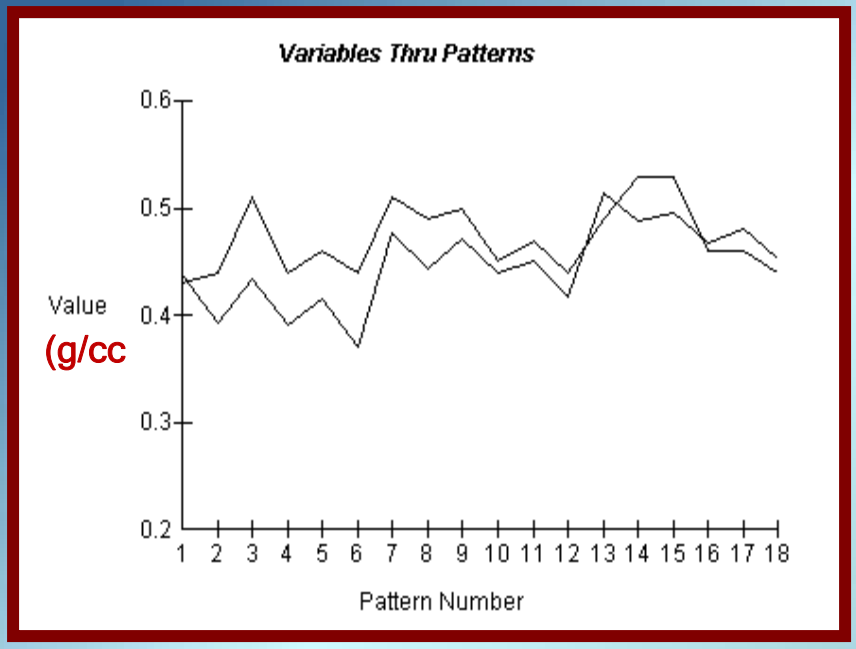


Actual and Predicted Moisture Content Values for Validation Data Set Using Rotary Nozzle Configuration

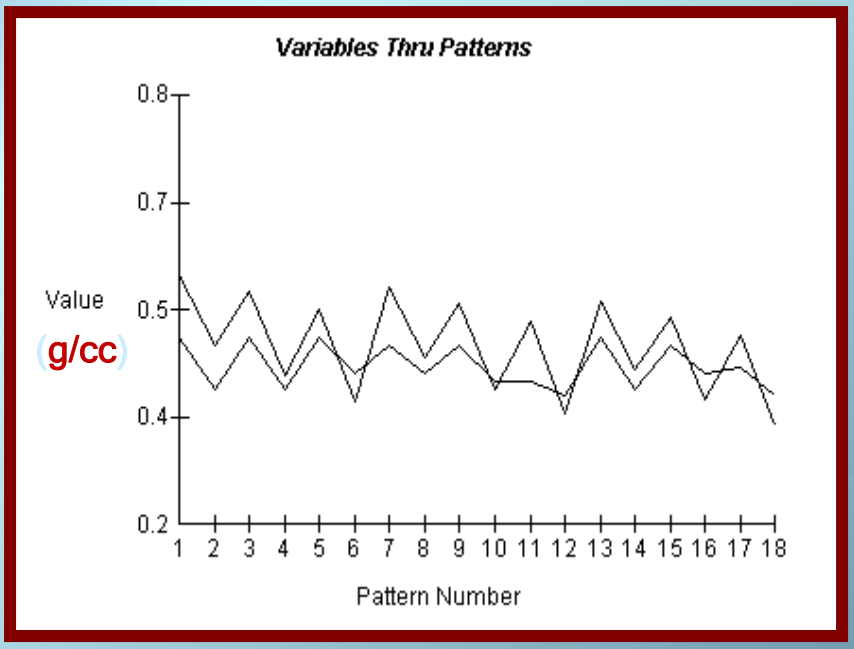


Actual and Predicted Moisture Content Values for Validation Data Set Using Two Fluid Nozzle Configuration

Bulk Density ANN Models

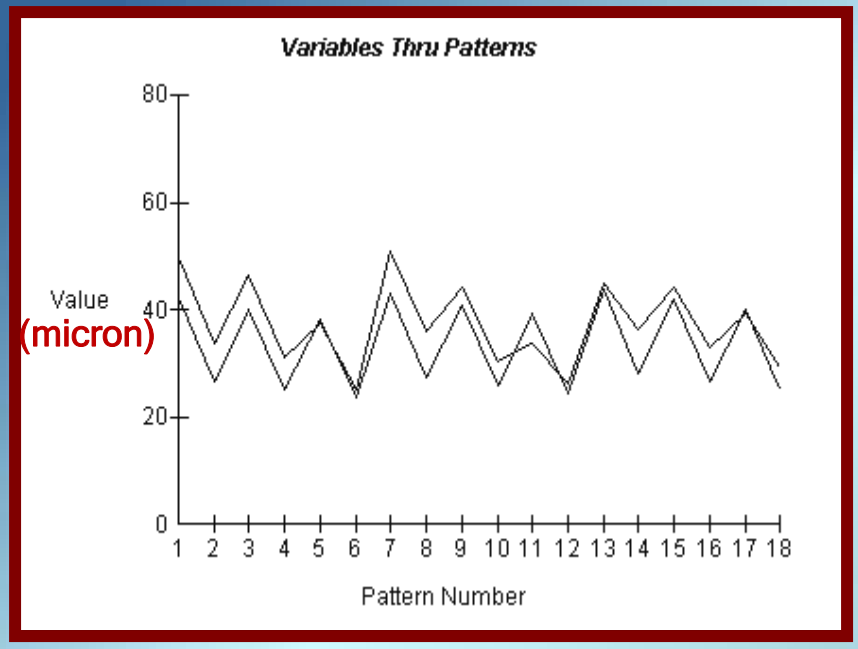


Actual and Predicted Bulk Density Values for Validation Data Set Using Rotary Nozzle Configuration

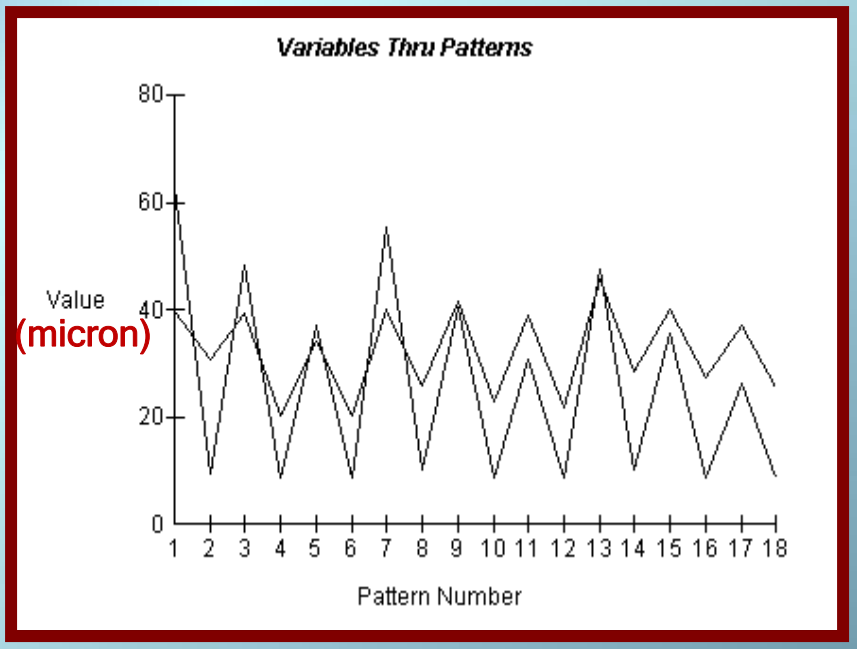


Actual and Predicted Bulk Density Values for Validation Data Set Using Two Fluid Configuration

Mean Particle Size ANN Models



Actual and Predicted Mean Particle Size Values for Validation Data Set Using Rotary Nozzle Configuration



Actual and Predicted Mean Particle Size Values for Validation Data Set Using Two Fluid Nozzle Configuration

Moisture Content, % 4.2

Mean Part Size

Bulk Density, g/ml

Angle of Repose

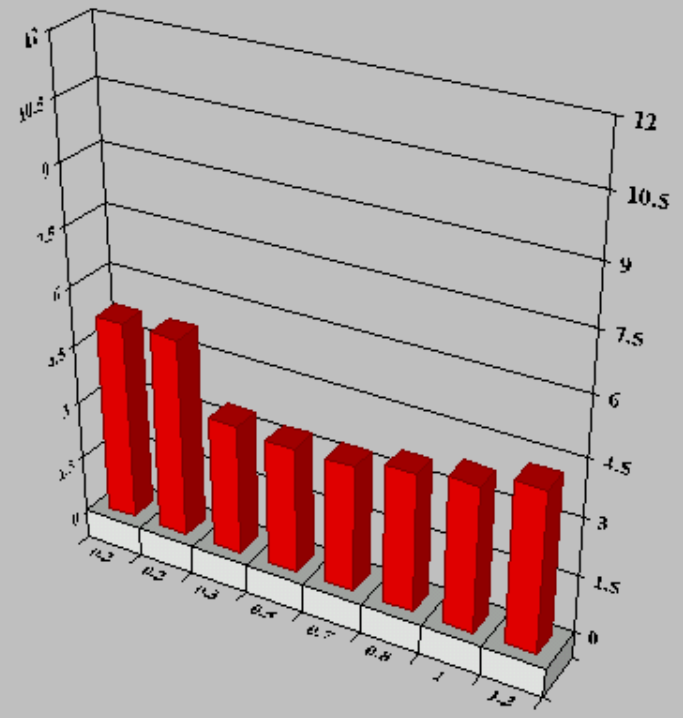
- (•) Moisture Content
- ( ) Mean Part. Size
- ( ) Bulk Density
- ( ) Repose Angle

