Workshop:
The Magnesium Stearate Solution

June 22-23rd, 2005, Saint Louis, MO

Mathis

Presentation Framework

- Integration for Control
- Determining action
- Understanding
- Retrofit
- Measurement
- Need to control

Agenda

DI PHARMA TECH	9:00 – 11:00	Mike Tousey Clark Sayer
Mathis	11:00 – 12:00 1:30 – 2:30	Nancy Mathis Stephen Closs
PK	2:30 – 4:00	Tom Chirkot
PATHEON	9:00 – 9:15 9:15 – 9:45 9:45 – 10:30	Patrick Okoye Stephen Closs Demo
NATOLI	10:30 – 12:00	Doug Kirch
BROCK solutions	1:00 – 2:30	Paul Lomelo

← Round the room intros

← Group dinner

← Survey & tour

Mathis

WORKSHOP

THE MAGNESIUM STEARATE SOLUTION

Date:
June 22nd -23rd, 2005

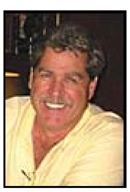
Location:
Natoli Technical Training Center, St Louis, MO

About Workshop: A practical, hands-on session in how to predictively determine the quality of your tablet by monitoring lubrication in real time with a PAT tool. The two-day event provides attendees with a general overview of how to reduce lengthy setup time of the tablet press, avoid wasted product and diminish failed dissolution tests by placing a window on the physical characteristics of your powder upstream. The workshop includes a demonstration of the optimization of tablet press setup parameters in response to monitoring the lubrication of incoming batch material.

Who should attend? This workshop has been constructed for those who are more interested in the practical applications of PAT tools vs. discussing the theoretical benefits. Specifically delivered for those tasked with introducing functional technologies to their organization's manufacturing operation in leveraging the window of opportunity the FDA has presented with the recent PAT Guidance. This isn't for the 'pie-in-the- sky' crowd; this is about what works and what is available today for manufacturing.

If you work in engineering, regulatory, QC/QA, manufacturing, or in the laboratory you will find this course to be extremely beneficial. Anyone involved in the optimization and control of lubrication and tablet press operation will find it of significant value.

Wednesday, June 22nd, 2005



Mike Tousey and Clark Sayer

Mike Tousey, Technical Services Director and Owner of DI Pharma, knows the pharmaceutical processing industry. DI Pharma Tech, a pharmaceutical equipment and training company, specializes in new and used manufacturing, processing and packaging equipment and provides comprehensive tablet manufacturing training programs. Mr. Tousey has over thirty years' experience in nutritional, pharmaceutical, and related industries. A graduate of William Rainey Harper College, he has held positions in sales and technical service for O'Hara Technologies, Thomas Engineering, and Pennwalt Stokes Merrill Corporation.

Time: 9 am – 11 am
When tablets fail … they fail at dissolution testing. That is too late in the process to make any changes. With advanced tablet presses that monitor hardness real time, the problem can still occur. The culprit is the lubricant.

Lubricant levels are a delicate balance between achieving good flow and achieving good compressibility. There is no magic amount of lubricant or post addition blend time that will account for variations in the excipients or the lubricant itself. By monitoring lubrication real time, physical characteristics of powder flow and tablet quality can be determined predictively.

(Continued on next page…)

Clark Sayer of Clark Sayer & Associates is a retail pharmacist, engineer, purchasing agent and consultant who has over forty years of experience in the pharmaceutical and nutraceutical industries. He has domestic and international experience in process development; tech services; cGMP's; production engineering; barrier technology; facility design; and preparation and review of customer requirements, design, and purchase specifications for and sourcing, procurement, installation, and startup of capital equipment in chemical manufacturing, pharmaceutical and nutraceutical manufacturing and packaging (Dry Products and Parenteral), basic research and development, biotechnology research and development; and biotechnology pilot plant operations.

DI PHARMA TECH

Topics Covered Include:

- Need for control
- Root cause analysis of punch sticking and dissolution failure
- Identification of optimal lubricant conditions

Nancy Mathis

Ph.D., P.Eng.

Nancy is the President and CEO of Mathis Instruments. She holds a Ph.D. in Chemical Engineering from the University of New Brunswick and a US patent on instrumentation for testing thermal effusivity and conductivity in a rapid nondestructive manner. The technology was awarded the prestigious R&D 100 award in 1999 as one of the top 100 new product introductions in the world – joining the ranks of Polaroid and the ATM. In 2003, Nancy won the $100,000 Manning Award, the top innovation prize in Canada. She is also a leading member of the PAT community. She is an active member of ASTM E55 and the author of the USP chapter <1073> on effusivity.

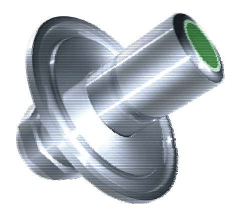
Mathis

Time: 11 am – 2:30 pm (with 1hr. lunch break)

Thermal effusivity relates to a material's ability to transfer heat. It is demonstrated when you touch a piece of metal with one hand while you touch a piece of wood with the other. Despite being the same temperature, the metal feels colder because it has a higher effusivity and draws heat away from your hand more readily. When magnesium stearate coats the particles, it causes the density of the granulation blend to increase and the heat to transfer more readily. This is measured through the increase in effusivity after the lubricant is added.

Topics Covered Include:

- PAT Basics
- Effusivity 101



Thomas Chirkot

Ph.D., P. E.

Tom is a scientist with Patterson-Kelley. He has authored many papers on granulation and blending and is widely cited as an authority in the field. Patterson-Kelley is the original developer of the V-blending technology. P-K provides proven and innovative process solutions for the pharmaceutical industry. Powder processing from process development to equipment design and manufacturing, systems integration and validation. The latest development is the P-K continuous blender. Patterson-Kelley can take any batch blending and granulation process and convert it into a continuous process. Patterson-Kelley has cooperated with Mathis Instruments on the original effusivity technology in Twin-shell® and Cross-flow® blenders.

PK

Time: 2:30 pm – 4 pm

Blending relationships, from API interactions to final lube...

Topics Covered Include:

- Blending Basics
- Content Uniformity Issues
- Physical Measurements
- Continuous vs Batch Processing

Stephen Closs

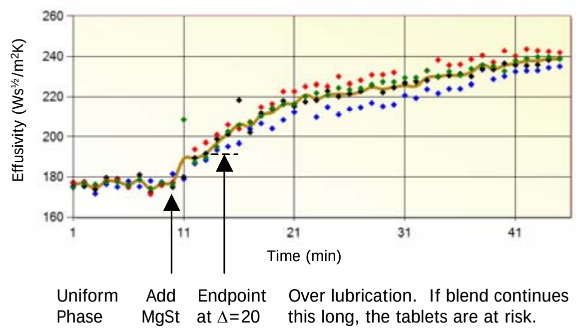
Stephen is the Manager of Process Development Engineering with the Patheon Pharmaceutical Development Services Group in Whitby, Ontario, Canada. Patheon is a leading global provider of dosage from manufacturing and development services to the pharmaceutical and biotechnology industries. Stephen has over 16 years of pharmaceutical production and development experience. He is a member of ISPE, the AAPS PDFG steering committee, and ASTM E55 PAT initiative. He is the author of multiple publications in industry magazines and journals, as well as a presenter at industry forums and conferences. Since early 2004, Mathis and Patheon have collaborated on application research, new technology beta testing and technical publications.

PATHEON

Time: 9 am – 10:30 am

A practical case study in the application of a PAT tool.

The effect of lubricant addition to a uniform material can be clearly identified with effusivity. Having a window on your operation allows you to monitor and control your process to the appropriate endpoint. This presentation will "connect the dots" from between blender monitoring and press optimization.



Doug Kirsch

Doug is the Technical Service Manager with Natoli and has over 35 years of experience in tablet press operation. He originally started his career by training with Manesty Machines in the UK and has helped pharmaceutical manufacturers on both sides of the Atlantic and around the world. Natoli is the world-wide source for punches and dies for the tablet press and pharmaceutical industry. The Natoli System of micro-precision engineering produces punches and dies of rarely matched quality by any producer anywhere in the world. Natoli continues to strive for innovation through new technology.

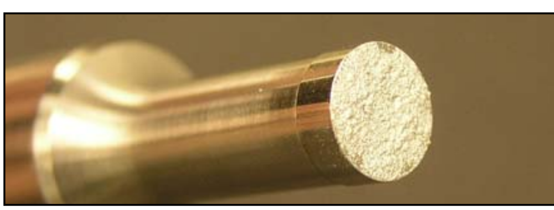
NATOLI

Time: 10:30 am – 12 pm

By knowing the effective lubrication level in advance, an operator can understand the powder characteristics from upstream and take appropriate actions to produce quality tablets. Ideally, the lowest risk alternative would be a preventative action taken at the blender rather than a potential corrective action at the press. Natoli is supportive of any technology that aids in the production of better tablets.

Topics Covered Include:

- Preventative actions at tablet press



DEMONSTRATION: A hands-on demonstration of adjusting a tablet press in response to improve the tablet quality.

Paul Lomelo

Paul is a Business Manager for the Pharmaceutical & Process Division of Brock Solutions. He has 15 years experience in manufacturing and process automation focused on developing compliant automation solutions for pharmaceutical applications. Brock is an Engineering Solutions company specializing in the design, development, and implementation of integrated controls systems. Brock has partnered with Mathis to provide an industrial effusivity package meeting the needs of those specifically in the manufacturing environment.

Time: 1 pm – 2:30 pm
Control of processes using analytical technology and industrial automation – and an HMI demonstration of a typical pharmaceutical blend / lubrication process will be presented from the operator perspective.

Topics Covered Include:

- Automation, integration and control aspects of a fully leveraged PAT tool
- Plant Floor Automation & Process Integration
- Industrialization of PAT

Natoli Plant

Natoli facilities include the latest "state of the art" production and quality-control equipment, allowing Natoli to meet their customer's highest specifications, while at the same time, assuring quick delivery.

Time: 2:30 pm – 4 pm
The workshop will conclude with a guided tour of the Natoli Engineering plant.

THE MAGNESIUM STEARATE SOLUTION WORKSHOP
June 22nd -23rd, 2005
Natoli Technical Training Center, St Louis, MO

Limited seating capacity of 48 people. Register now for one of the available seats at this one of a kind session. Confirm your spot by faxing this completed form to (506) 462-7210, email Nadine@MathisInstruments.com or **call toll-free 1-877-827-7623**. The registration fee of $695 is payable by credit card or check. **Book by May 31st and receive a 10% discount**.

Company: ________________________

Participant Name: __________________

Address: __________________________

City: ______________________________

State: __________ **Zip:** _____________

Tel: (_____) ____-________ Ext:______

Fax: (_____) ____-________

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Credit Card #:______________________

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( ) Check Please make checks payable to "Mathis Instruments Limited" and mail to Attn: Nadine Chiasson, Mathis Instruments, 21 Alison Boulevard, Fredericton. NB Canada E3C 2N5

Travel and Accommodations: St. Louis Lambert International Airport is located approximately 35 minutes from the Hilton Garden Inn St. Louis / Chesterfield. Mathis recommends staying at the Hilton Garden Inn St.Louis / Chesterfield, Missouri. (16631 Chesterfield Grove Rd.). Book your rooms by calling (636) 532-9400.

Lubricants and the Tablet Making Process

Mike Tousey & Clark Sayer

22 June 2005

DI Pharma Tech 152 Wilkerson Drive Madison, SC 29693-4519
Phone 864 647 5400 Website www.dipharma.com Email sales@dipharmatech.com

Scope

Tablet Making Process

Process Control in Tablet Making

Problem Solving and Root Cause Analysis in Assessment of Lubrication Issues

Lubrication and Tablet Specifications

- Lubrication impacts ejection, tablet hardness, friability, disintegration, and dissolution
- Lubrication is not the only variable that impacts final tablet specifications
  - Press Operations
  - Particle Size
  - Density
  - Upstream Operations
  - Raw Material Specifications

Monitor and Control of Lubrication

- Manages one variable in the manufacturing process
- Can be Validated
- Value can be lessened
  - Poor press operations
  - Environmental controls
  - Variable quality in incoming powder mass
  - Variable quality in incoming raw materials

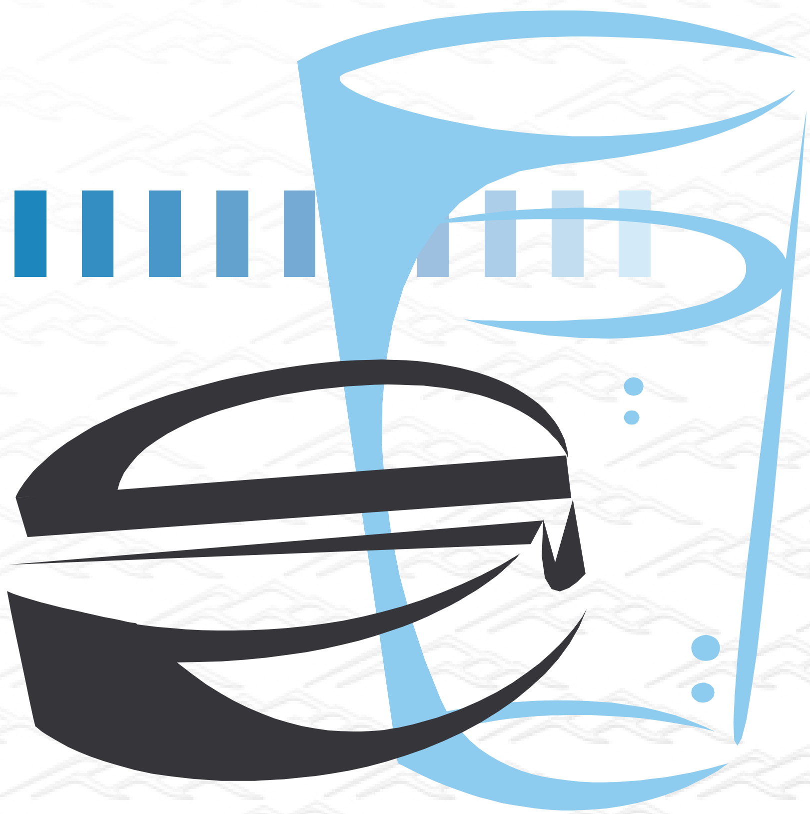
The Correct Objective

- The objective is to deliver a ingredient in a controlled and predictable manner
- Focusing on one issue may cause problems in other areas

Bioavailability

- Ultimate Outcome of Making a Tablet
- A Combination of Therapeutically Effective Dose and Dose Response Curve
- Best measured *in vitro* by analysis of dissolution medium for API
- Excess Lubrication can slow or prevent dissolution and bioavailability

Outcomes Required
as a result of Making Tablets



- Bioavailability
- Content Uniformity
- Dissolution
- Disintegration
- Friability
- Hardness
- Weight

All of us are betting our lives that a granulation flows well!