- (•) 3D-Bar
- ( ) 2D-Bar
- ( ) 3D-Line
- ( ) 2D-Line
- [x] Multi points
- [ ] Full Profile

Graph & E/OP Switch

Edit Default Inputs

Effect of Atom Air P., barr on Moisture Content



Nozzle Size, mm	1.3	Feed Rate, ml/min	75
Solids in Feed, %	50	Cyclone Diff. P, mmWG	95
Inlet Temp., °C	144	Atom Air P., barr	1.2
Outlet Temp., °C	90	Moisture Absorption Fctr	14

Enhanced Generalization Level

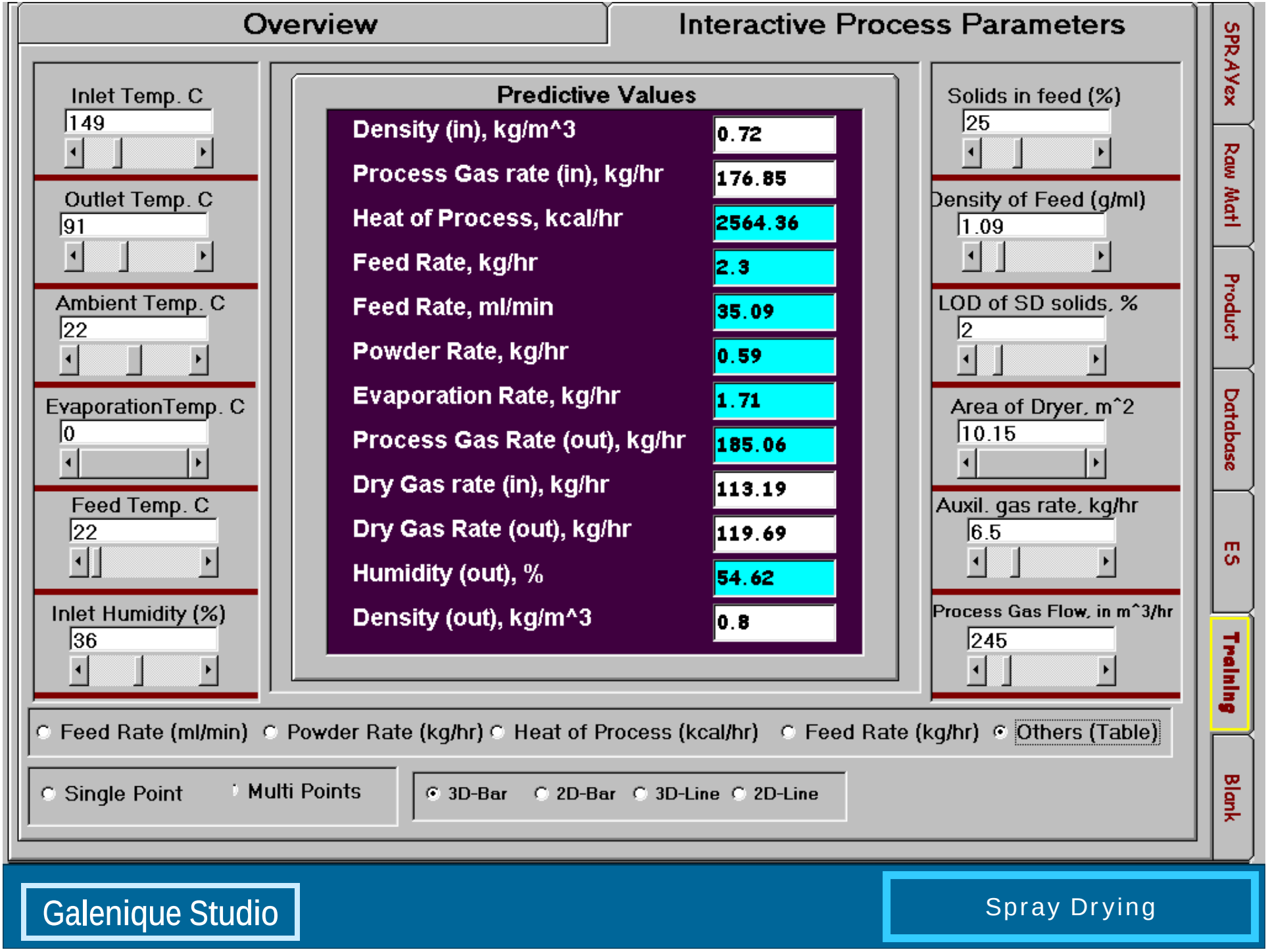
Predictor

Optimizer

SPRAYex | Raw Matl | Product | Database | ES | Training | Blank

Galenique Studio

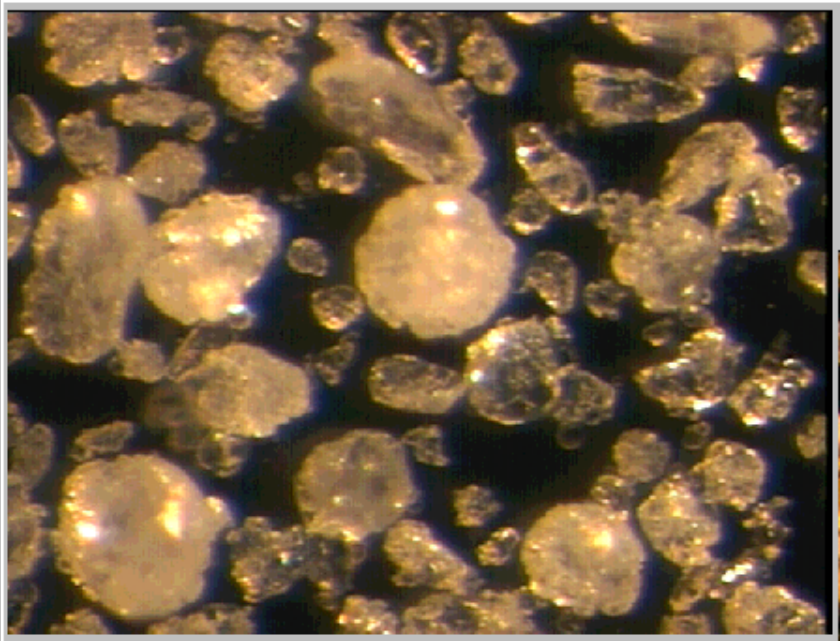
Spray Drying


Overview
Interactive Process Parameters
Inlet Temp. C
149
Outlet Temp. C
91
Ambient Temp. C
22
EvaporationTemp. C
0
Feed Temp. C
22
Inlet Humidity (%)
36
Predictive Values
Density (in), kg/m^3
0.72
Process Gas rate (in), kg/hr
176.85
Heat of Process, kcal/hr
2564.36
Feed Rate, kg/hr
2.3
Feed Rate, ml/min
35.09
Powder Rate, kg/hr
0.59
Evaporation Rate, kg/hr
1.71
Process Gas Rate (out), kg/hr
185.06
Dry Gas rate (in), kg/hr
113.19
Dry Gas Rate (out), kg/hr
119.69
Humidity (out), %
54.62
Density (out), kg/m^3
0.8
Solids in feed (%)
25
Density of Feed (g/ml)
1.09
LOD of SD solids, %
2
Area of Dryer, m^2
10.15
Auxil. gas rate, kg/hr
6.5
Process Gas Flow, in m^3/hr
245
Feed Rate (ml/min)
Powder Rate (kg/hr)
Heat of Process (kcal/hr)
Feed Rate (kg/hr)
Others (Table)
Single Point
Multi Points
3D-Bar
2D-Bar
3D-Line
2D-Line
SPRAYex
Raw Matl
Product
Database
ES
Training
Blank
Galenique Studio
Spray Drying

Raw Material | Processing Conditions | **Spray Dried Product**

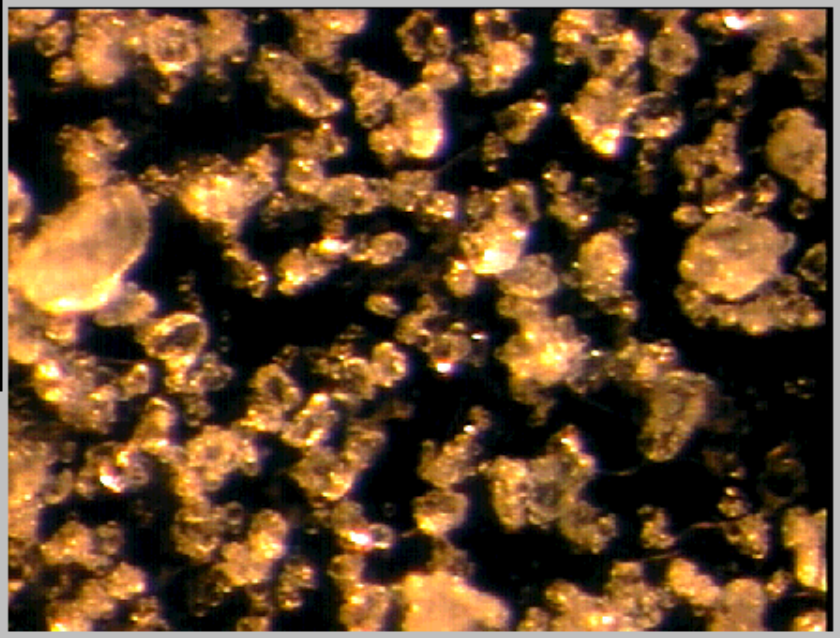
SPRAYex | Raw Matl | Product | Database | ES | Training | Blank

Database | DSC Scans | Photo Micrographs



Primary

Secondary



☐ 1° ○ 2° ○ 1°_2°

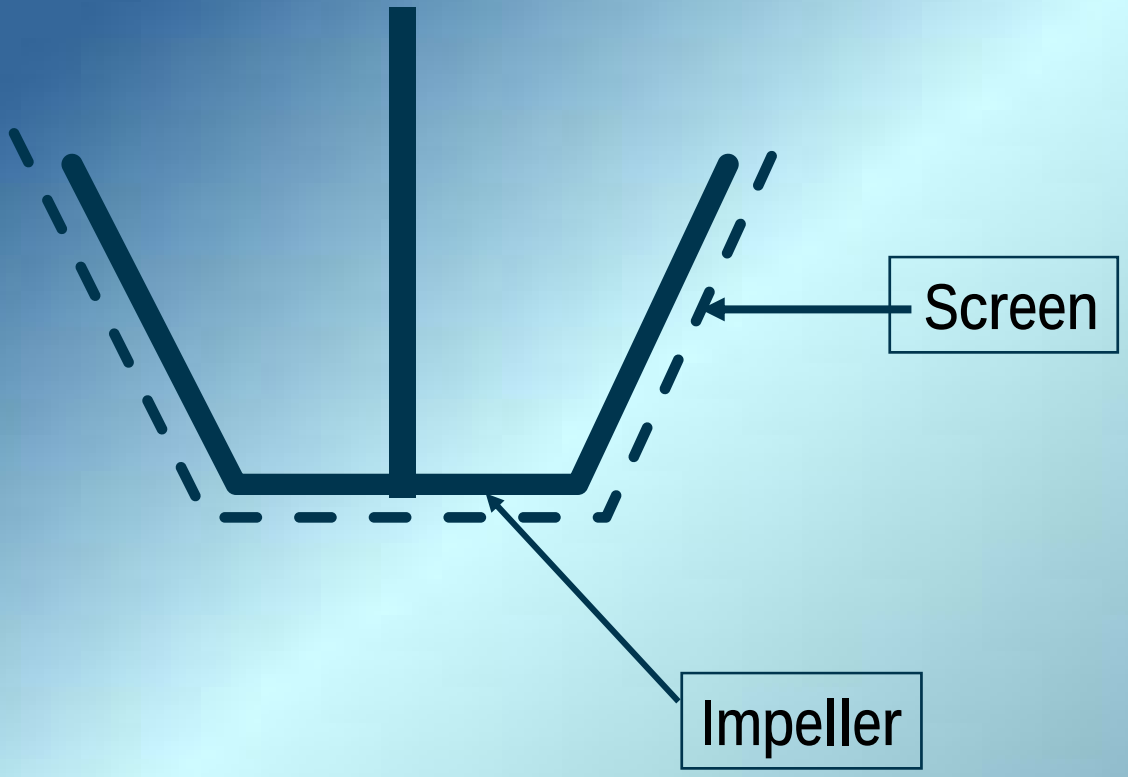
☐ ○ Raw Material + 1° + 2°

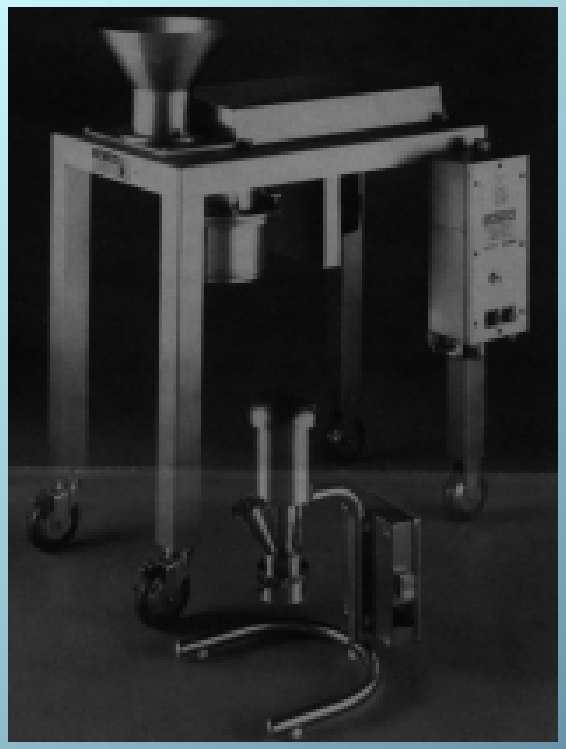
○ Database ☐ ◉ Photo Micrographs

980707B-SW | 1

Entry ID: 21