- With the average press speed at 3,000 TPM, 50 tablets are made each second.
- Sub potent pharmaceutical.
- Super potent pharmaceutical.
- Dependable and reproducible powder flow, compressibility and ejection are critical.
- The Key is FLOW

Characteristics of Powder Mass Required to Make a Good Tablet

- Cohesion

  The tendency of powders to naturally stick together

- Flow

  Mass Flow vs. Funnel Flow

- Content Uniformity (CU)
  Even distribution of API throughout the powder mass
  Maintain CU throughout the manufacturing process

Excipients

- Binder
- Filler
- Lubricant
- Disintegrant
- Glidant
- Compression aid
- Color
- Sweetener
- Dispensing agent
- Coating
- Preservative
- Flavors

Powder Variables

- Particle size
- Size distribution
- Shape
- Surface texture
- Cohesivity
- Surface coating
- Particle interaction
- Electro-static charge
- Compaction recovery
- Wear/attrition characteristics

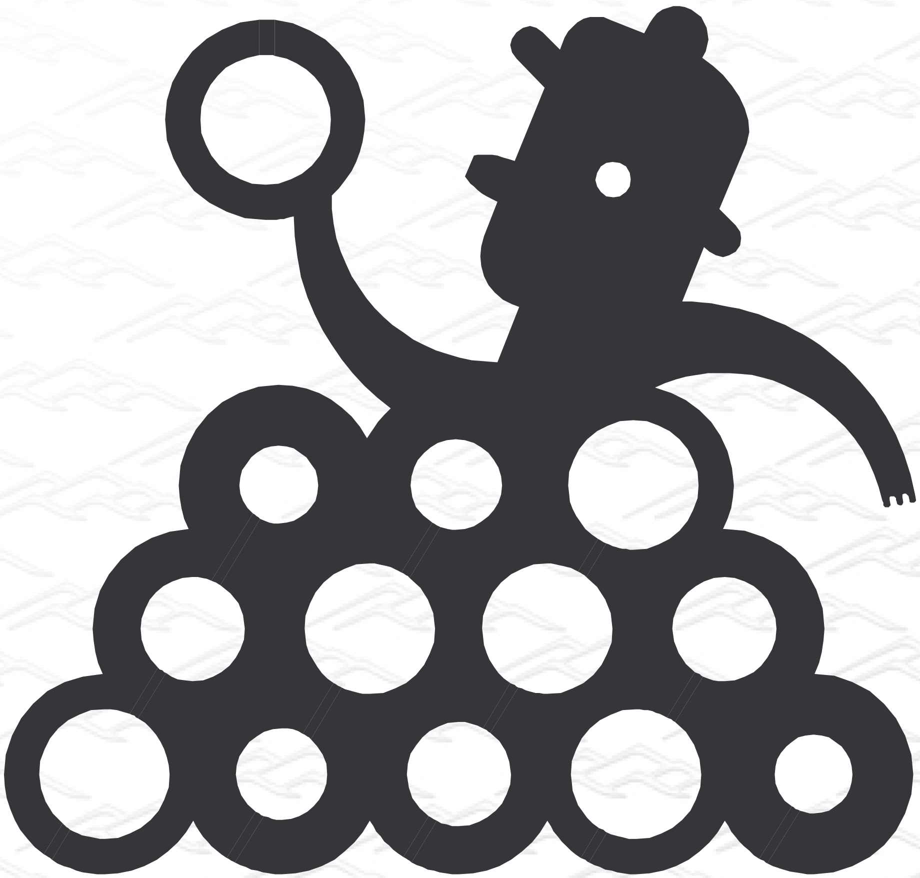
Compaction

- Free flowing powders are little affected by vibration.
- Deadweight compaction of cohesive powders (powders in a hopper for instance) may produce a significant decrease of flow properties.

Powders Must Flow!

- Good flow can be compared to granulated sugar
- Bad flow can be compared to powdered sugar
- Products must flow freely to achieve proper weight

Powders Must Compress



- Particles must lock together
- Over wet particles will cause **Sticking**
- Over dry particles will cause **Lamination**
- Fine particles escape during compression
- Time under pressure is **Dwell time**
- Press speed relates to compressibility

Content Uniformity

- Essential for Proper Therapeutic Dose Levels
- Essential for Proper Response to Dose
- Especially Difficult where API is Low % of Total Tablet Weight
- Affected by Relative Particle Size of API and Excipients
- Affected by Relative Bulk and Tapped Bulk Densities of API and Excipients
- Affected by Manufacturing Process, Transportation, and Storage
- An Example is Sugar and API in Pediatric Antibiotic Formulations

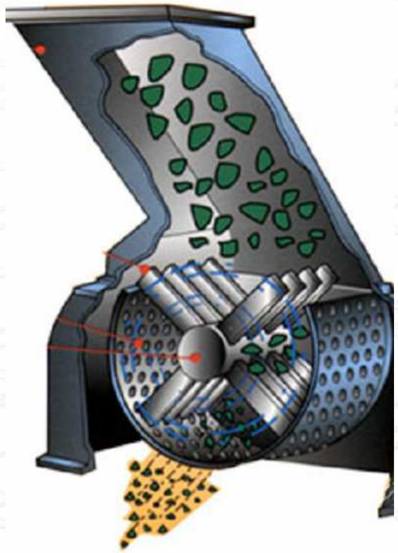
Particle Size and Bulk Density

- This discussion will focus on particle size and bulk density and their impact on making tablets
- Three types of density
  - Bulk (Loose) – density of powders in their natural state
  - Tapped – a USP method for removing air from the powder mass in a controlled, validated way
  - Free – all air removed; rarely used as a tool
- Particle size is independent of morphology (shape) of particle
- Morphology can impact compression
- Particle size and bulk density have a direct influence on segregation

Bulk Density

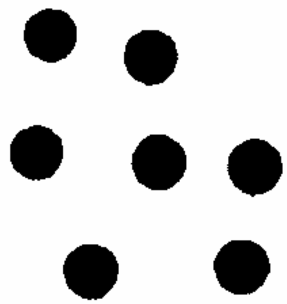
- Usually recorded as mg./ml. Or gm./cc.
- Not particularly sensitive.
- Not entirely predictive.
- May be recorded as “bulk” or “tapped”.
- Carr’s Index and Hausner’s Ratio are common tools used to predict compressibility

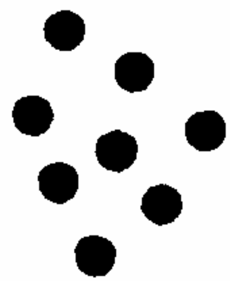
Particle Size Distribution

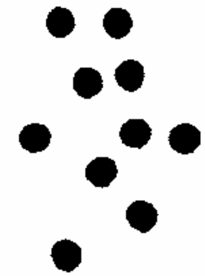


- Usually recorded as a percentage on a specific screen.
- Very sensitive and predictive.
- Excellent test.

Particle Size Distribution: Good Tablets Need A Range

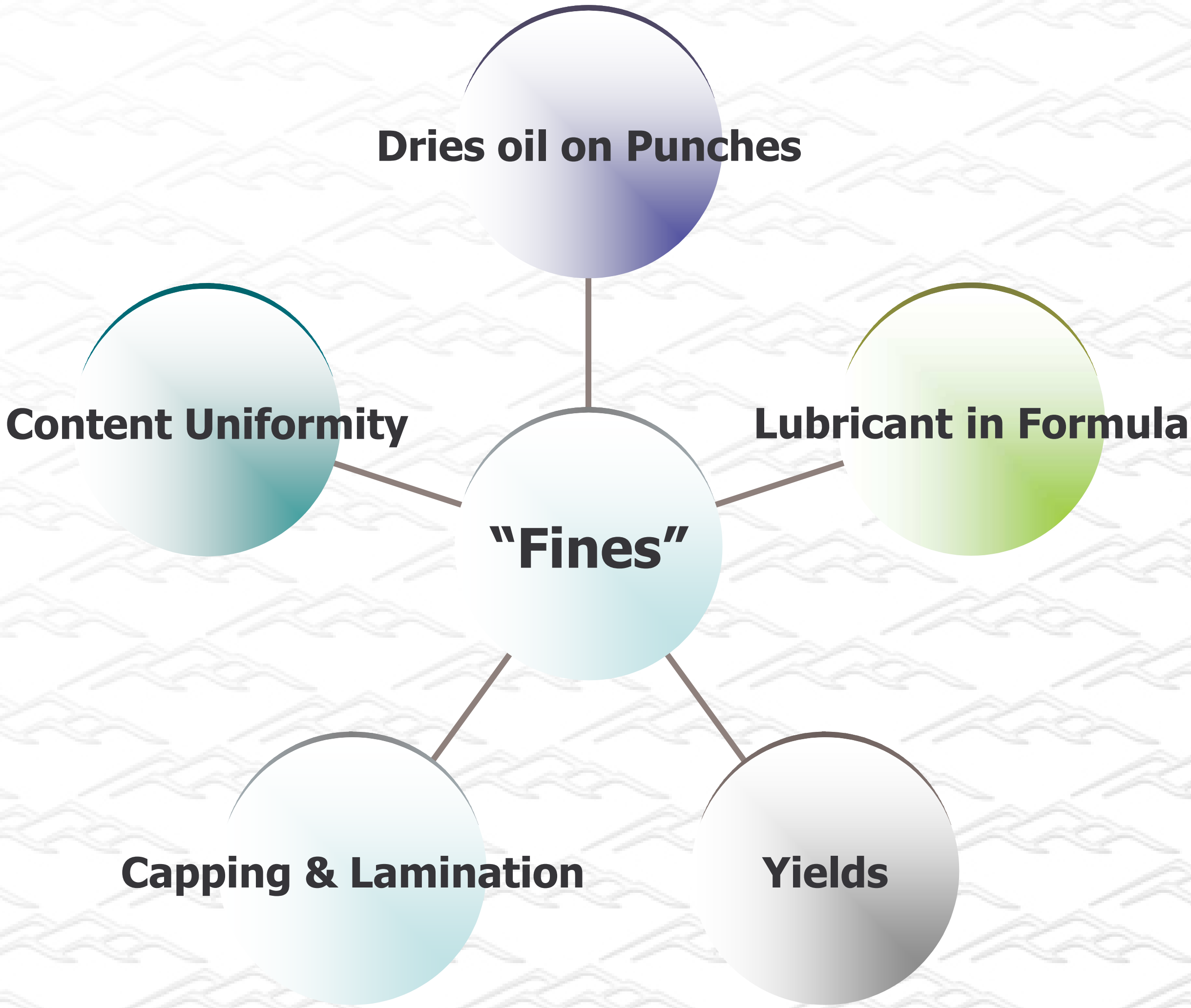






“ Rocks”,	Intermediates	Fines,
<20 Mesh	40-120 Mesh	>200 Mesh
10-20%	70-80%	10-20%

"Fines" Affect Many Areas



Particle Size Control

- Flow & weight control are the objective
- To reduce large agglomerates without producing “fines”.
- Particle size relationship to final tablet size

Milling for Tablet Making

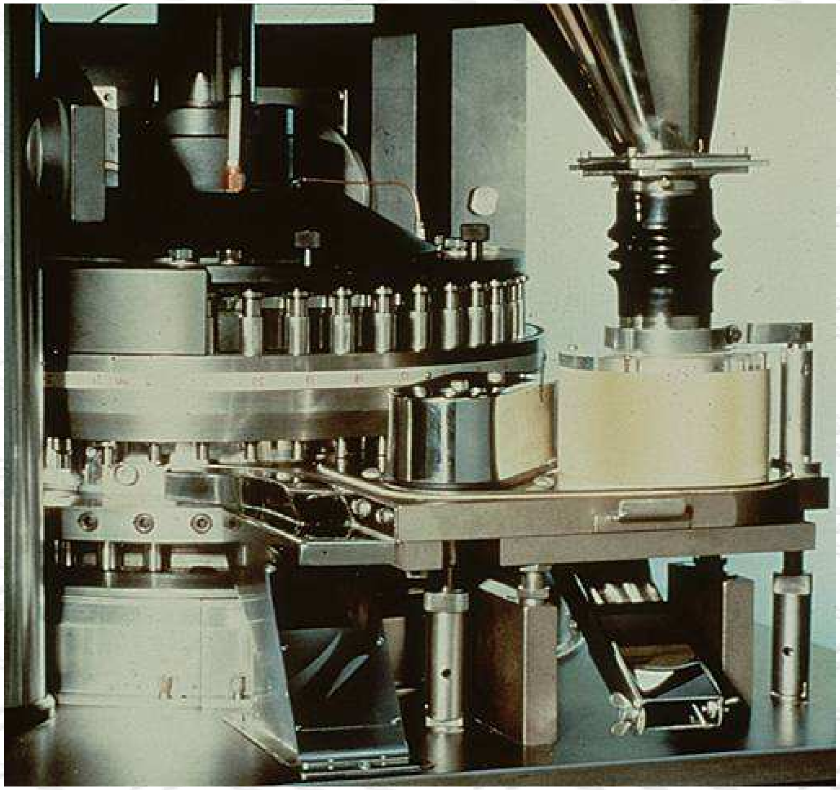
- Improve Flow
- Reduce Segregation
- Enhance Drying
- Control Particle Size
- Consistency – batch to batch

Requirements for Making Tablets

- Flow
  Powder must flow freely into the die
  Mass flow vs. Funnel Flow
- Compress
  Plastic Deformation
  Fracture
  Interparticulate Attraction
  Melting Point
- Eject
  Sole purpose of lubricant in making tablets
  Lubricant not required to make a tablet
  No ejection without lubricant
  There are products with natural lubricity
  There are excipients with integrated lubricants

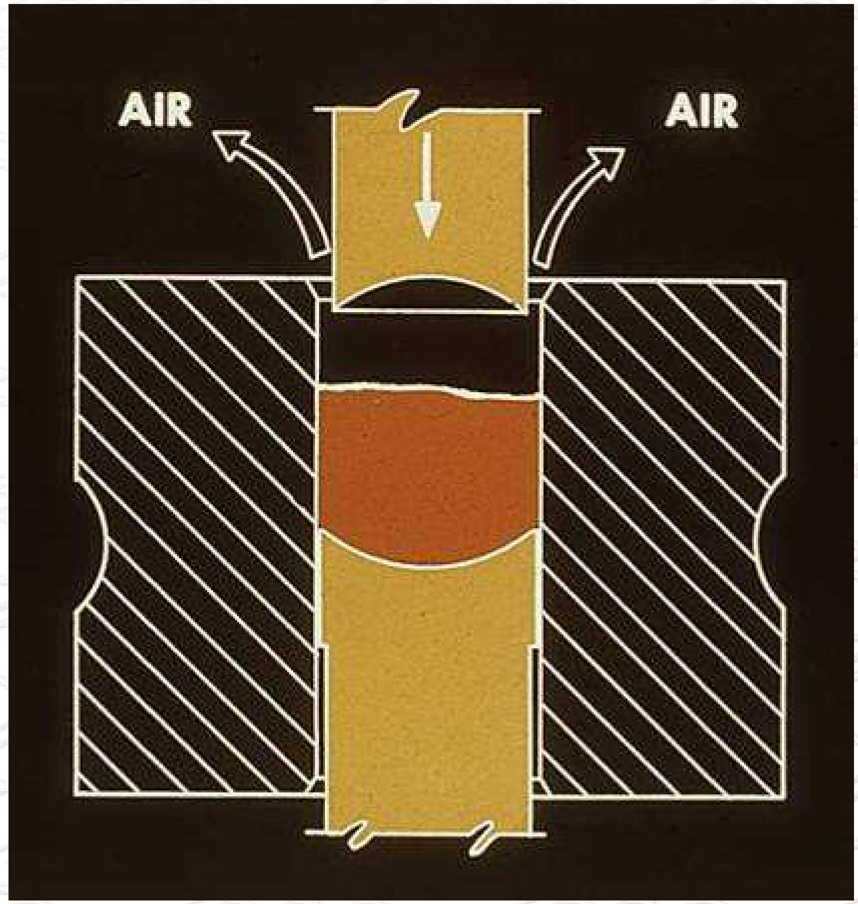
Characteristics of Powder Mass that Affect Tablet Compression

- Powder characteristics determine the need for control
- Compare soft highly compressible powders to tough friable ones
- Good flow on one press does not always equal flow on another press



Compression

- During compression air must leave in order to form a good tablet.
- This Upper punch tip clearance is very important.
- Remove all the air and prevent migration of fine particles
- Dwell time must allow for adequate locking of particle to one another



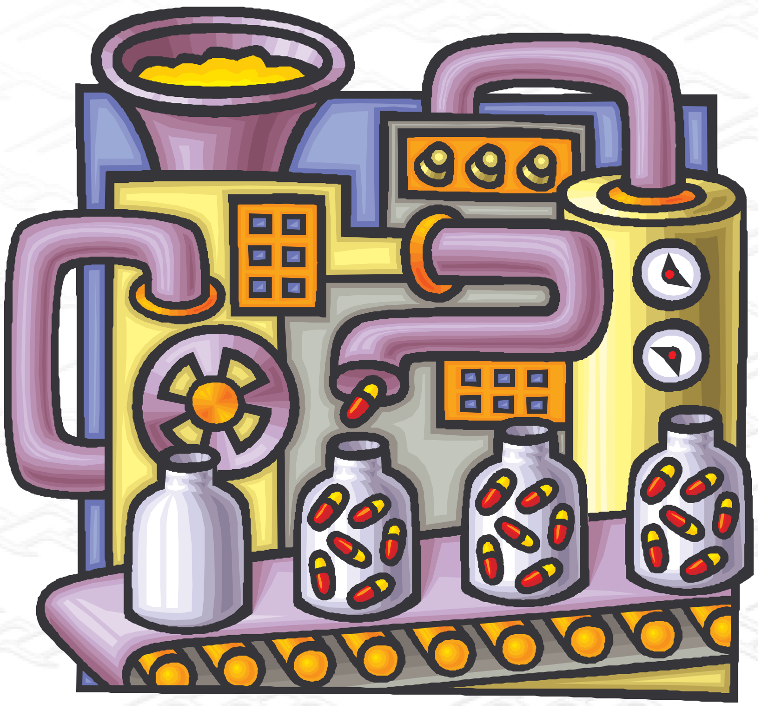
Look and Listen

- The one thing that is rarely on a SOP is to listen to the machine
- An experienced operator can hear when the machine is optimized
- A powder lacking lubricant does sound different, harder, rougher and usually resulting in a higher operating temperature.

Ejection

- Once compressed, the tablet must eject
- The tablet can break up at ejection
- Most ingredients will not eject without the addition of a lubricant
- Modern machines monitor ejection force
- The process path can influence the role of the lubricant

Tablet Press and Tooling



- Tablet Press RPM
- Tablet Press Feeder RPM
- Tablet Press Condition
- Tooling: Punch Cup Surface
- Tooling: Wear factors
- Tooling: Polishing Technique
- Air release during compaction
- Other Mold Release Agents

Punch Cup Finish & Sticking

- The need to polish punches is to maintain a high quality finish
- Most sticking is not related to tool design or punch surface finish
- Mid-stream polishing is a Band-aid, an the formula or process is at fault.

Tablet Defects

- Later, the tablet press will be called the report card for how well powders have been prepared to flow, compress and eject.
- Bioavailability is the final exam
- Tablet defects are the mid-terms
- Two types
  - Process – e.g., weight, hardness, thickness
  - Performance – e.g., picking, sticking, capping
- Let's talk first about performance defects

Common Tablet Defects

- Capping – splitting of the tablet where the radius meets the straight wall
- Lamination – occurs when groups of powders will not lock together
- Picking – occurs when bits of the tablet are pulled away from its surface
- Sticking – occurs when bits of the tablet stick to the punch tip

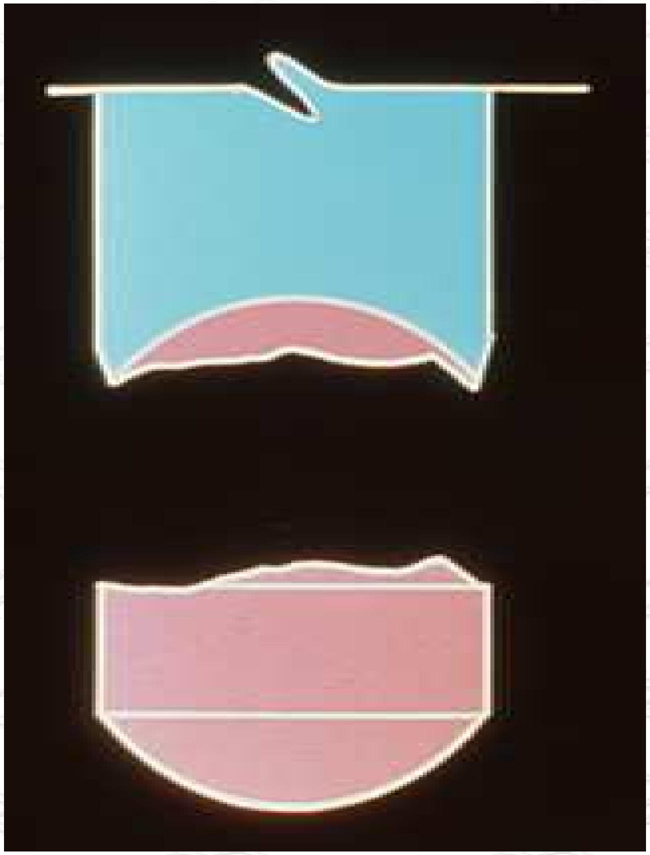
Why do Powders Stick

- Inadequate amount of Lubricant
- Lubricant under mixed
- Lubricant over mixed
- Temperature
- Moisture
- Particle size
- Particle structure
- Fines
- Static electricity
- Hardness
- Tablet Press and Tooling

Sticking or Capping or Something?

- This photo shows that the tooling has pulled the cap away which can be appear as sticking or capping

- Capping is caused by a lack of lock-ability between particles along the upper cap and the tablet band. It is often associated with air entrapment and fines.



If Powders do not cooperate:

- Combining powders with other powders can help them flow, compress and eject.
- Sometimes the powders must be altered to make them work: particle size, moisture content, and density control are the most common ways to influence powders to make them perform.

Powders must stay mixed on the press

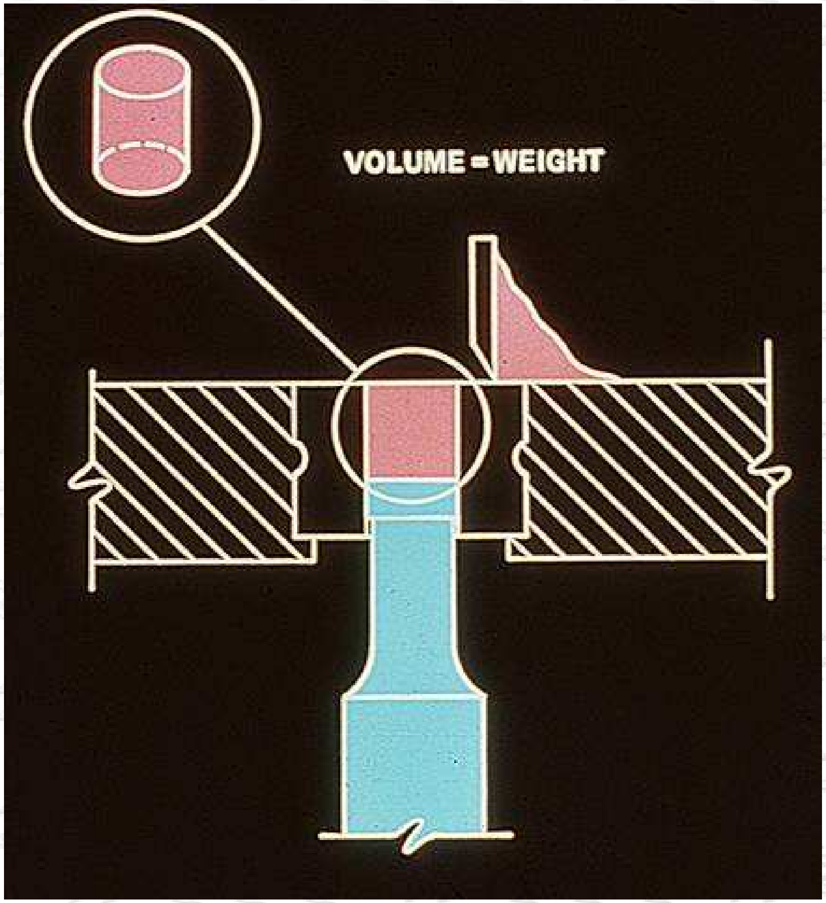
- Same weight, different bulk densities.
- Segregation is a common issue most often related to combining powders
- Segregation occurs when different densities and particle sizes are confronted by gravity

Volume Control = Weight Control

- Tablet weight is defined by volume of the cavity formed by the tip of the lower punch, the side walls of the die, and scrape-off.
- Weight is derived from volume by way of the bulk density of the powder mass.
- Weight variations can only arise from segregation and changes flow
- Segregation can derive from changes in particle size, bulk density, or flow characteristics of the powder mass.

Volume=Weight

- The press does not weigh powder, it fills by volume.
- Particle size and density are the key factors for good weight control
- Scrape off is critical



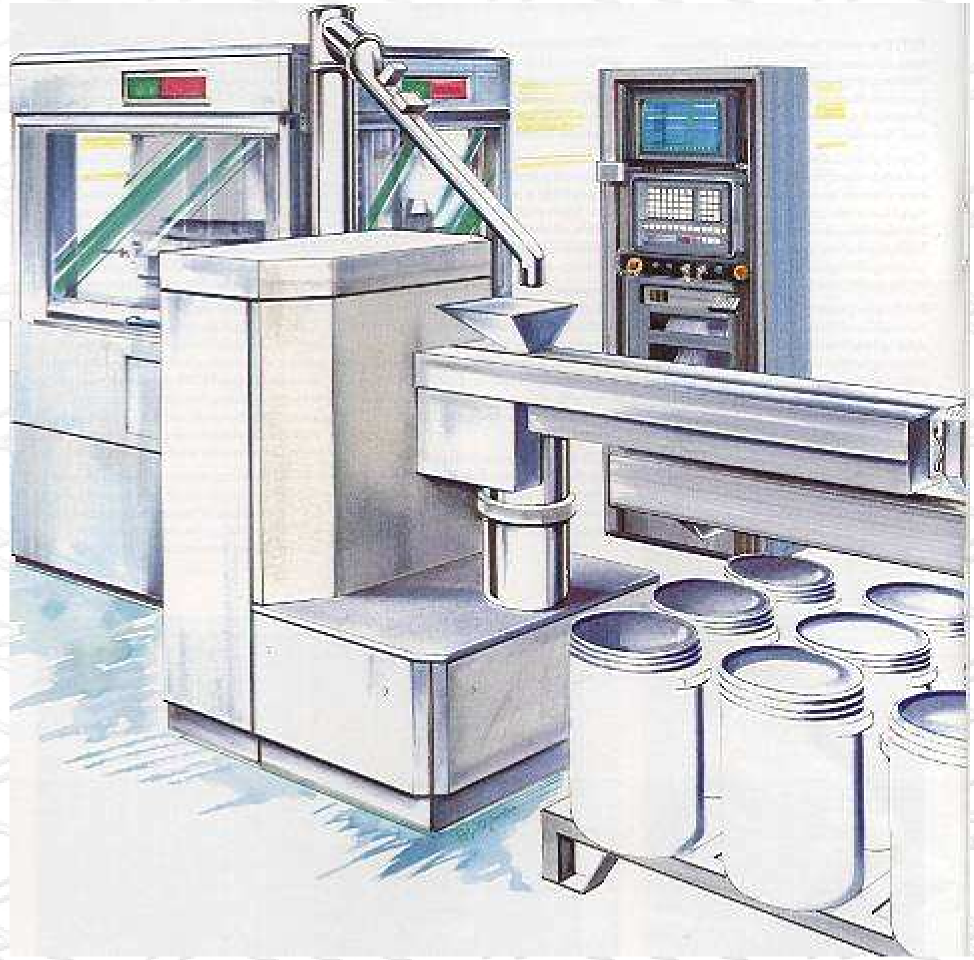
Tablet Weight

- Target & Range
- Weight vs content
- Many scales & procedures amongst the companies.
- Usually +/- 1/2, 3 and 5% off target.
- Easily achieved with a good granulation.

The Need for Control

- The press is the report card for how well powders are prepared to flow, compress and eject

- Disintegration and Dissolution are the final measures of process performance



Disintegration and Dissolution

Disintegration

- How long does it take?
- Measured in Minutes
- Indirectly related to bioavailability
- Physical phenomenon

Dissolution

- How long does it take?
- Measured as % of total API present
- Directly related to bioavailability
- Chemical phenomenon

Summary of Tablet Making

- Characteristics of the powder mass,
- Nature and variety of APIs and excipients,
- Functions of the tablet press,
- Markers for good tablets,
- Indicators of unacceptable tablets
- Measures of press and tablet performance
- Tools used to measure performance

Process Control in Tablet Making

- Elements of Process Control
  - identification of process variables
  - identification of key process variables
  - knowledge of the interaction of the variables
  - analysis of final product
  - PAT (e.g., effusivity)
  - instrument calibration
  - environmental controls

Reasons For Control

- Why do we care (why do we need to manage and control the factors that impact the tablet making process)
  - professional integrity
  - regulatory requirements
  - avoidance of lawsuits

Problem Solving as a Part of Process Control

- Bioavailability is dose and dose response
- Bioavailability dependent on dissolution and CU
- Dissolution dependent on disintegration and access of dissolution media to API
- CU dependent of the manufacturing process of which making tablets is a part
- Tablet defects are an indication that process may be out of control

Application

- Root Cause Analysis as a Problem Solving Tool
  - In tablet making, proximate causes are few and possible root causes are many
  - Example: Lubrication as a root cause
  - CU – yes - e.g., segregation and altered flow
  - Dissolution – yes - e.g., prevention or slowing of dissolution by too much lubricant
  - Tablet defects – yes
    - Process - e.g., weight, hardness, and friability
    - Performance – e.g., capping, picking, and sticking

Conclusions

- Process control technology can be useful in monitoring application and distribution of lubricant in a powder mass
- Maximize benefit of lubricant (ejection of tablet) while minimizing risk (promotion of segregation and negative effects on dissolution and flow)
- Assure thorough distribution of lubricant to minimize demixing

Thank You!

Lubricants and the Tablet Making Process

Mike Tousey & Clark Sayer
22 June 2005

DI Pharma Tech 152 Wilkerson Drive Madison, SC 29693-4519
Phone 864 647 5400 Website www.dipharma.com Email sales@dipharmatech.com

The Magnesium Stearate Solution

An application of effusivity PAT

www.MathisInstruments.com June 2005 1-866-425-3637

Agenda

Mathis

PAT Basics

Effusivity 101

- Why it works
- Results
- Actions that can be taken

Summary and Q & A

Mathis:
Who we are …. and who we aren't

Mathis - What We Do

Non-destructive, thermal sensor technology solutions for R&D, production, and QC applications, delivering fast, **accurate** measurement of **thermal conductivity** and effusivity **in seconds** with virtually unlimited sample size.

From pharmaceuticals to petroleum – providing **manufacturers** with **on-line** solutions to better understand and **improve** product **consistency**.

Our **innovation** never stops.

Mathis

Mathis - What We AREN'T

Mathis is a piece of the pie in providing a meaningful solution to your process control needs.

We pride ourselves in our partnerships with other OEMs and vendors who provide critical elements to that solution.

In that way, clients get experience delivered by experts in the fields.

Mathis

Implementation Partners

O'HARA TECHNOLOGIES

invensys Validation Technologies™

PATHEON

MOVA

PK

TOTE SYSTEMS®

symex mixing technology

CardinalHealth

AFI ABILITY FABRICATORS INC.
Your custom stainless steel fabrication partner

SENTRY ISOLOK® BEC
The Sampling Connection

BROCK solutions

NATOLI

Tunnell Consulting

Laboratoires Confab Laboratories inc.

FMC | FMC BioPolymer
THE SCIENCE OF FORMULATION

vectorcorporation
A FREUND GROUP COMPANY
Our Vision: To be our customer's most trusted and valuable supplier.

PAT:
Why do it… and why not now?

PAT helps you know where you are, so you can get where you are going.