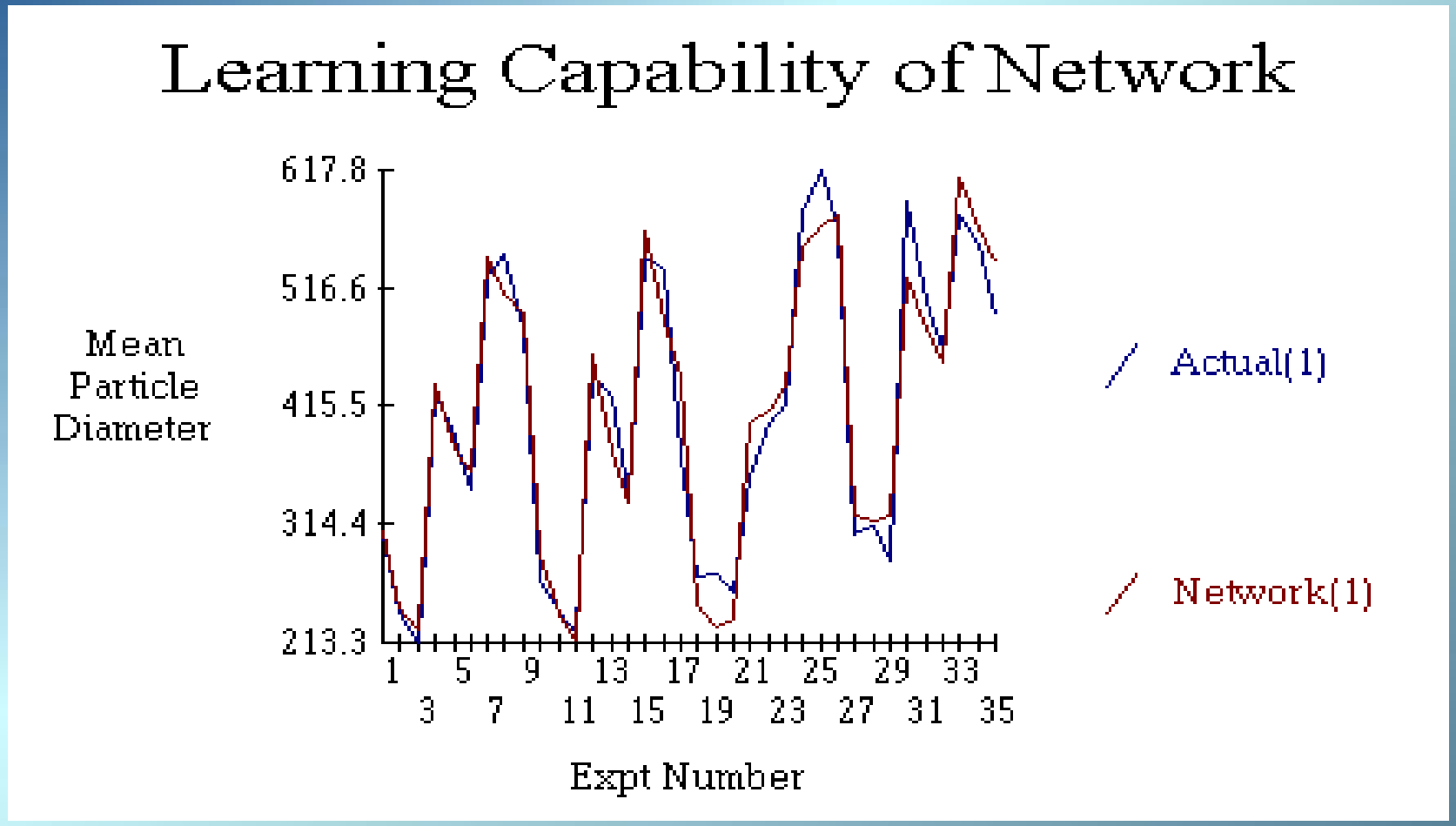
Case Study - Milling



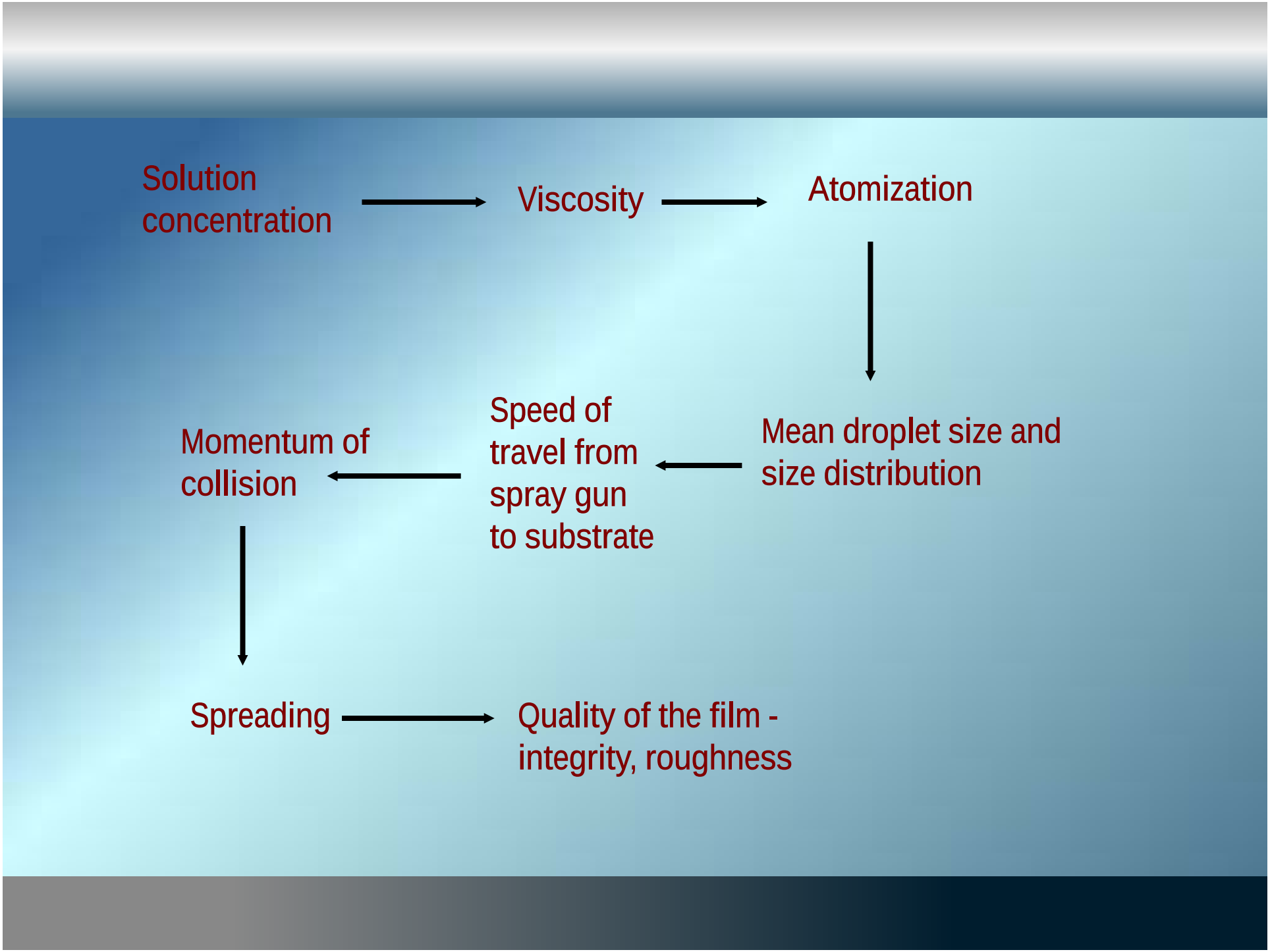


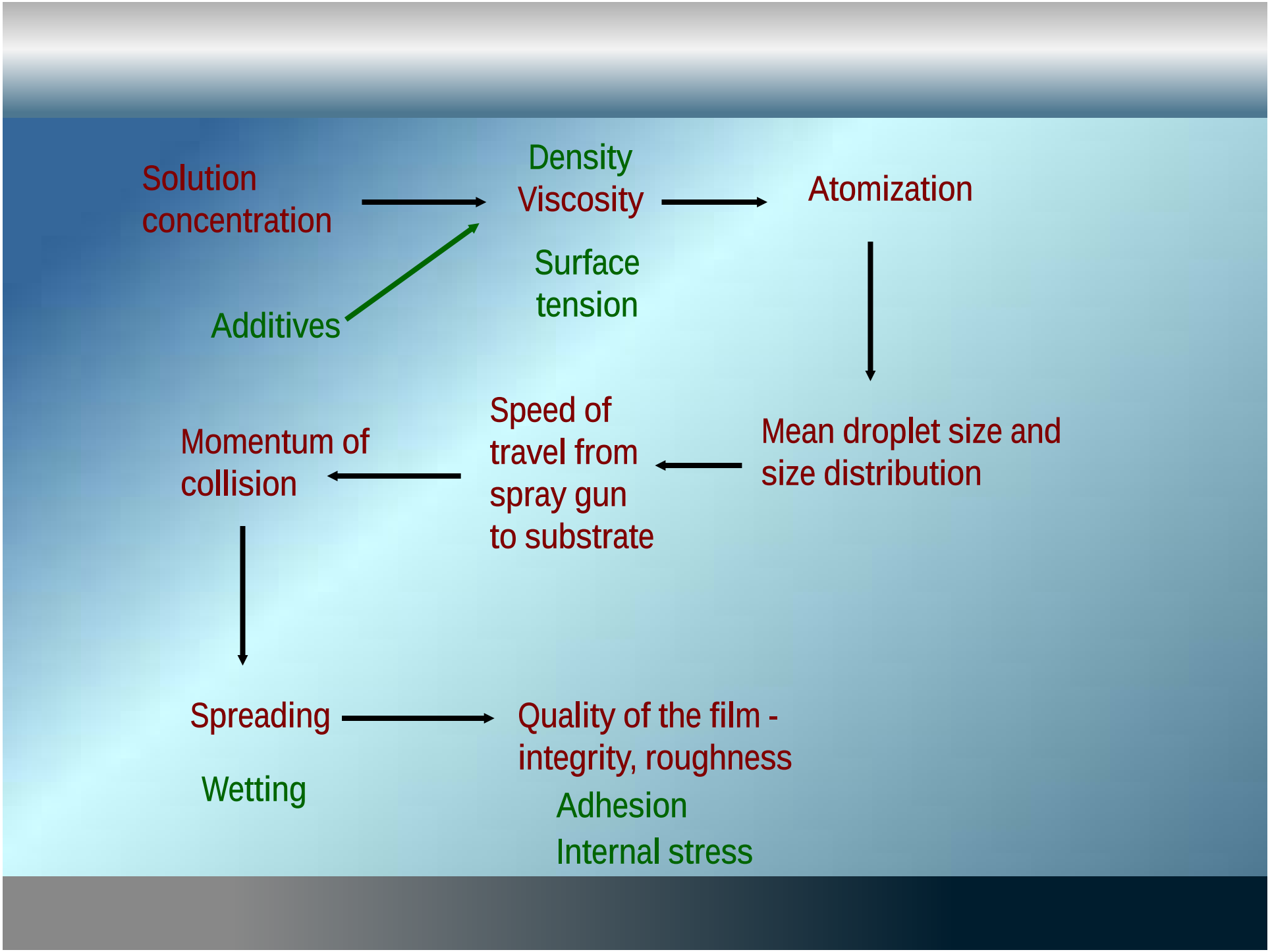
Case Study - Milling

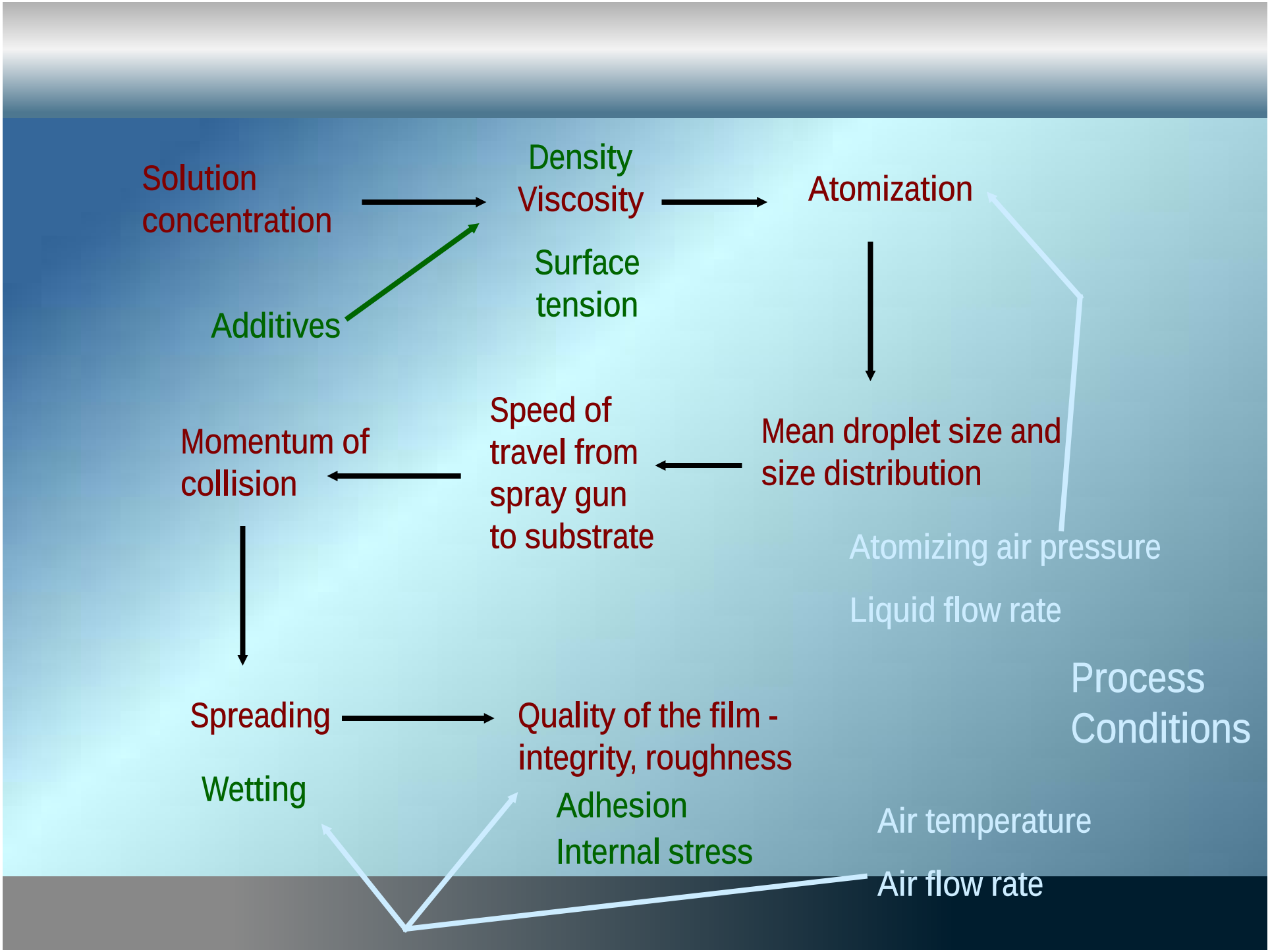
Screen size	48.4%	Speed	20.8%
Impeller	16.4%	Model	14.4%