GMP.... "Great Mounds of Paper", Ken Leiper

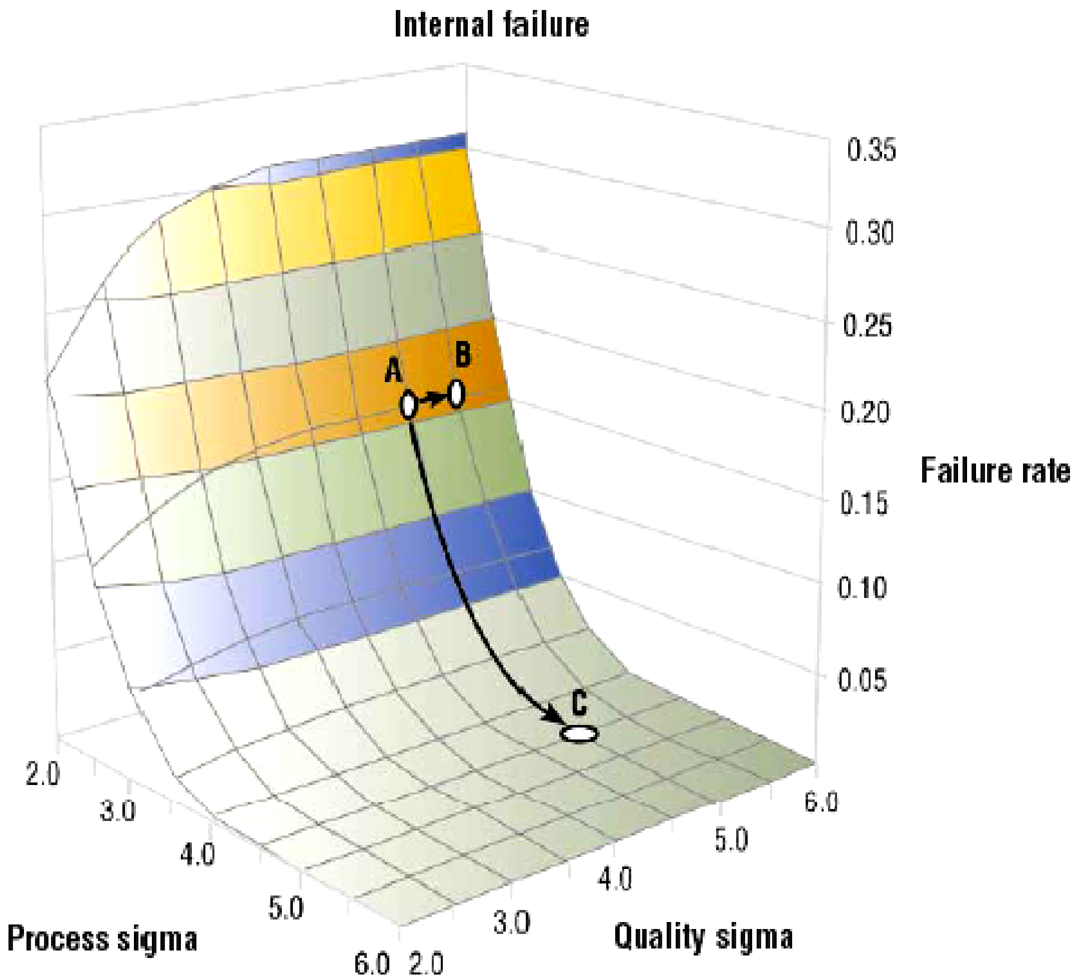
Delivering higher-quality products – the interplay between process and quality system capabilities[40]

Poor quality comprises internal failures and external failures. The process sigma is derived from internal failure rates (scrap, rework, waste) and provides a measure of process robustness and understanding. The quality sigma is derived from the ability of the quality system to prevent any of the internal failures created by the production process from escaping to the external environment, and in so doing to create no "false negatives."

A – Most companies are here with process sigma of 2.5 and quality sigma of 5.0, i.e. (2.5, 5.0).

B – Many companies will invest to improve "quality by inspection" without changing production processes to get here, i.e.(2.5, 5.5). This will actually increase the internal failure rate.

C – If a company were to invest to bring process sigma levels to 4.5 or greater to reach (4.5, 5.0), the impact on failure rate reduction would be over 1000 times greater than that obtained by improving the quality system alone.



Source: IBM Business Consulting Services, 2005.

Sigma Shift: 2.5 σ to 4σ

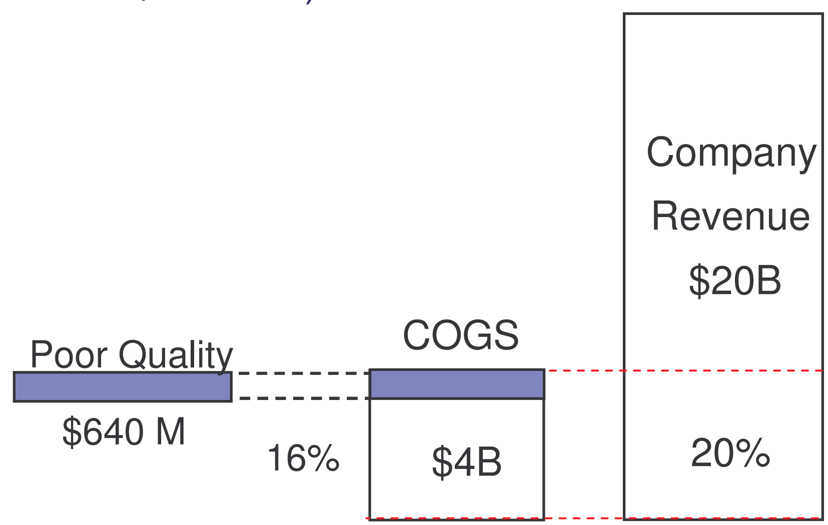
COGS = 20% of sales (e.g. 20% of $20 Billion = $4 Billion)

Current Quality Performance
- 2.5 Sigma Productivity Loss = 16%

$ cost of poor quality = 16% of COGS
- e.g. 16% of $4 Billion = $640 Million

Improve performance to 4 Sigma
- 4 Sigma Productivity Loss = 0.6%

$ cost of poor quality = 0.6 % of COGS
- e.g. 0.6% of $4 Billion = $24 Million



COGS reduction of $616 Million for a company with $20 Billion revenues

Source: Frances Bruttin and Doug Dean, IBM Consulting
IVT PAT Conference, Philadelphia, June 13-16, 2005

Knowledge Evolution

	Development culture	*Technology platform knowledge*
5	Ability to predict and refine processes based on mathematical models of the interaction of critical control parameters	First principle knowledge
4	Understanding of critical control parameters and mechanisms by which they affect process	Mechanistic knowledge
3	Understanding of how process outcomes are affected by critical control parameters	Causal knowledge
2	Correlational understanding of process behavior under defined circumstances	Process knowledge
1	Trial and error experimentation	Descriptive knowledge

Source: Frances Bruttin and Doug Dean, IBM Consulting
IVT PAT Conference, Philadelphia, June 13-16, 2005

PAT – Why or Why Not?

Facilitators - 2

1. Desire for process understanding
2. Usage of data (safe harbor concept)

Barriers - 5

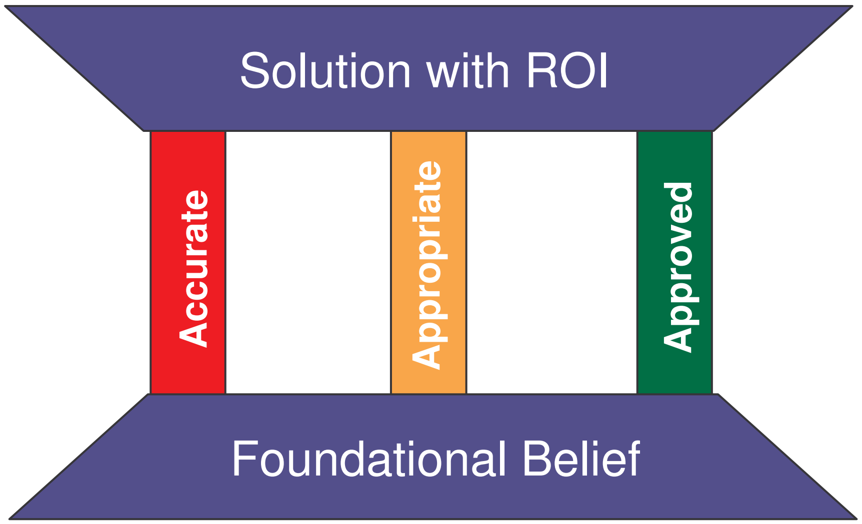
1. Management buy-in
2. PAT scope understanding
3. Resources and skill set availability
4. Validation strategy
5. Cost

A Bit of Both - 4

1. Regulatory environment
2. Appropriate technologies
3. Corporate change culture
4. Data and information management

Mathis Workshop survey results
IVT June 2005

Pillars of Management Buy-in



"The data must be meaningful. It must be calibrated, consistent and correlated",
Director of Analytical

"The equipment must be manufacturing ready. It must be robust and integrated",
Director of Engineering.

"The approach must be approved. It must be compliant and validatable",
Director of QA

" I want better returns from my process. I need reduced scrap/rework, increased throughput and better quality … all with fewer resources",
Site Director or VP Operations

Effusivity:

Basics on what the technology does

Our Technology

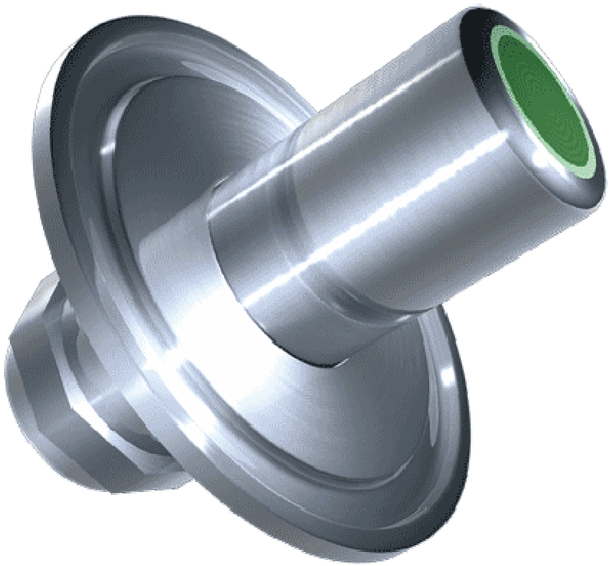
Heat always flows from a hot object to a cold object.

Wood is not a good conductor of heat, so it is **slow** to absorb the heat.

Metal has higher **"thermal effusivity"** so the heat from your hand flows into the metal **quickly** - creating the sensation of it being cold.

Mathis sensors work like your hand, by **rapidly** determining the **rate** of heat flow from one material to another. Like your hands, our sensors **supply** the heat source *and* **detect** the heat flow. They also have no **sample size** issues, and do not destroy the sample being tested.

Instrument Results



$$Effusivity = \sqrt{k \rho c_p}$$

$$Where:$$

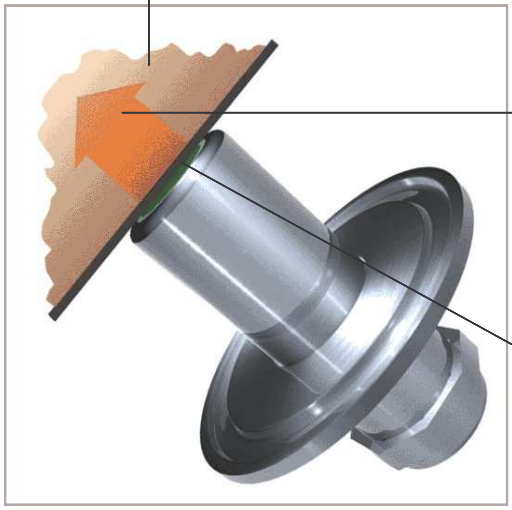
$$k = thermal\ conductivity\ (W/m \cdot K)$$

$$\rho = density\ (kg/m^3)$$

$$c_p = heat\ capacity\ (J/kg \cdot K)$$

Principles of Operation

Materials inside the blender have different thermal properties at the onset of blending



Heat is generated by the sensor. Some Heat penetrates the materials, but some is retained.

The amount of heat retained at the surface of the sensor causes a temperature increase. The rate of increase is compared and used to determine the uniformity.

Test times can be varied to optimize the scale of scrutiny. A 2s test penetrates into the powder roughly 0.5 mm.

Multiple Influences

Effusivity is a function of

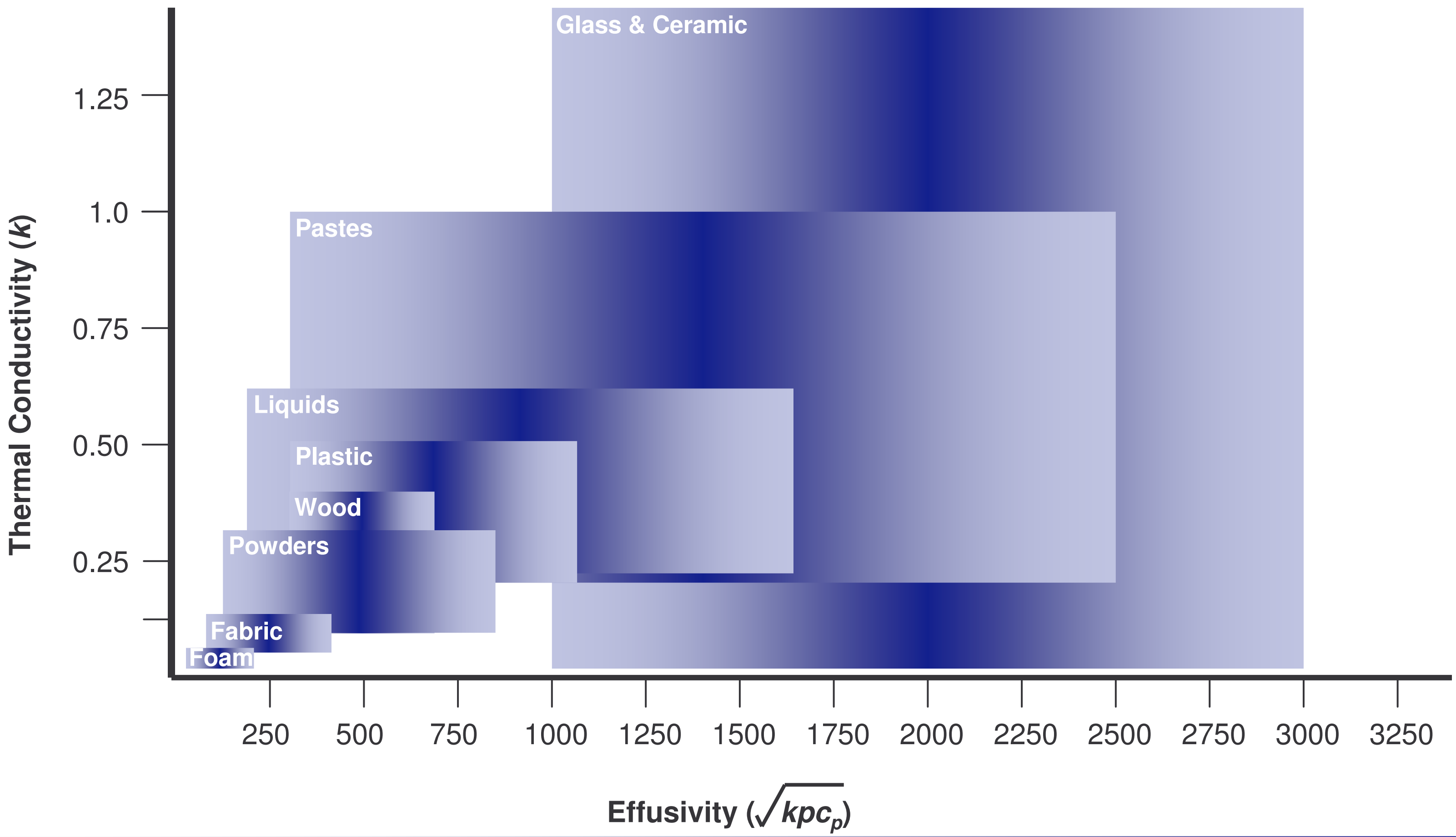
Particle structure
- Crystallinity
- Morphology

Packing & particle "connection"
- Particle size and shape
- Particle size distribution
- Lubricant effect

Composition
- Moisture level
- Weight % ingredients

Changes in these factors with time and/or space make Effusivity RSD% a sensitive multivariable measure that is often orthogonal to other measurement techniques.