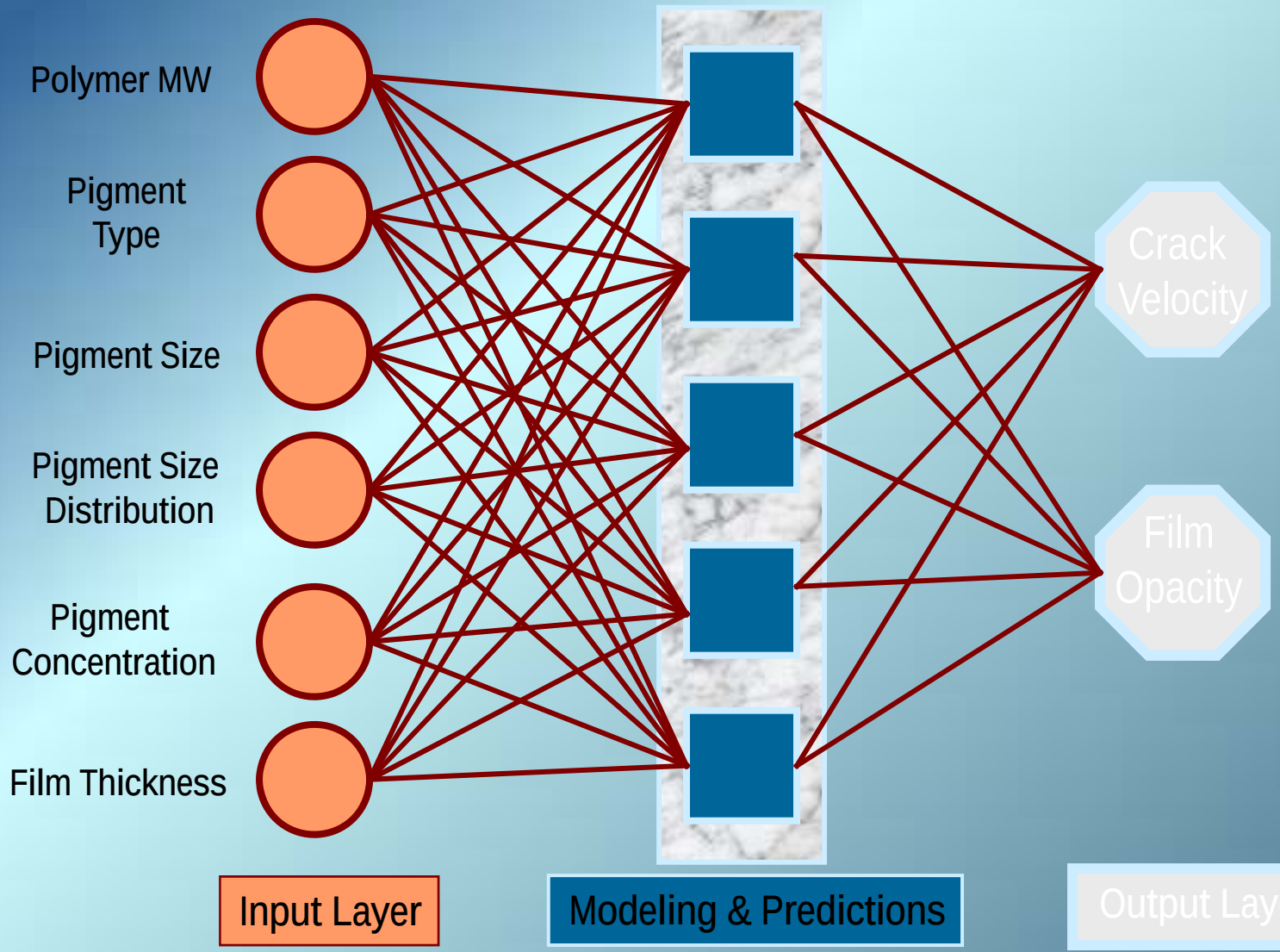
PROCESS PREDICTION/TRAINING
FILM COATING
Film Coating Trouble Shooting


Solution concentration
Viscosity
Atomization
Mean droplet size and size distribution
Speed of travel from spray gun to substrate
Momentum of collision
Spreading
Quality of the film - integrity, roughness


Solution concentration
Density
Viscosity
Surface tension
Additives
Atomization
Mean droplet size and size distribution
Speed of travel from spray gun to substrate
Momentum of collision
Spreading
Wetting
Quality of the film - integrity, roughness
Adhesion
Internal stress


Solution concentration
Density
Viscosity
Surface tension
Additives
Atomization
Mean droplet size and size distribution
Speed of travel from spray gun to substrate
Momentum of collision
Spreading
Quality of the film - integrity, roughness
Wetting
Adhesion
Internal stress
Atomizing air pressure
Liquid flow rate
Process Conditions
Air temperature
Air flow rate