Spectrum of Properties



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Effusivity:
In blending and lubrication

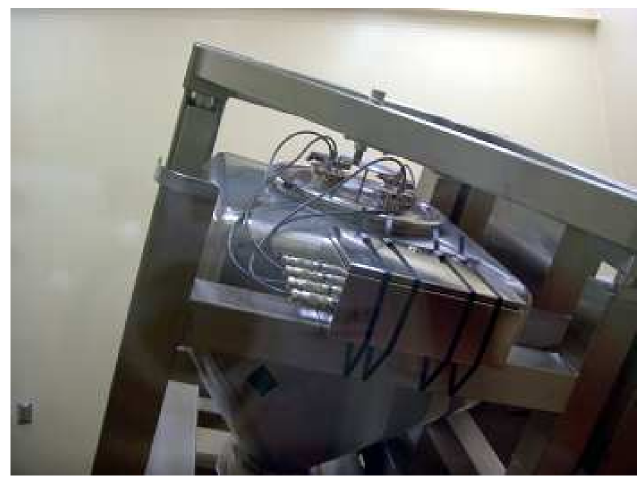
Configuration for blenders – wireless ESP™

1 - Wall mounted "toughbook" or HMI options
- dust and spill proof
- integrated wireless
- able to monitor outside suite

2 - Mountable controller
- wireless transceiver
- battery with recharger

3 - Software
- coordinated testing
- feedback for close loop
- multi-unit capability

4 - Sensors
- solid state and liquid proof
- 17 mm diameter
- In direct contact with the material



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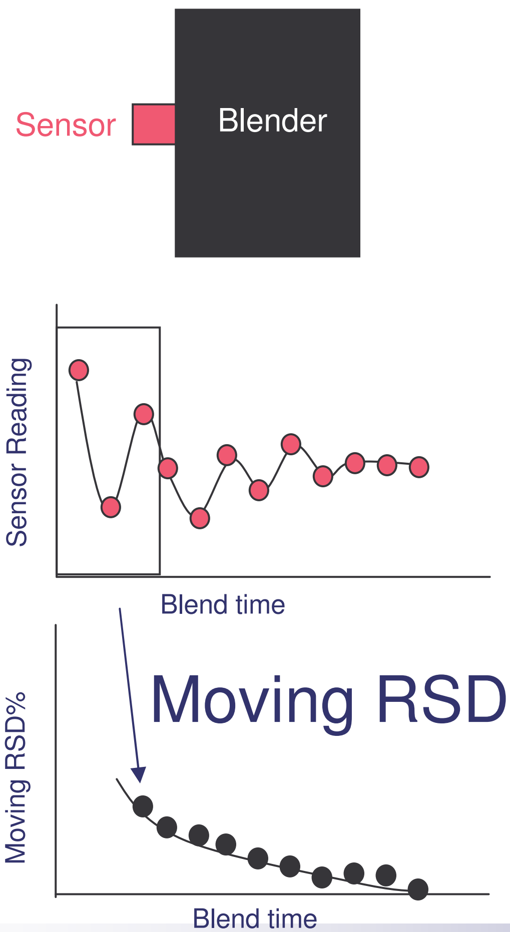
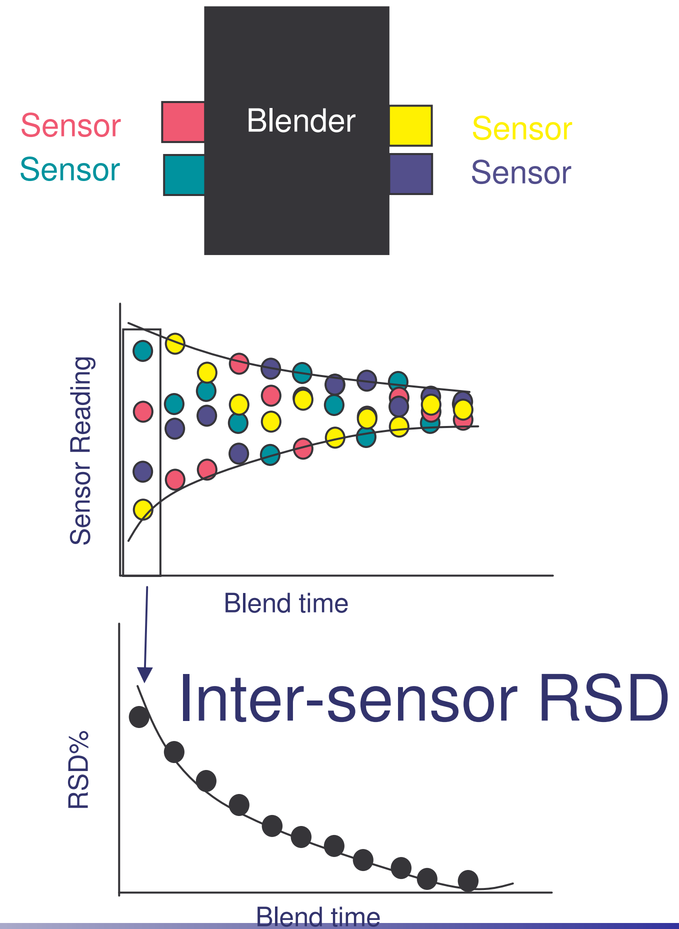
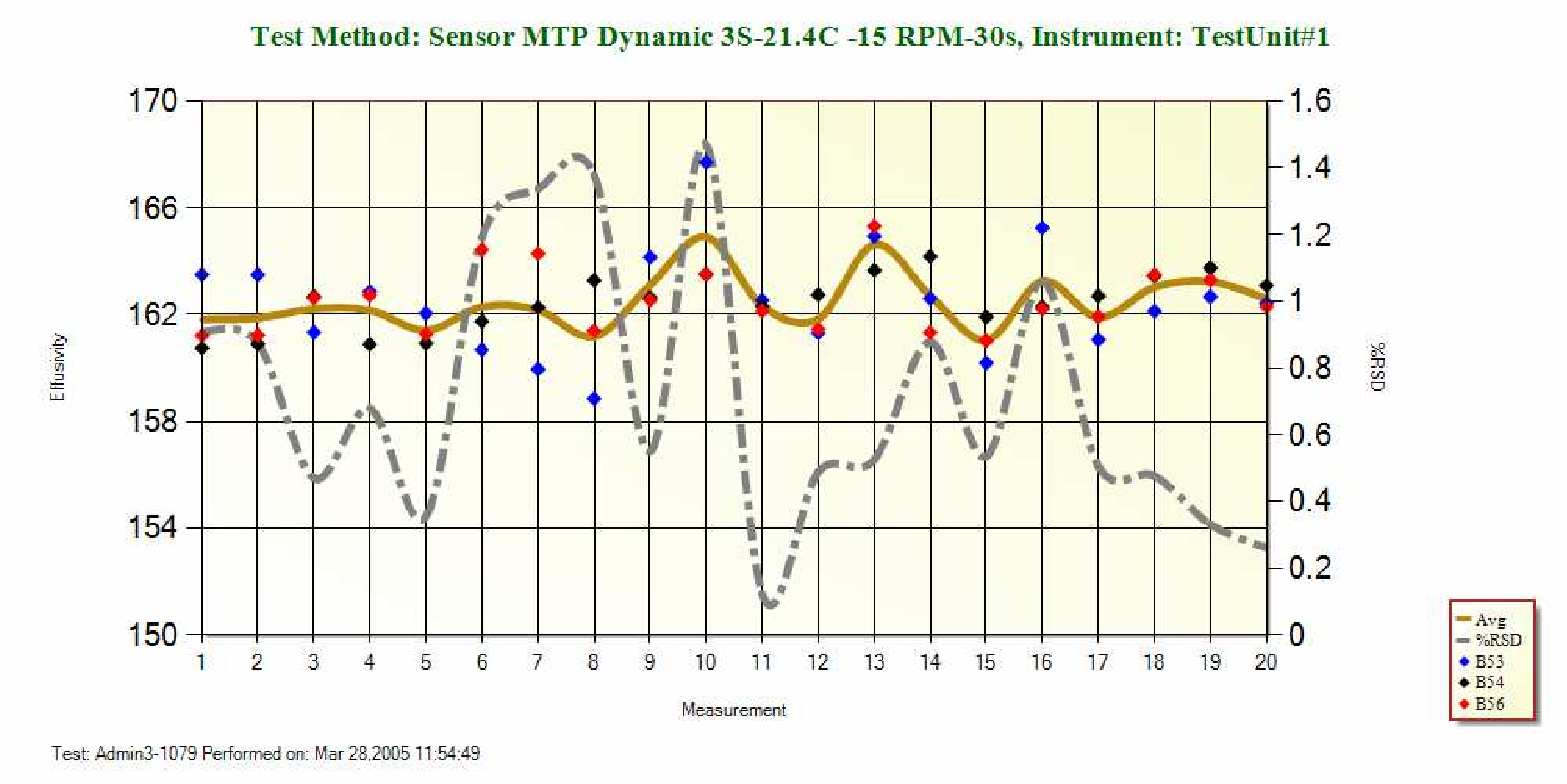
Single or Multi Sensor

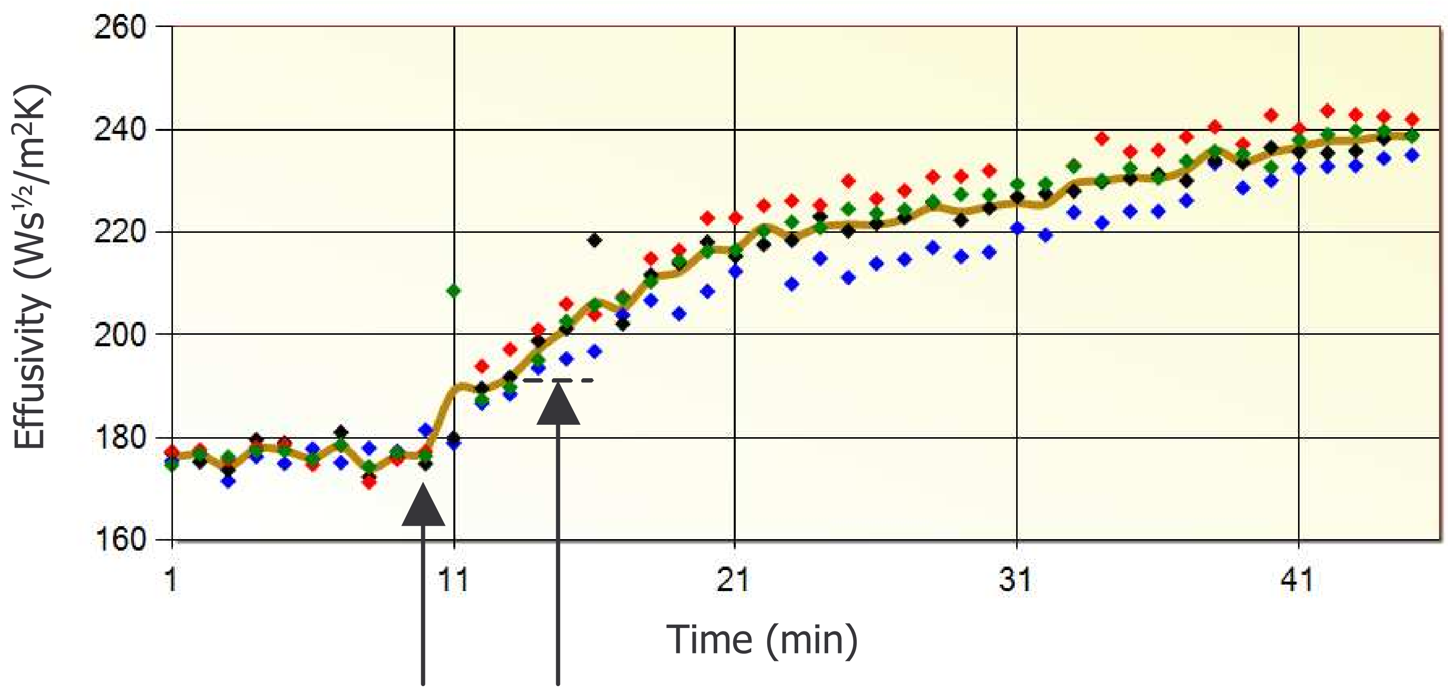




Background variability <1.5% - Avicel™



Lubricant Influence



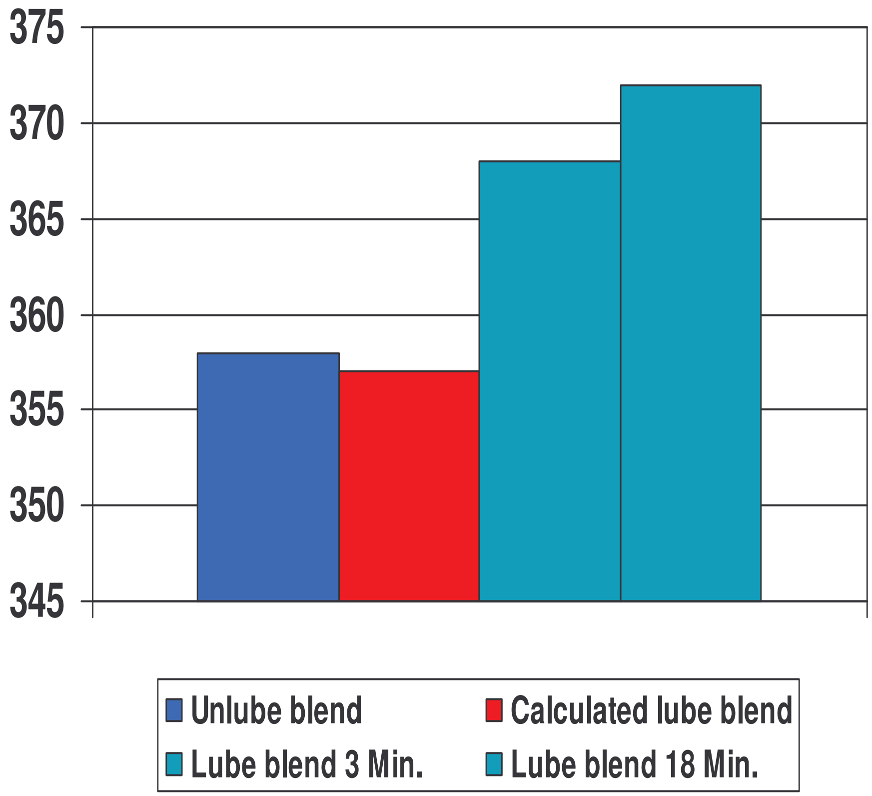
Uniform Phase

Add MgSt

Endpoint at Δ=20

Over lubrication. If blend continues this long, the tablets are at risk.

Not weighted average



0.5% addition of MgSt at Eff<200 should cause slight decrease if the influence was purely weighted average

MgSt is coating the particles

↓

Reducing the interstitial space between particles

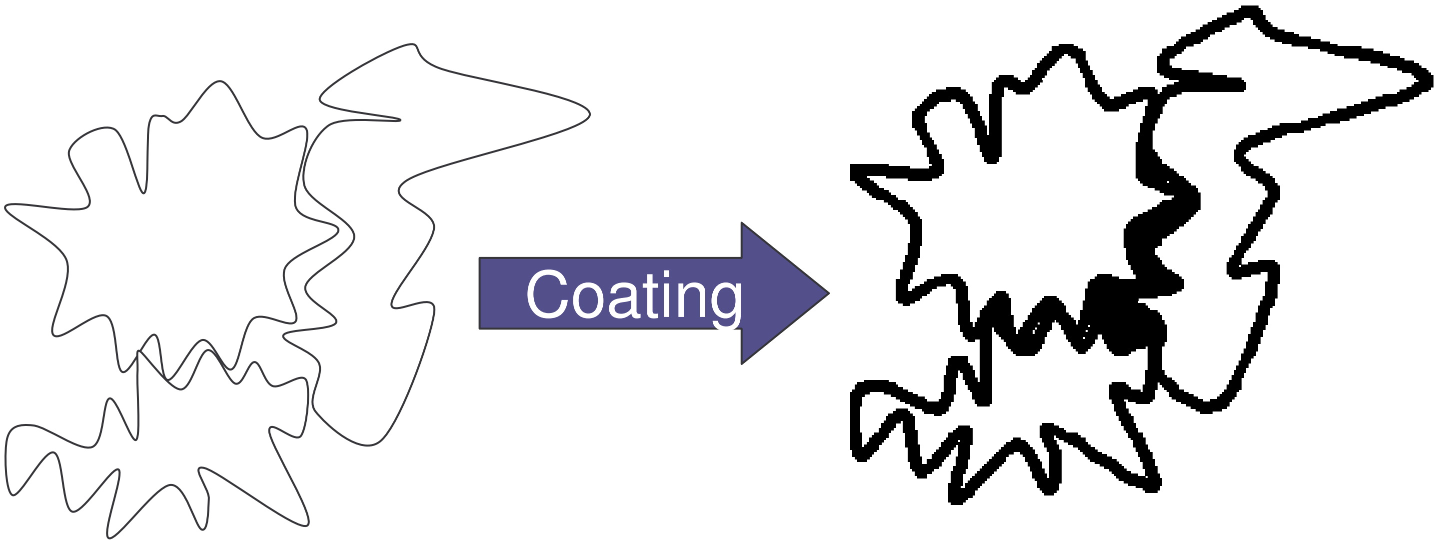
↓

Increasing density

↓

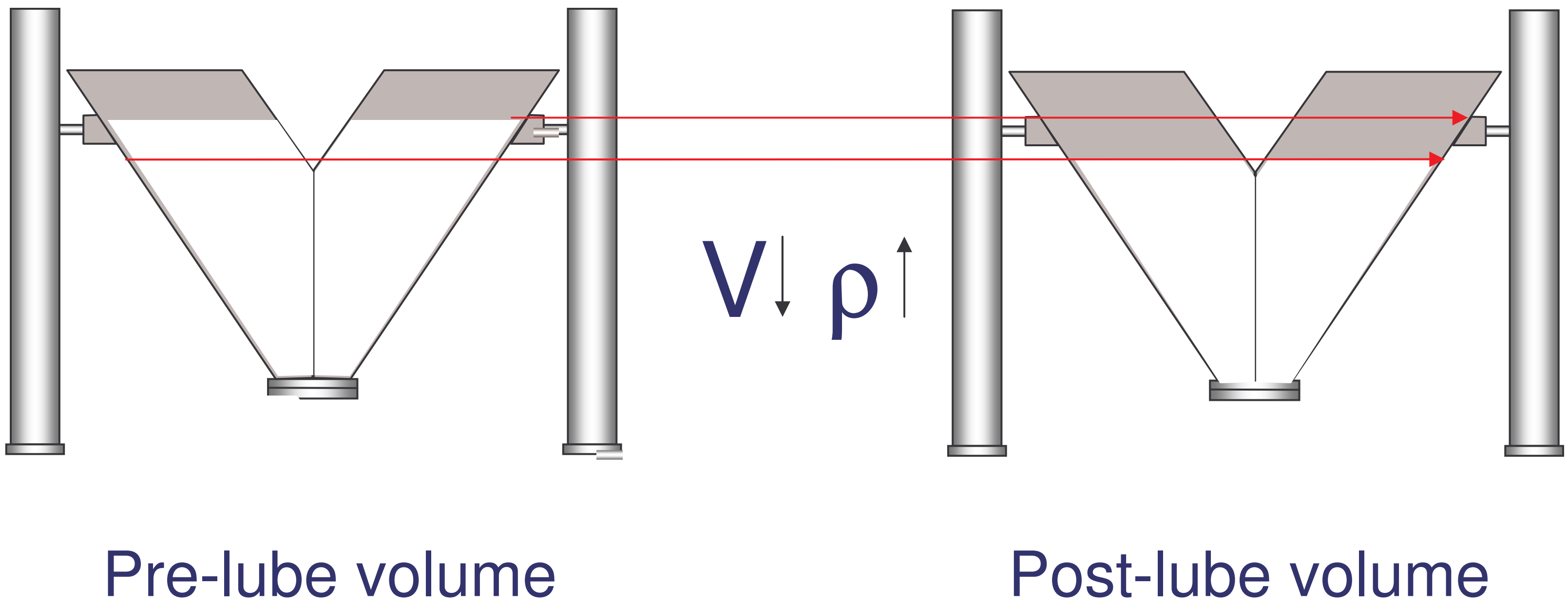
Increasing Effusivity

Mg Stearate Influence



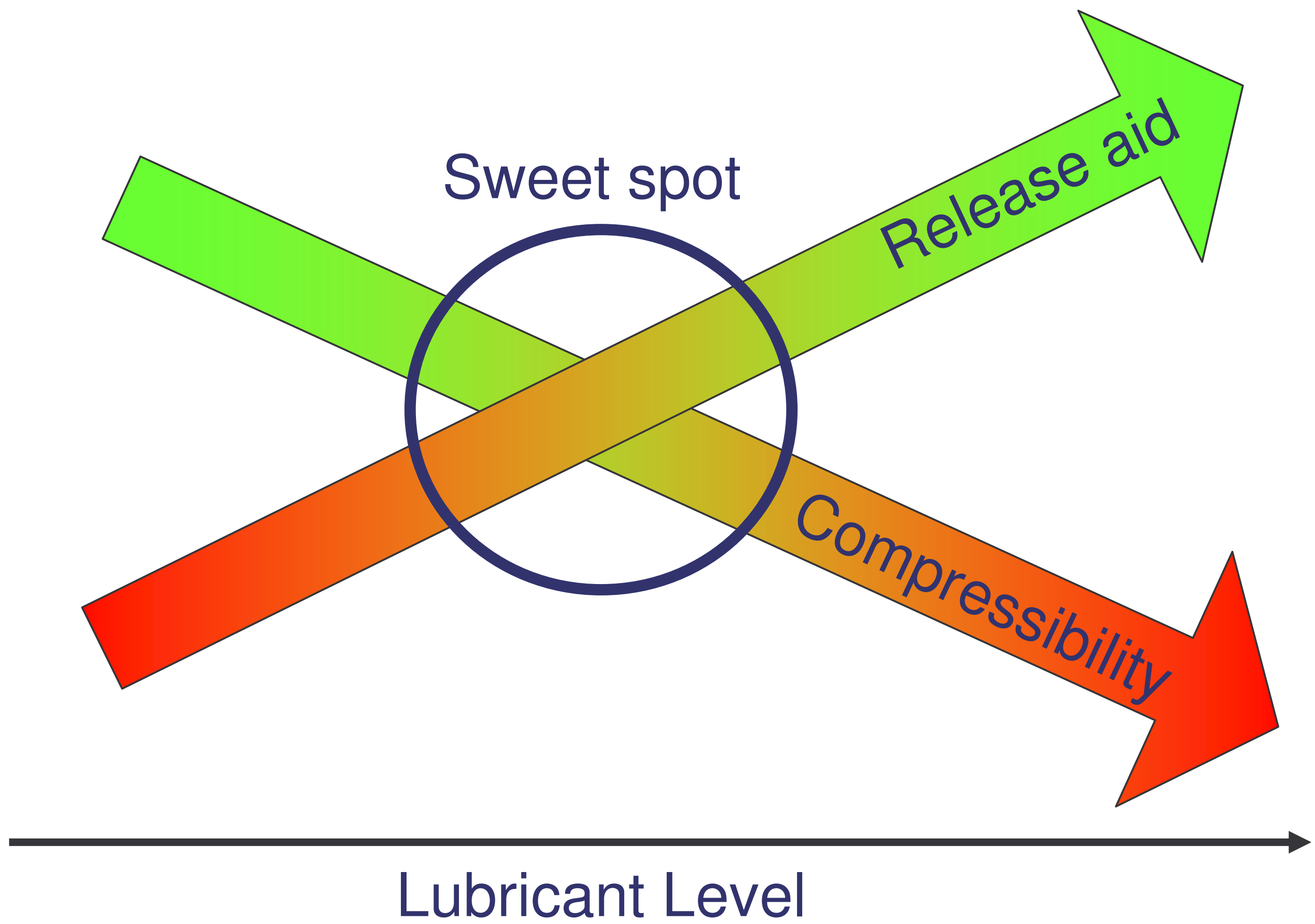
Mg Stearate coats the particles, which increases the thermal conductivity as well as the density of the powder blend.

Density increase – common observation

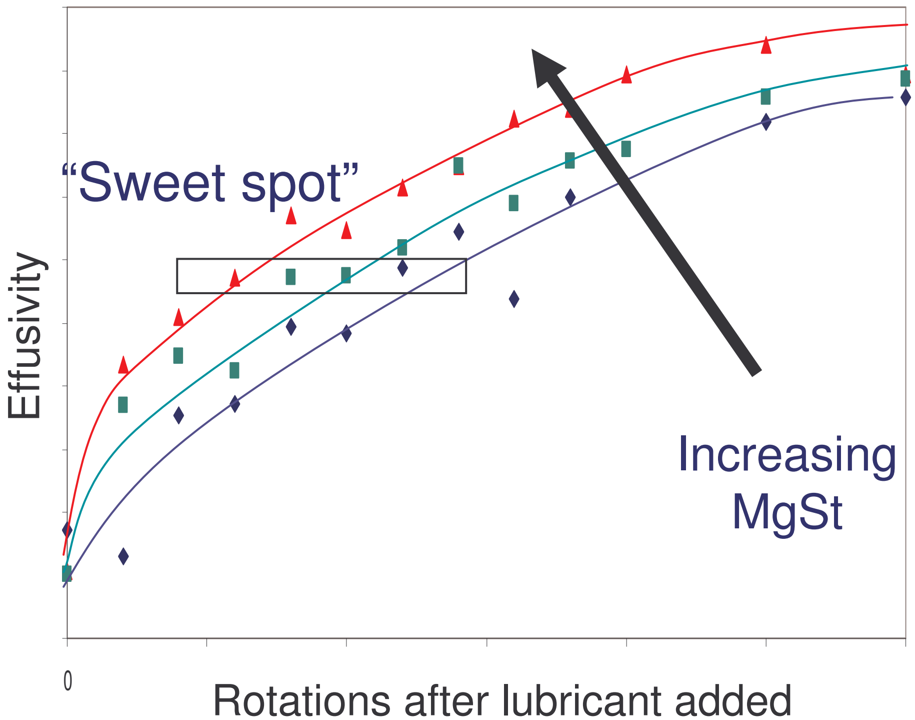


Effusivity:
Actions for reduced variabilty

A delicate balance

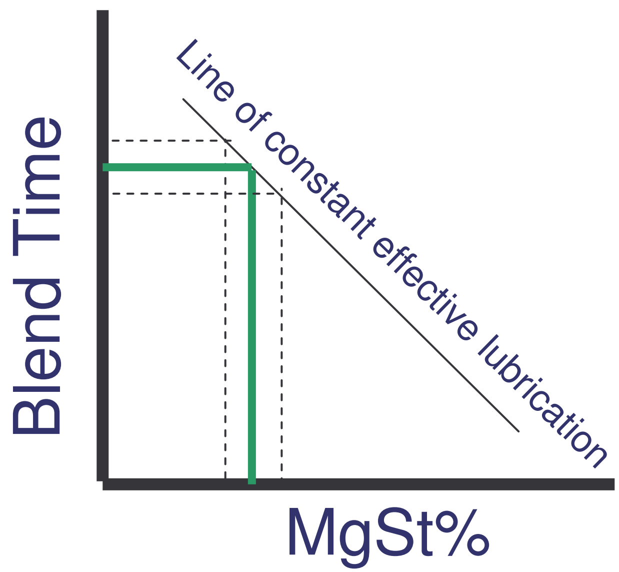


Lubricant Influence

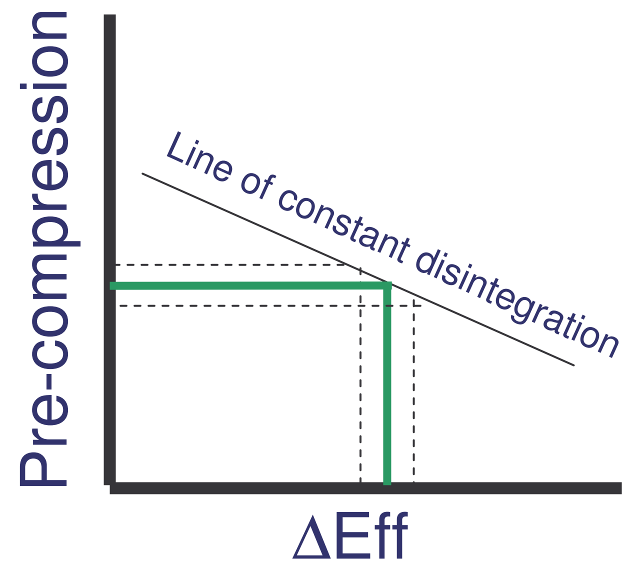


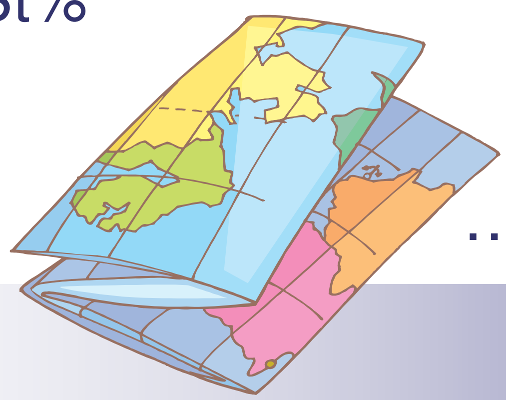
The same effective lubrication can be gained with longer blend times or more Mg Stearate.

Mapping the course



-or-





…but first you need the map

Stepwise Progression

Blender Action	Effective Lube	Press Set-up	Scrap	Material from Press	Disintegration variability
No Lube Monitoring	??	Trial & Error	High	Specified hardness and weight	Unknown
Lube Monitoring	Known	Known	Med		Med
Lube Control	Constant	Constant	Low		Low

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So What?

	Delta Effusivity	Characteristics	Actions at blender or tablet press
GOOD	0 –15	• Poor powder flow • Normal compressibility • Punch sticking	Additional lube needed by: • blending longer • adding more at blender or press
BEST	15 – 25	• Good flow • Normal compressibility • Typical press parameters	Acceptable target range. Standard operating procedures should produce in spec product.
WORST	25 – 40 Ranges are example	• Great powder flow • Reduced compressibility	• Lower press rpm to increase dwell time. • Increase compression force. NOTE: Even with these actions, the tablets are at risk of failing analytical release specs

** Ranges are formulation specific**

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ROI – Return on Investment under 1 year

Automated Effusivity Tablet Press Solution - ROI Calculation

Savings		**Increased Revenue**	
Reduced press parameter set-up time		**Recovered scrap**	
Current time per bin (min)	20	Current scrap during set-up (kg/bin)	16
Expected reduction of time (%)	40%	Material mass processed (kg/bin)	1000
Throughput at one press (bins/day)	3	% scrap	1.6%
Days per year of operation (days)	200	Expected reduction of scrap (%)	40.0%
Hourly analyst cost with overhead ($)	150	Expected reduction of scrap (kg/day)	18.8
Is direct labor reduction possible? (1yes/0no)	-	Market value of increased capacity ($/kg)	250
Annual savings	-	Margin on additional capacity ($)	65%
Amount to use in reduced cycle time per bin (hr)	0.4	Annual additional return	609,960
Reduced scrap disposal		**Reduced cycle time/increased throughput**	
Raw material cost (%)	15%	Tablets (#/hr)	100,000
Raw material cost ($/bin)	10,000	Mass of a tablet (g)	1.564
Waste disposal (% or raw material)	20%	Throughput (kg/hr)	156
Waste disposal cost ($/bin)	2,000	Cycle time (hr/bin)	6.39
Waste reduction (kg/day)	18.8	Saved set-up time (hr)	0.4
Waste reduction (bins/day)	0.0188	New cycle time (hr)	5.99
Waste reduction ($/day)	38	Additional bins per week	1.31
Annual savings	7,507	Can this be realized? (1 yes/0no)	-
		Value ($/bin)	250,000
		Margin ($/week)	213,486
© 2005 Mathis Instruments Ltd		Annual Increased throughput	-

ROI – Return on Investment

Increased Revenue	
Recovered scrap	
Current scrap during set-up (kg/bin)	16
Material mass processed (kg/bin)	1000
% scrap	1.6%
Expected reduction of scrap (%)	40.0%
Expected reduction of scrap (kg/day)	18.8
Market value of increased capacity ($/kg)	250
Margin on additional capacity ($)	65%
Annual additional return	609,960
© 2005 Mathis Instruments Ltd	

In one mode alone, increasing throughput justifies investment.

Effusivity: Targeted Value

Simplicity
Ready out of the box

Knowledge
Window on your process

Productivity
Scale up with confidence

Safety
Containment not compromised

“Run your process with knowledge…

not a stopwatch”

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Learn more?