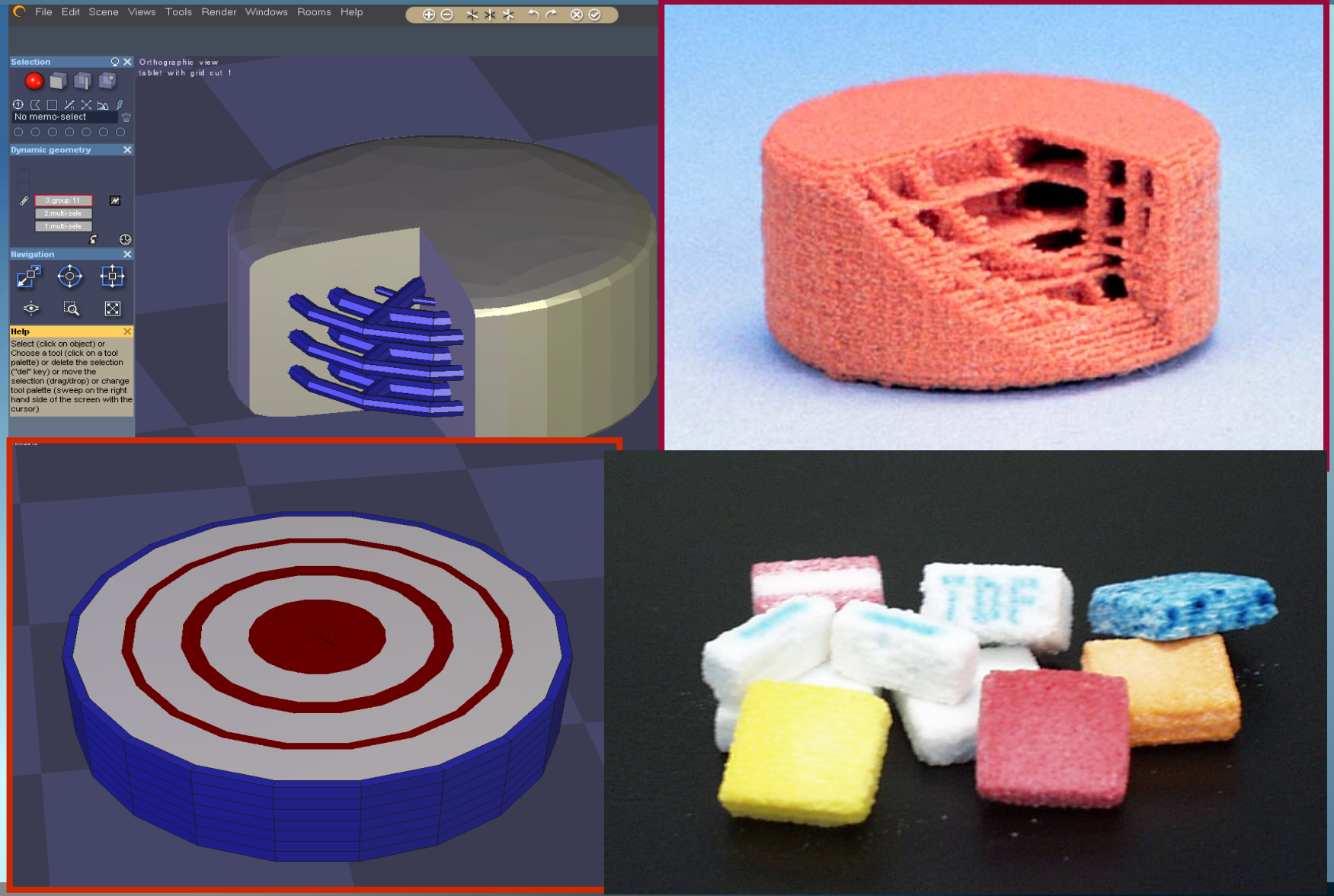
Example of ANN for Film Coating



FORMULATION AND PROCESS DEVELOPMENT

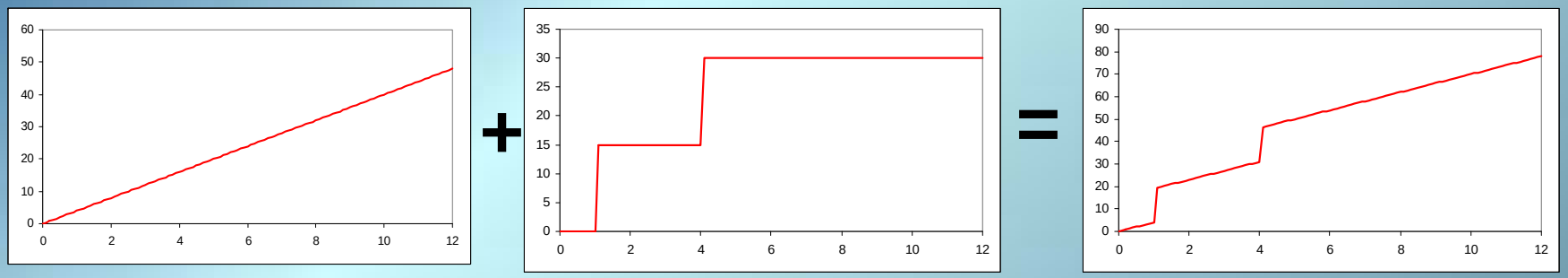
Immediate & Controlled Release

3DP™


File Edit Scene Views Tools Render Windows Rooms Help
Selection
No memo-select
Dynamic geometry
3.group 11
2.multi-sele
1.multi-sele
Navigation
Help
Select (click on object) or Choose a tool (click on a tool palette) or delete the selection ("del" key) or move the selection (drag/drop) or change tool palette (sweep on the right hand side of the screen with the cursor)
Orthographic view
tablet with grid cut 1
TDP

Building Control Release Profiles

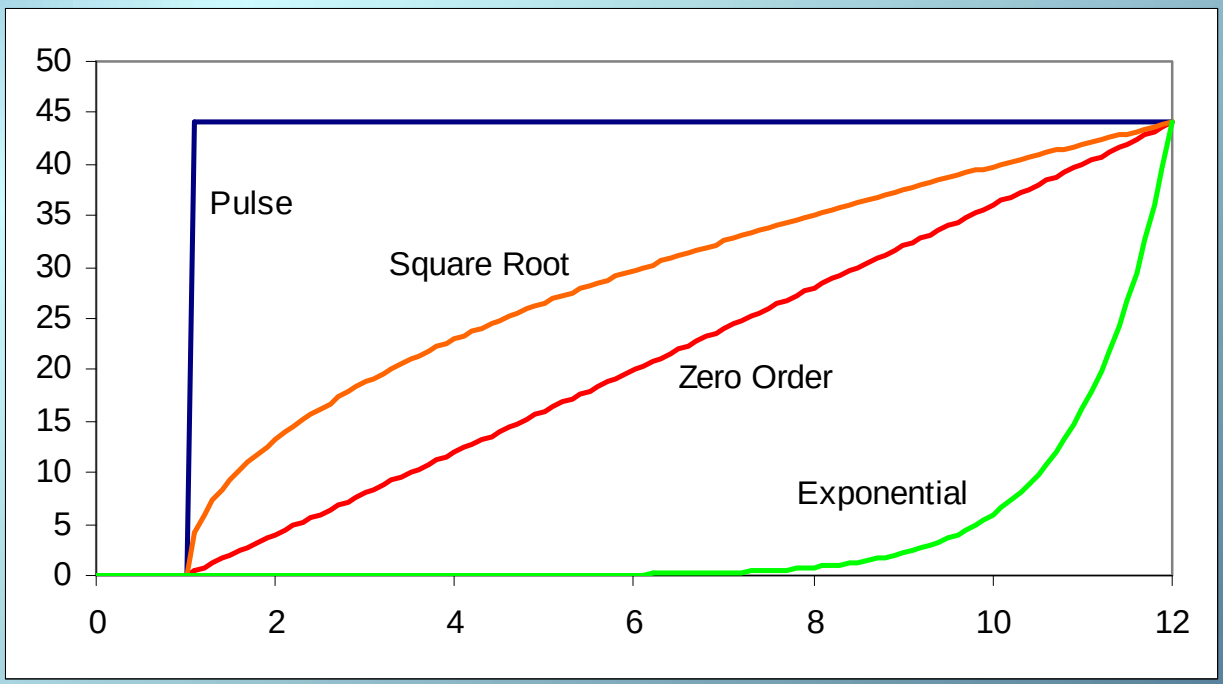
- Complex release profiles can be treated as the sum of simpler “component” release profiles