Custom Webinars

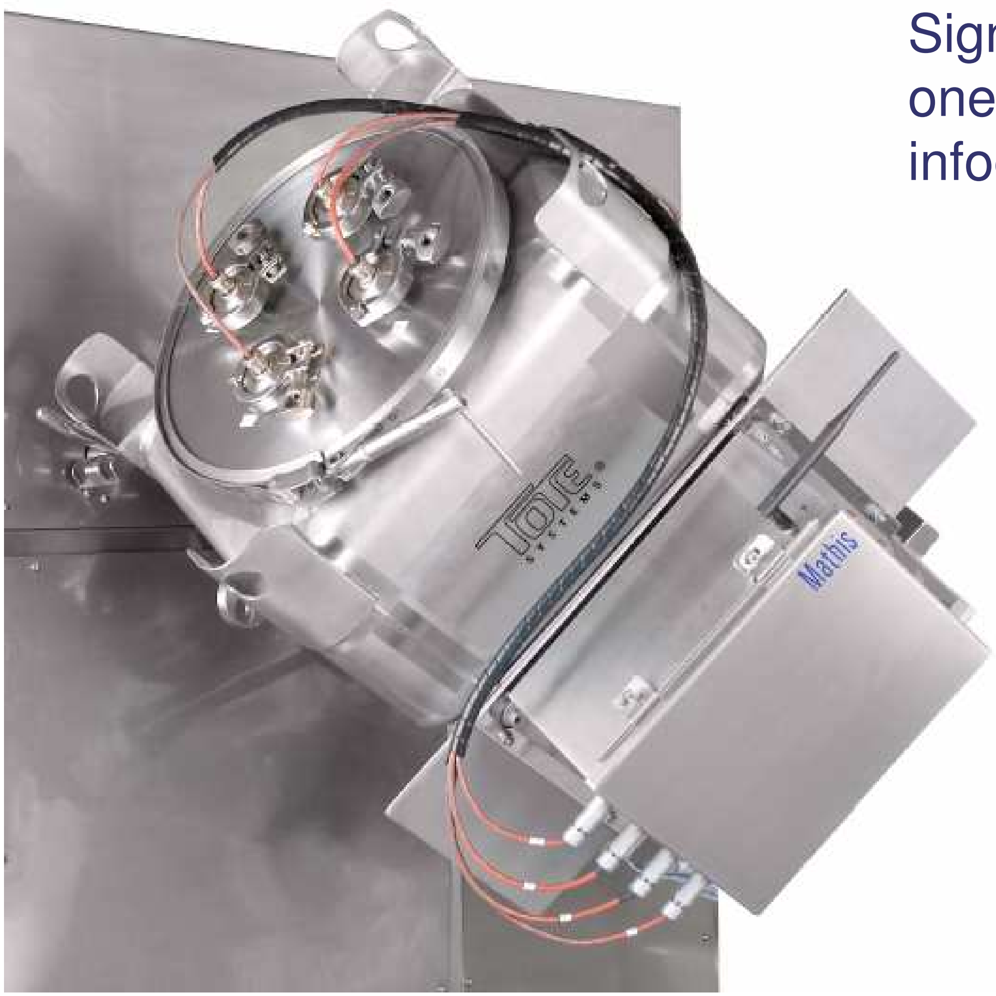
If this presentation was of interest, and you would like to share the concept within your group, you can request a custom, private webinar from one of the Mathis instructors. (Info@MathisInstruments.com)

Papers and technical information from the web

See a demo

Talk to Mathis about visiting one of our demo locations to see the application "in action" and talk to users.

See it in action



Sign up for a ½ day demonstration at one of the following by emailing info@mathisinstruments.com:

Mathis Instruments
Fredericton, NB Canada

Patheon Inc.
Mississauga, ON Canada

Tote Systems International
Fort Worth, TX USA

Confab Laboratories
St. Hubert, QC Canada

MOVA Pharmaceuticals
Caguas, Puerto Rico

Cardinal Health
Somerset, NJ USA

Patterson-Kelley Company
East Stroudsburg, PA USA

Blending Relationships

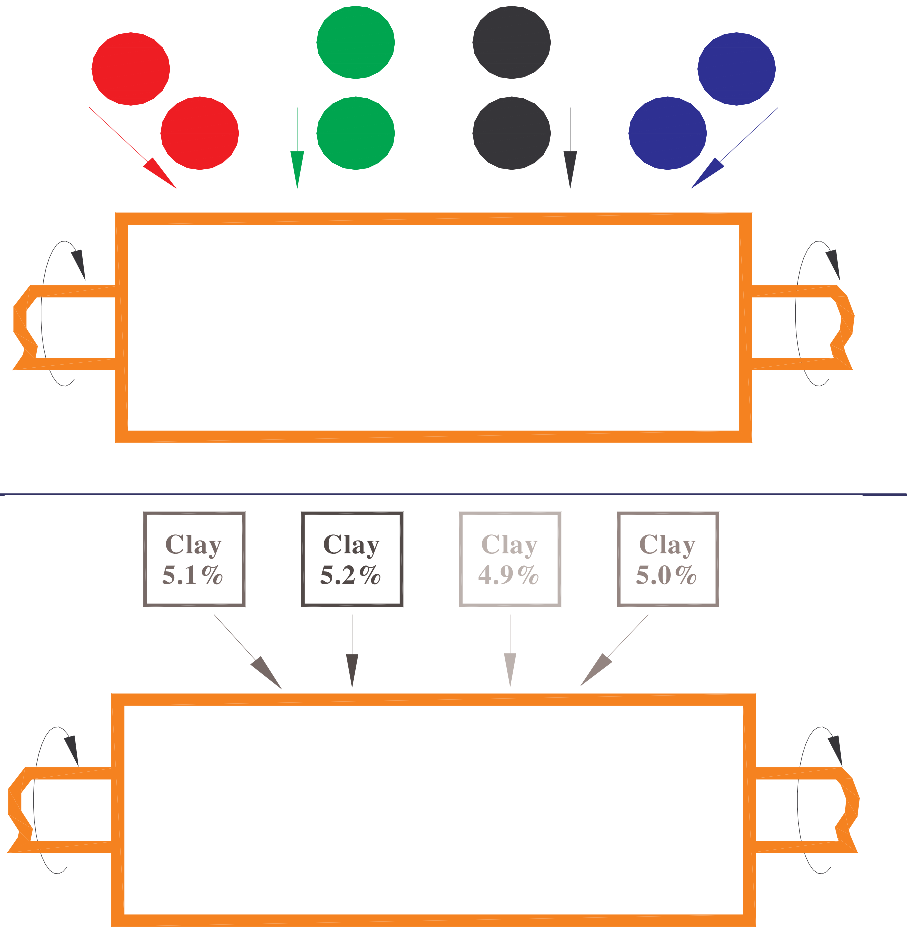
API Interactions to Final Lube

DEFINITIONS

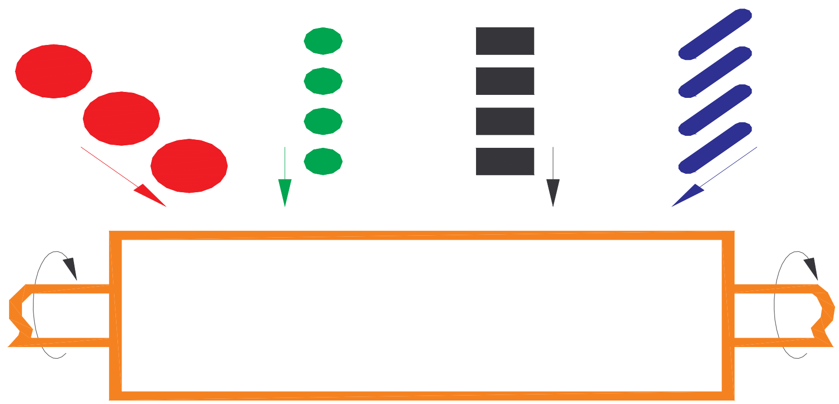
Blending-the thorough intermingling of powders having the same nominal composition. For example, blending two different lots of the same raw material to smooth out any minor variations.

Mixing-the thorough intermingling of two or more materials.

Examples of Blending Applications



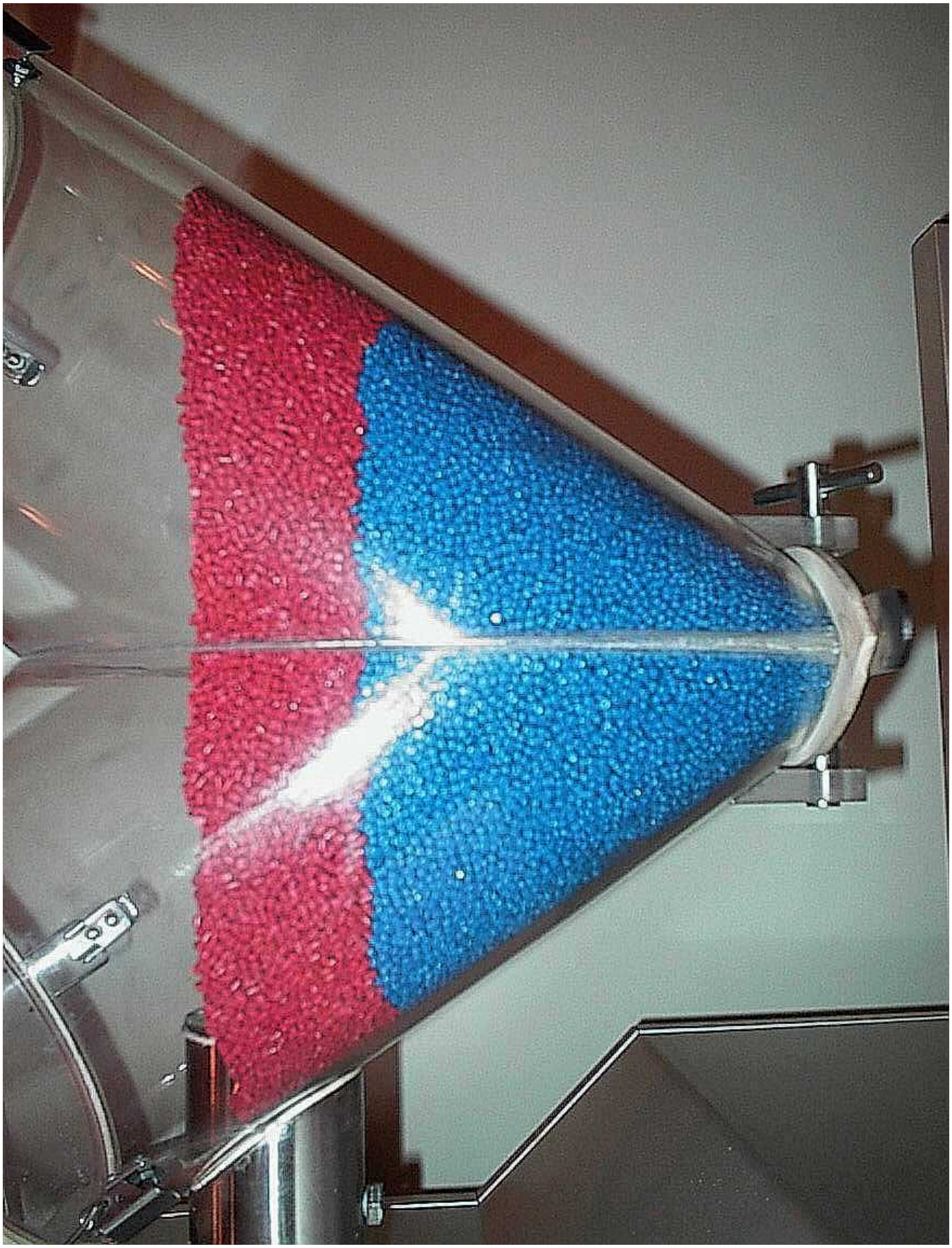
Mixing Applications

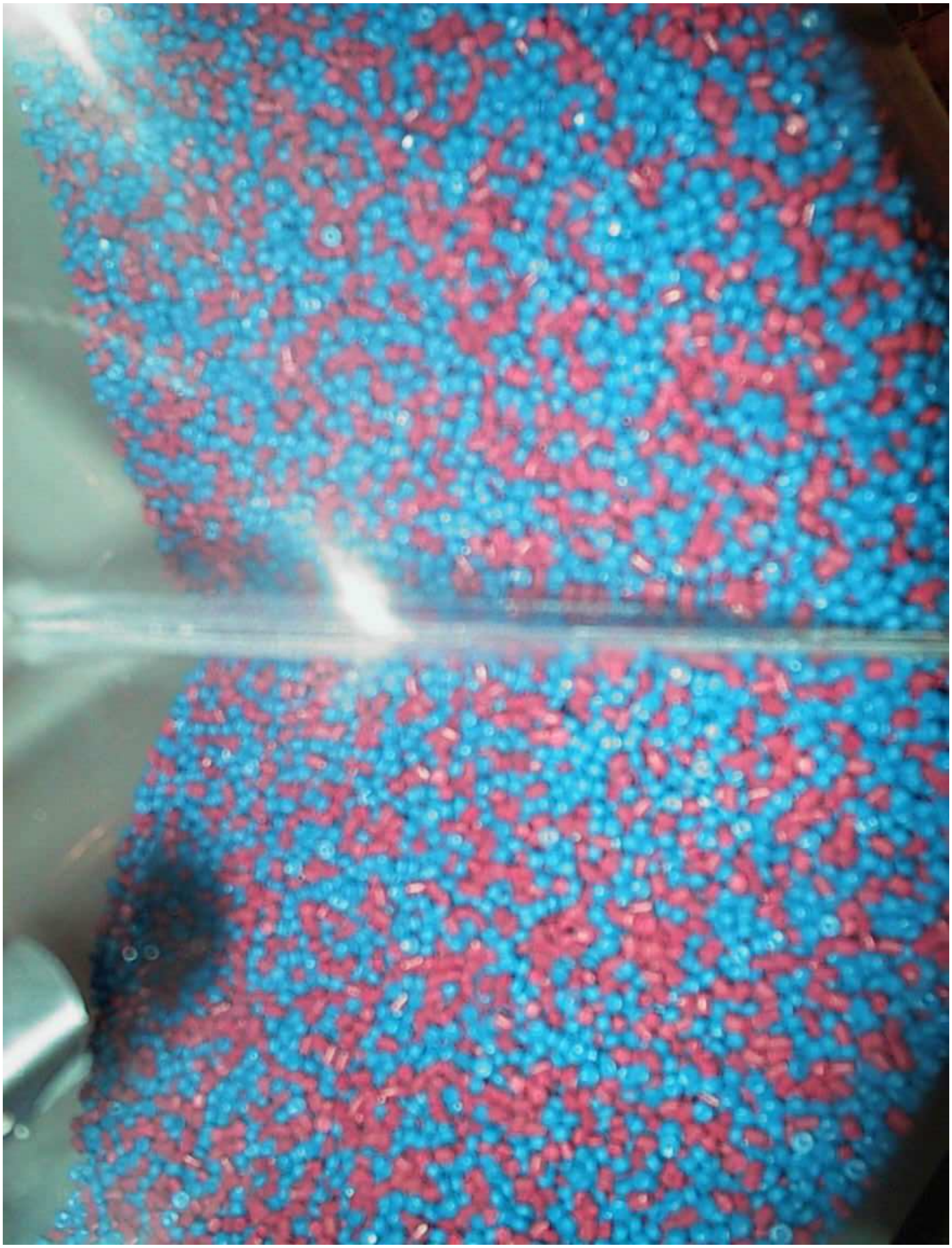


MIXING CATEGORIES

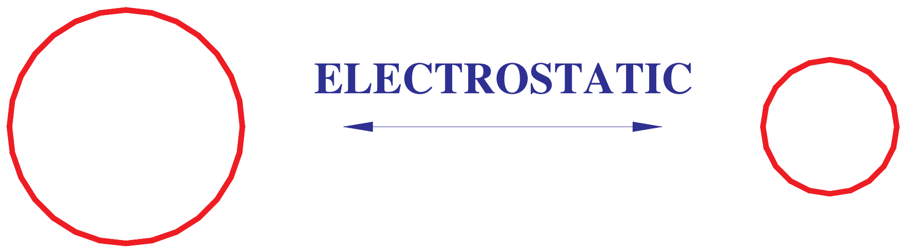
Random-governed by the laws of probability; materials to be mixed are virtually identical.

Ordered-materials to be mixed have disparate physical properties; ordering may be induced mechanically, by adhesion or by coating.





Ordering Mechanism – Attractive Force



- Frictional encounters resulting in electron transfer.
- Staniforth and Rees (1982) measured electrostatic charge of excipients poured from glass and polyethylene beakers.
- Electrostatic is difficult to control.
- Pilot work in a plastic vessel may show different behavior in a scaled-up metal vessel.
- Electrostatic is important as an initiator to get powders close enough for other forces to become operative.