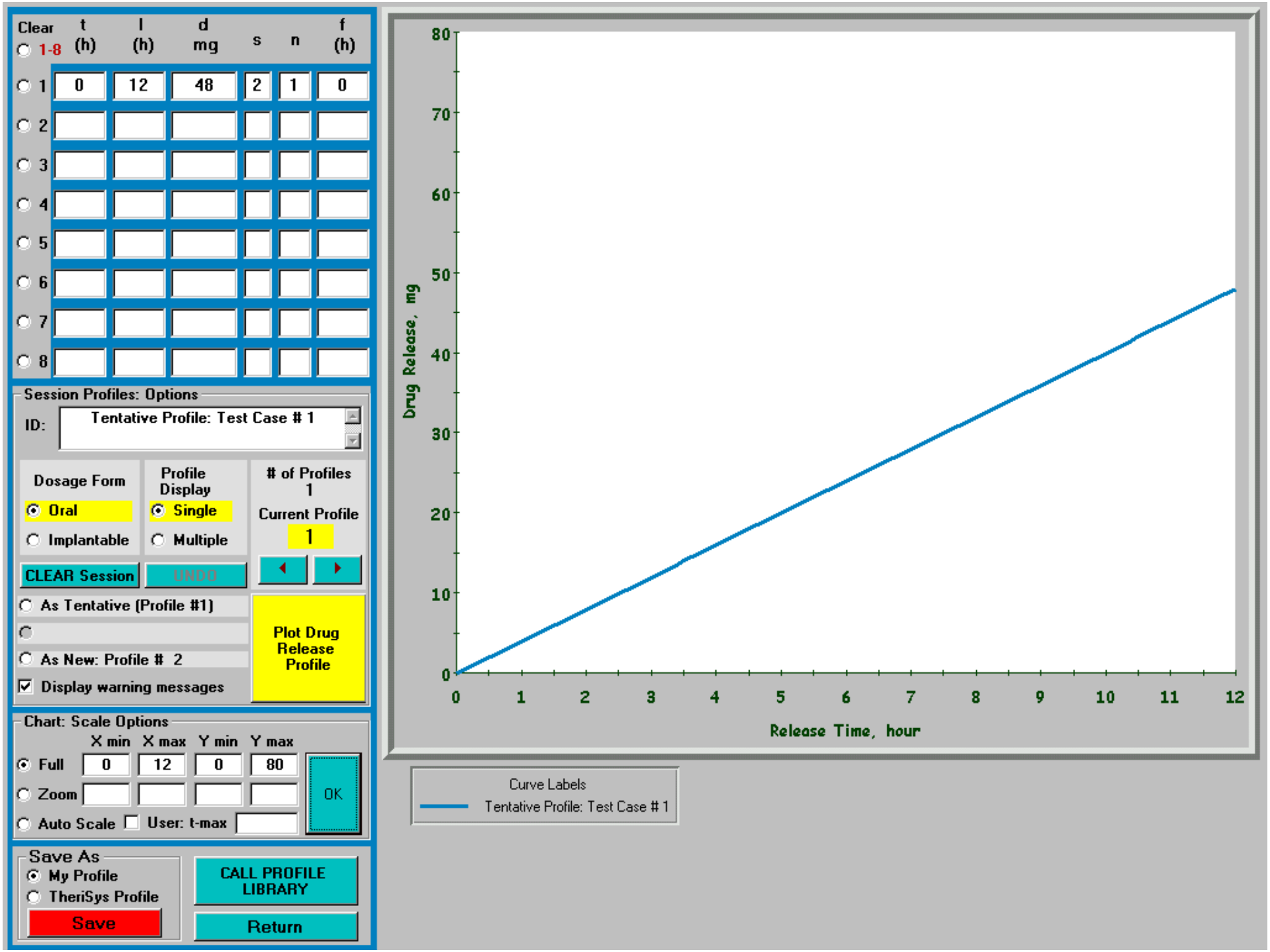


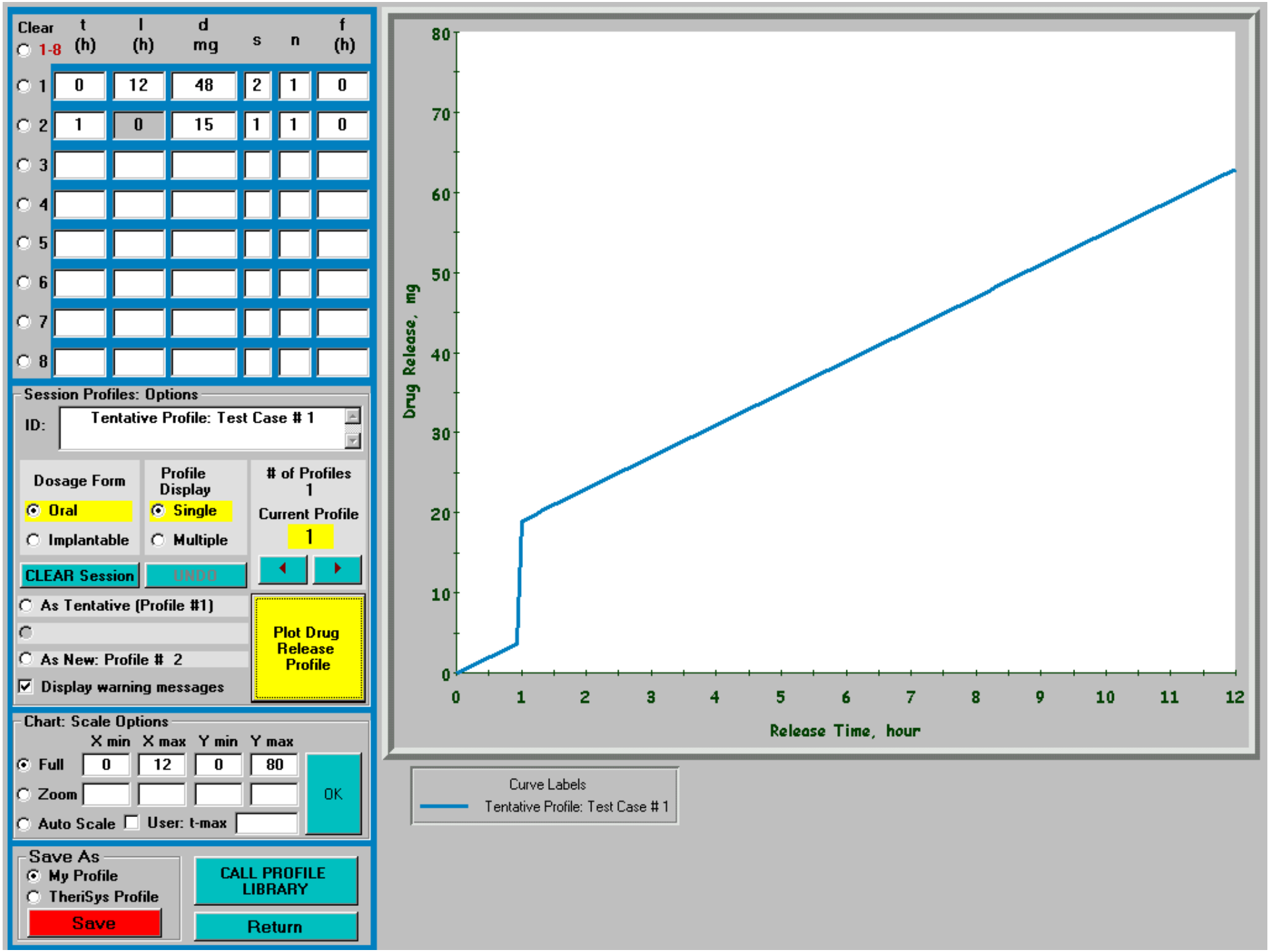
- Specification of desired release profile is done by selecting appropriate components

Building Release Profiles

- Component attributes
  - Start time
  - Duration
  - Dose
  - Shape (kinetics)




Clear 1-8
t (h)
l (h)
d mg
s
n
f (h)
1 0 12 48 2 1 0
2
3
4
5
6
7
8
Session Profiles: Options
ID:
Tentative Profile: Test Case # 1
Dosage Form
Oral
Implantable
Profile Display
Single
Multiple
# of Profiles
1
Current Profile
1
CLEAR Session
UNDO
As Tentative (Profile #1)
As New: Profile # 2
Display warning messages
Plot Drug Release Profile
Chart: Scale Options
X min X max Y min Y max
Full 0 12 0 80
Zoom
Auto Scale
User: t-max
OK
Save As
My Profile
TheriSys Profile
Save
CALL PROFILE LIBRARY
Return
Drug Release, mg
0 10 20 30 40 50 60 70 80
Release Time, hour
0 1 2 3 4 5 6 7 8 9 10 11 12
Curve Labels
Tentative Profile: Test Case # 1


Clear
1-8
t (h)
l (h)
d mg
s
n
f (h)
1 0 12 48 2 1 0
2 1 0 15 1 1 0
3
4
5
6
7
8
Session Profiles: Options
ID:
Tentative Profile: Test Case # 1
Dosage Form
Oral
Implantable
Profile Display
Single
Multiple
# of Profiles
1
Current Profile
1
CLEAR Session
UNDO
As Tentative (Profile #1)
As New: Profile # 2
Display warning messages
Plot Drug Release Profile
Chart: Scale Options
X min X max Y min Y max
Full 0 12 0 80
Zoom
Auto Scale
User: t-max
OK
Save As
My Profile
TheriSys Profile
Save
CALL PROFILE LIBRARY
Return
Drug Release, mg
0 10 20 30 40 50 60 70 80
0 1 2 3 4 5 6 7 8 9 10 11 12
Release Time, hour
Curve Labels
Tentative Profile: Test Case # 1

Clear 1-8	t (h)	l (h)	d mg	s	n	f (h)
1	0	12	48	2	1	0
2	1	0	15	1	1	0
3	4	0	15	1	1	0
4						
5						
6						
7						
8						

Session Profiles: Options

ID: Tentative Profile: Test Case # 1

Dosage Form: (•) Oral ( ) Implantable

Profile Display: (•) Single ( ) Multiple

# of Profiles 1

Current Profile 1

CLEAR Session | UNDO

( ) As Tentative (Profile #1)

( )

( ) As New: Profile # 2

[✓] Display warning messages

Plot Drug Release Profile

Chart: Scale Options

	X min	X max	Y min	Y max
(•) Full	0	12	0	80
( ) Zoom				
( ) Auto Scale [ ] User: t-max				

OK

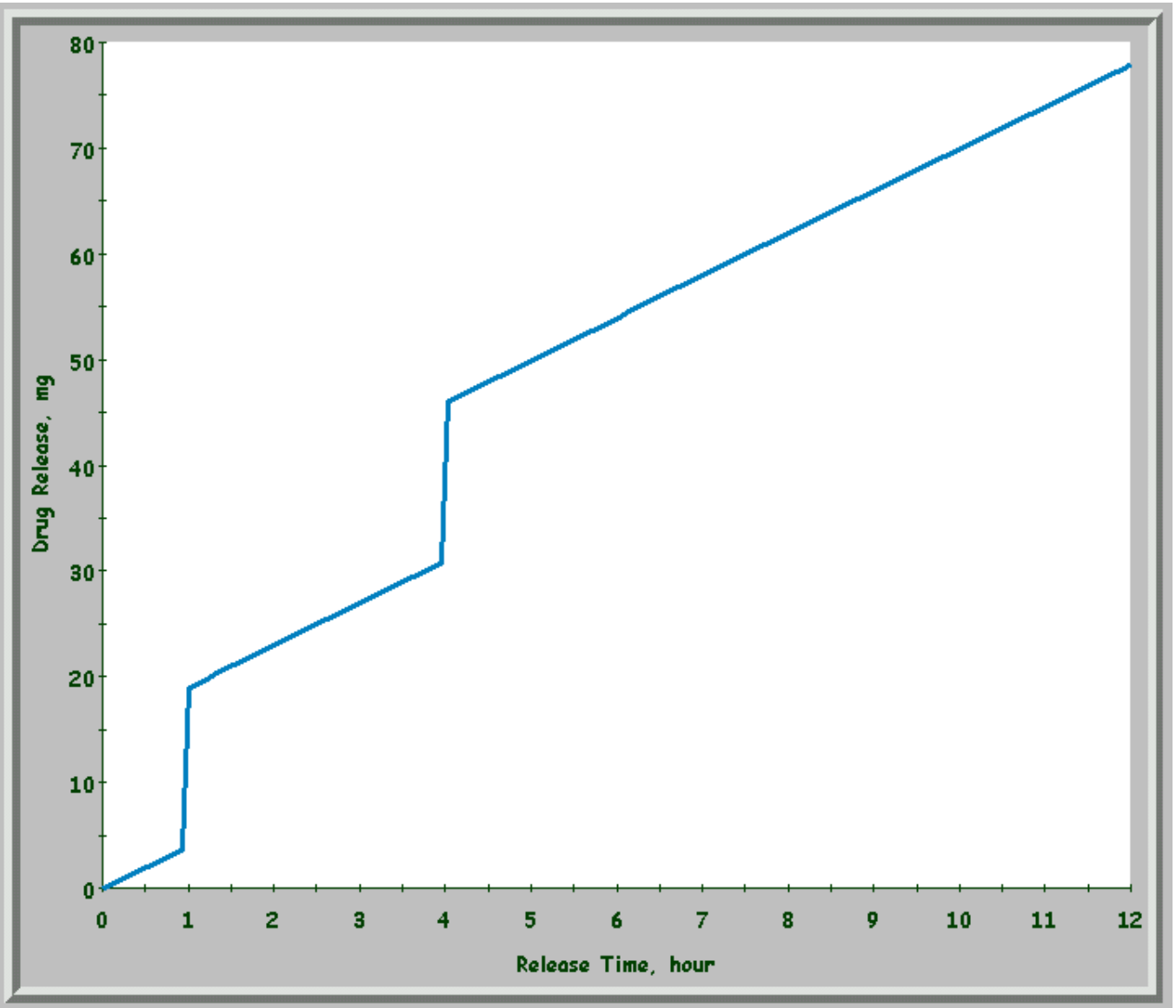
Save As

(•) My Profile ( ) TheriSys Profile

Save

CALL PROFILE LIBRARY

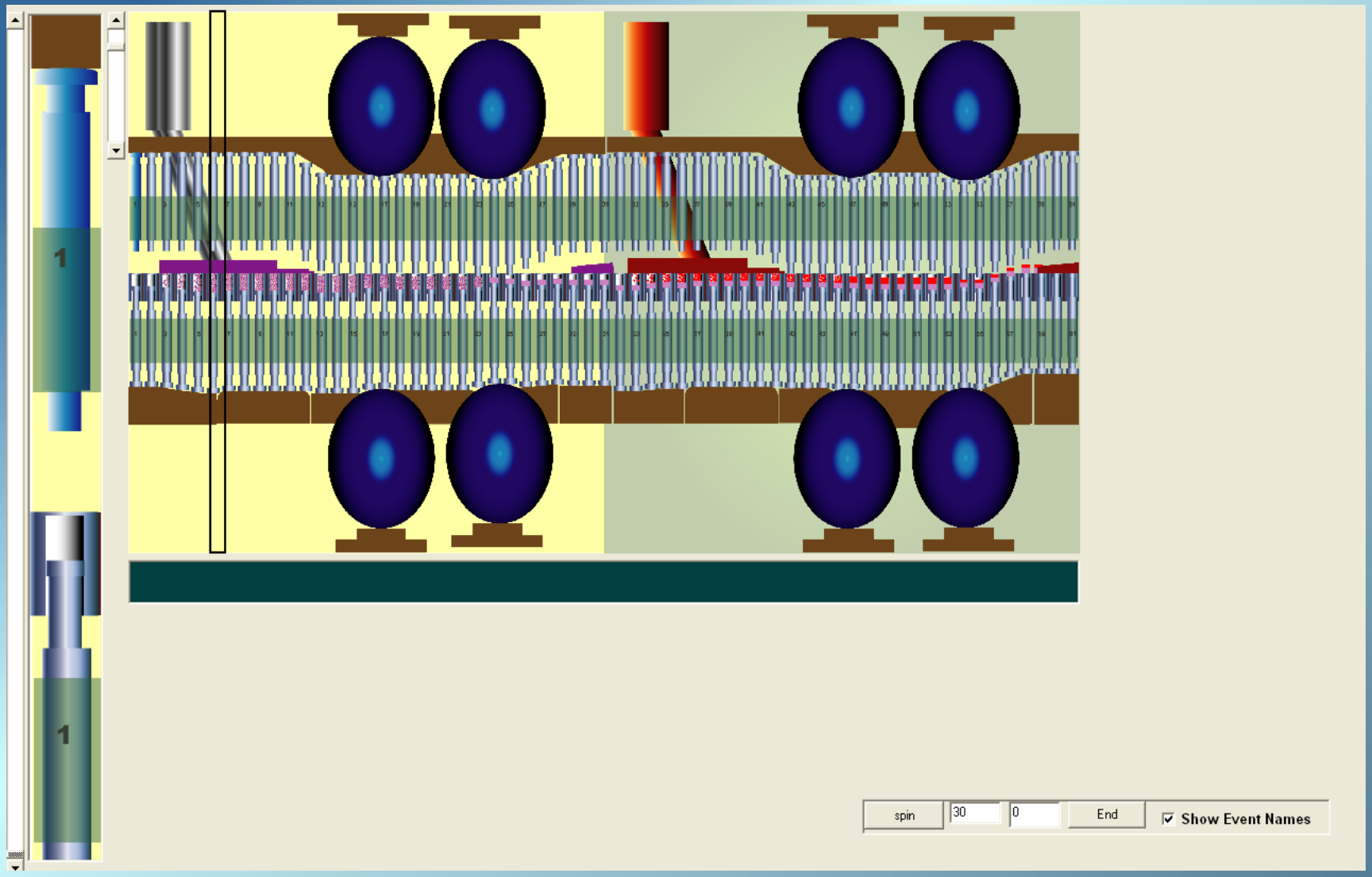
Return



3DP ES Demo | Galenique Studio

MONO LAYER AND BILAYER TABLET PRESS SIMULATION

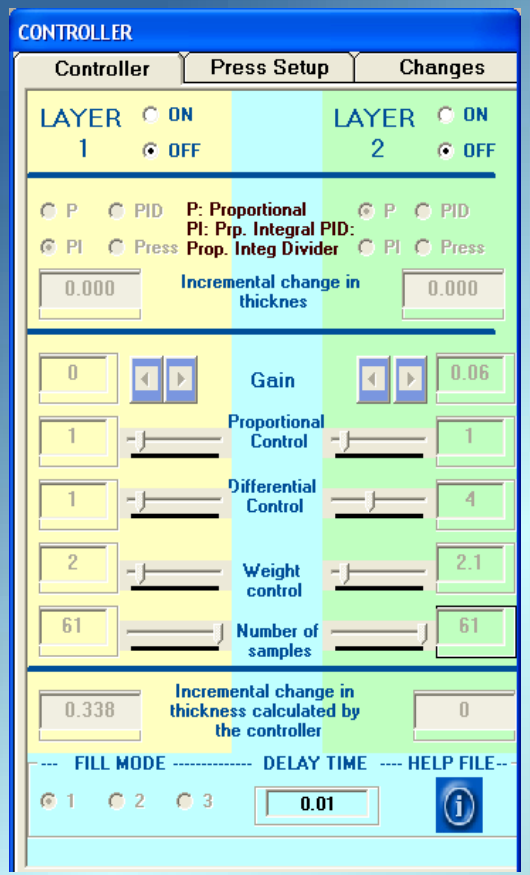
BILAYER PRESS SIMULATION

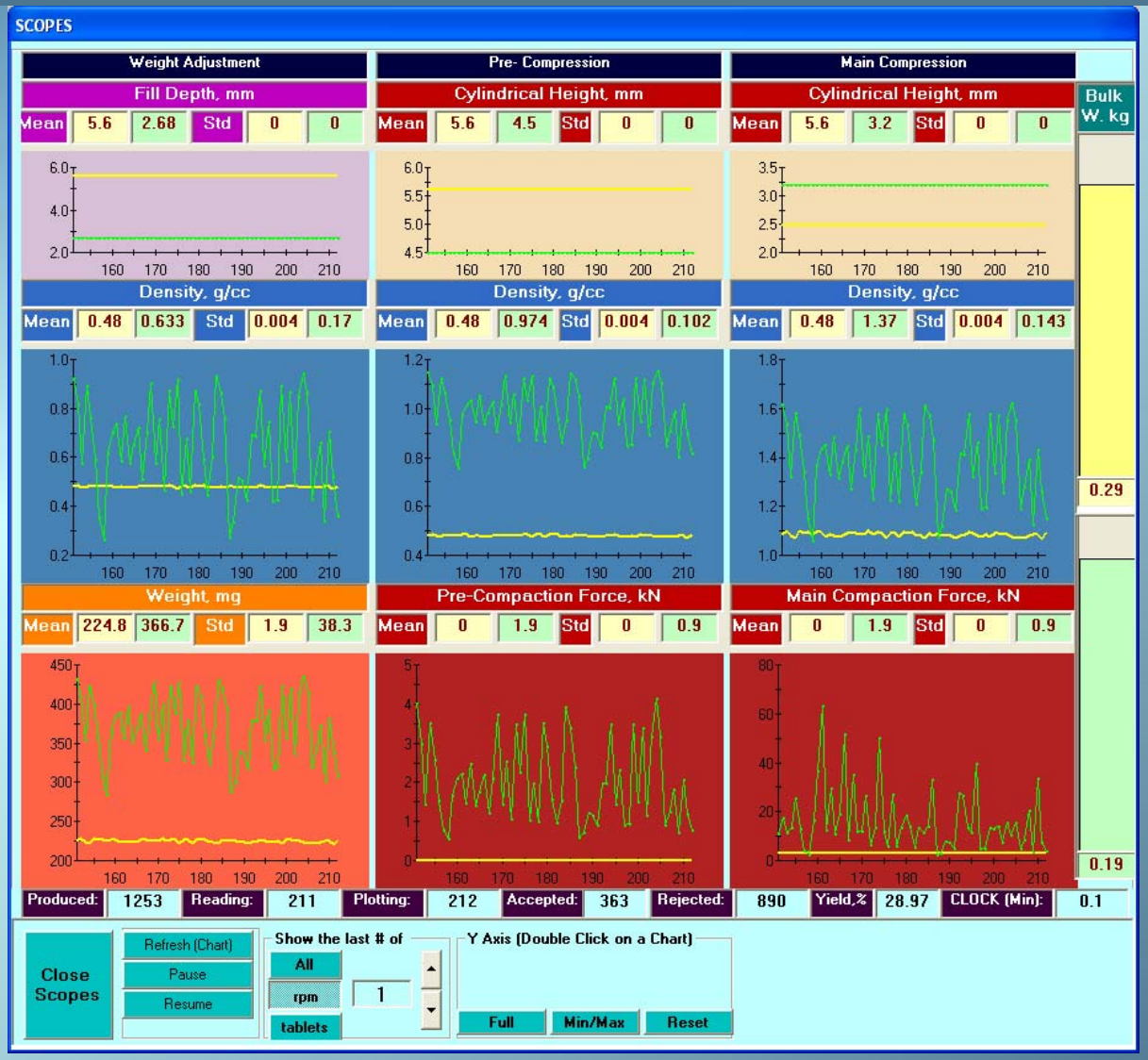


Simulation

Prediction

BILAYER PRESS SIMULATION





Prediction

Conclusions

- The expert system is a guide to understand the development process and it serves as a means of sharing knowledge (transparency) between different centers which is essential in a successful technology transfer. This ultimately will result in a successful PAI, NDA and approval of the product in a speedy manner.
- Several predictive tools to answer “what if” or modeling questions, have emerged to mimic realistic processing conditions in dosage forms development.
- Using the expert system, the quality and effectiveness of the company’s NDAs will improve through our understanding of
  - Regulatory agencies and their requirements
  - Interpretation and application of the regulations

Any Questions?

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Metin.Celik@pt-int.com

Galenique Studio