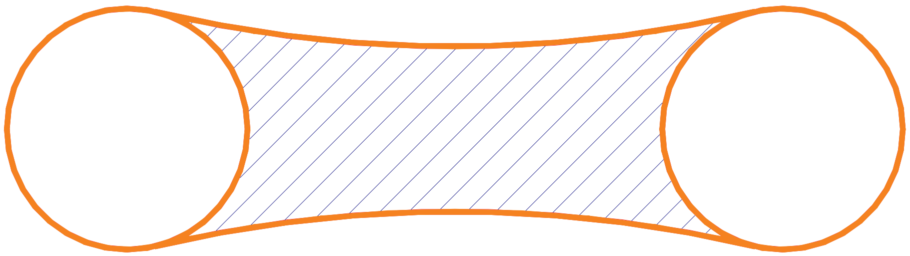
ORDERING MECHANISM
OTHER ATTRACTIVE FORCES

-van der Waal

-Gravitational

-Magnetic

Ordering Mechanism – Hydrodynamic Forces



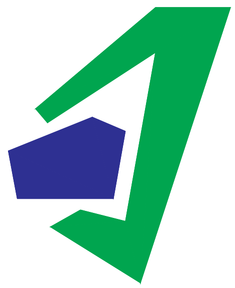
- Contact area and liquid surface tension are important factors.

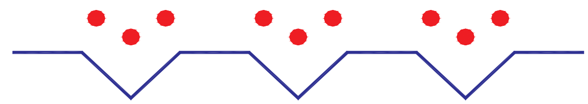
- Increased particle sphericity allows increased bond strength

- Overlapping of adsorbed layers of moisture is the initial expression of hydrodynamic forces.

- Additional available liquid creates liquid bridges and infiltration of capillary spaces.

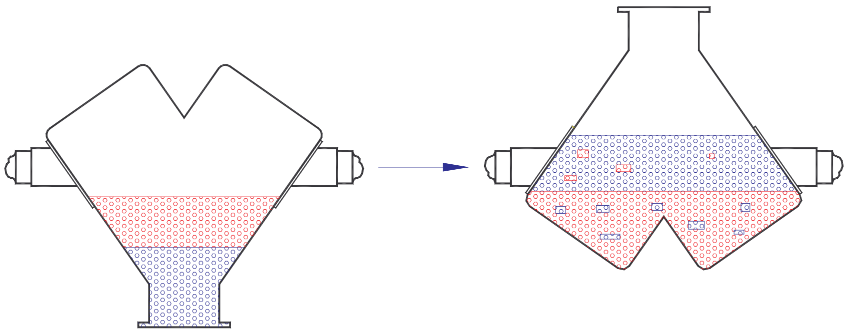
Ordering Mechanism – Particle Morphology





- Notched particles may interlock.
- Erose surfaces may trap smaller particles.
- This mechanism may be ephemeral if particles are friable.
- Rees and Staniforth (1979) and Travers and White (1971) observed the impact of surface roughness on achieving an ordered mix.
- Staniforth et al (1981) showed irregularly shaped mannitol provided better ordering than anhydrous lactose.

Ordering Mechanism – Mechanical



- Non-cohesive ordering prone to segregation.
- Vessel shape induces flow patterns.

DIFFUSIVE MECHANISM

-An individual particle or ordered unit phenomenon.

-Often an analogy is drawn to gaseous or liquid motion in order to use Fick's second law of diffusion to describe motion.

-True diffusive character requires **random motion** of the particles.

-Diffusive mechanism is recognized when particles are striking and rebounding or when particles drop into void spaces created within the bed.

-Equations of diffusive motion have been solved for rotating drums.

CONVECTIVE MECHANISM

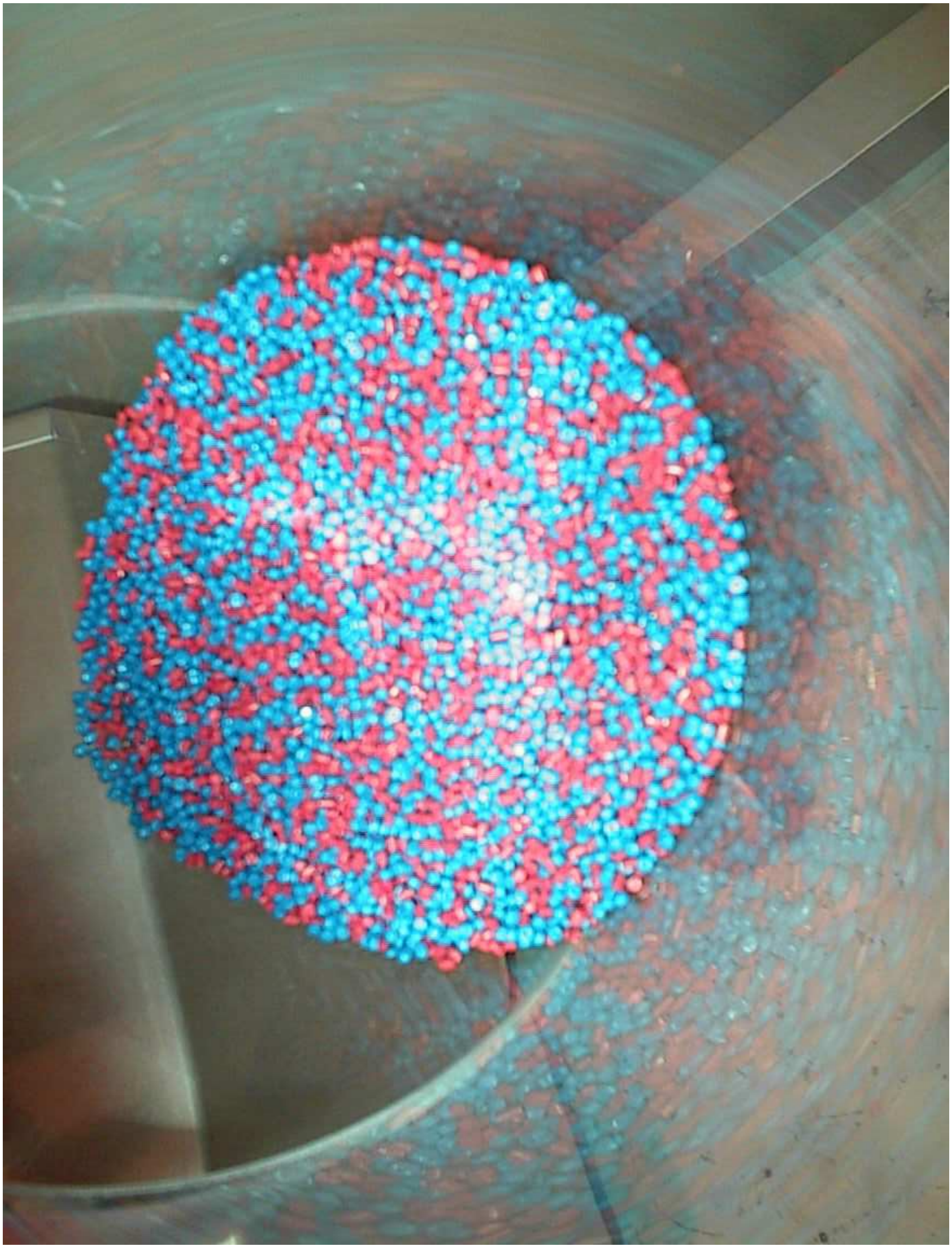
-Operates on **groups of particles** in convective cells.

-Convective cells may be induced by splitting of the bed at a bifurcation point, pneumatic methods or use of mechanical agitation.

-Convective cells may gain or shed volume during movement.

-Smaller cells provide better intimacy.

-Diffusion may occur at a cell surface or within a cell.



SHEAR MECHANISM

-Bed expansion may be impeded by static forces.

-Energy to overcome static forces may induce bed shearing along **slip planes**.

-Shearing may break down ordered units.

-Cohesive forces may benefit from shear.

INTRINSIC FACTORS
PARTICLE SIZE

-Average value.

-Distribution histogram for major size fractions and size range.

-Smaller particles are more cohesive.

-Johnson (1979) found that ultimate mix homogeneity was more sensitive to reduction in the particle size of the active ingredient than to the particle size of the excipient.

-Micronizing the active may aid in an ordered unit coating of the excipient.

INTRINSIC FACTORS
DENSITY

-**True density** involves particle volume exclusive of any void volume within a particle.

-Particle density takes into consideration volume occupied by pore spaces.

-**Bulk density** is the mass of powder within a known volume.

-Tap density uses some force to pack the powder within a known volume. The number of taps must be reported to give the density value relevance.

INTRINSIC FACTORS
OTHERS

-Particle shape.

-Flow character.

-Angle of repose.

-Moisture content.

-Friability.

-Coefficient of friction.

-Surface forces.

EXTRINSIC FACTORS
VESSEL SHAPE

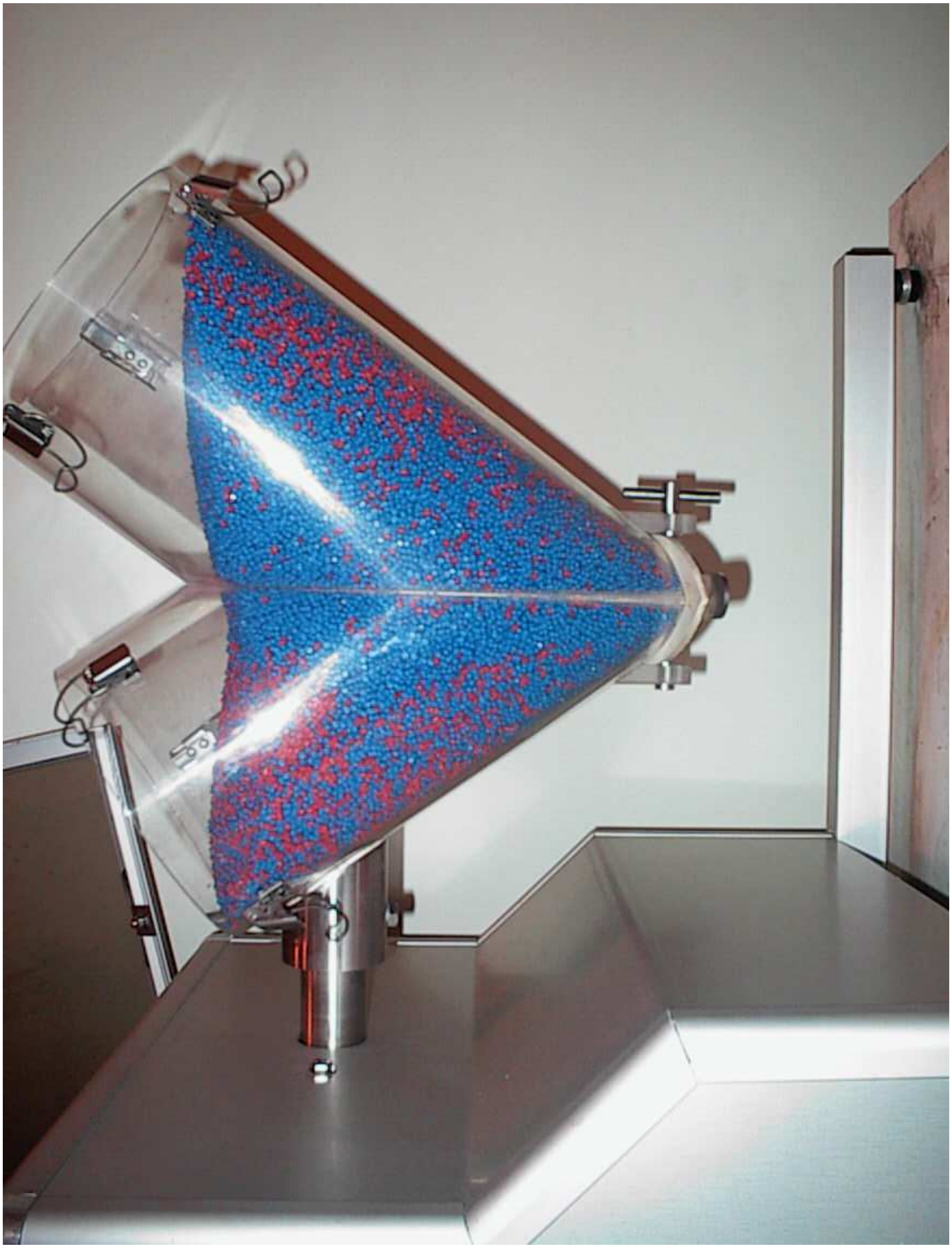
-May include drums, cones, cubes, spheres and variations of these shapes.

-Shape is very important to mixing behavior when vessel rotation is the only energy available for moving the powder.

-Simple drums have walls perpendicular to the axis of rotation minimizing axial flow.

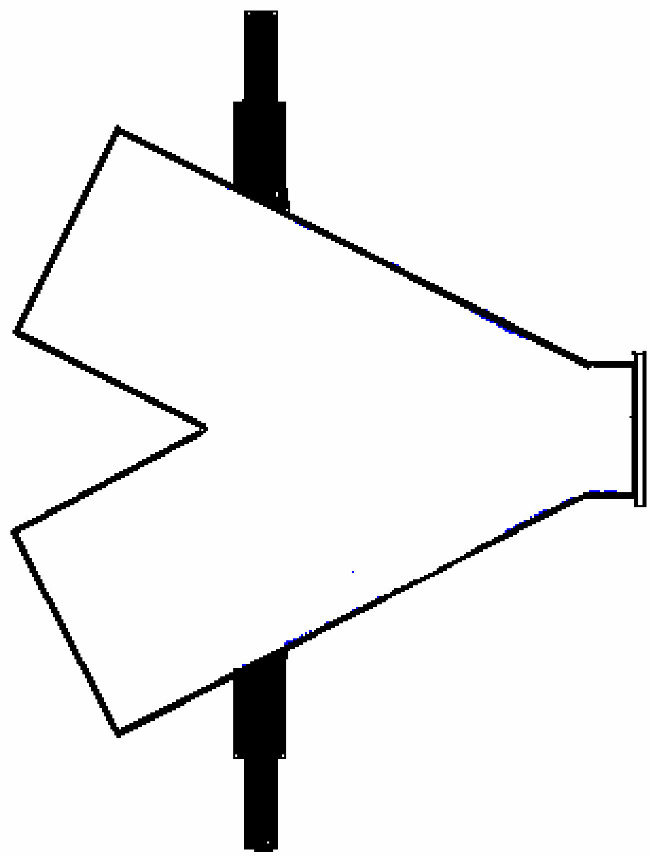
-Other shapes have angled sides that aid axial flow.

-Chang *et al.* (1995) studied several angles and leg modifications in a V-mixer and reported on their influence in aiding axial flow.



Environmental Analysis

- Select vessel geometry of interest.
- Evaluate areas within the mixer.
- Tally “good” vs. “bad” environments.
- Reconcile tally with experimental work.



EXTRINSIC FACTORS
VESSEL SPEED

-Each formulation has an optimum speed.

-Practicality dictates a mean speed that works for a wide variety of materials.

-Typical shell speed is about **1.5 m/s.**

-Typical bar speed is about **15 m/s.**

-If speed is too slow, the material slides and does not flow properly through its angle of repose. The diffusive mechanism is impeded.

-If speed is too fast, the material is forced against the vessel wall.

EXTRINSIC FACTORS
OTHERS

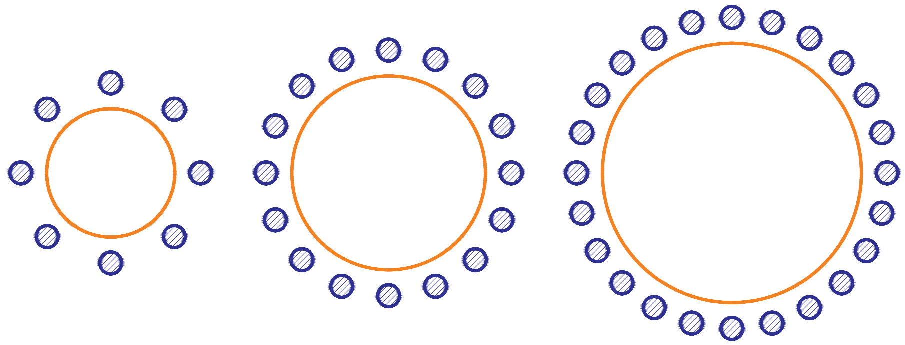
-Vessel loading volume ratio.

-Vessel loading method.

-Design of the internal agitator device.

-Mixing time.

Segregation – Ordered Unit

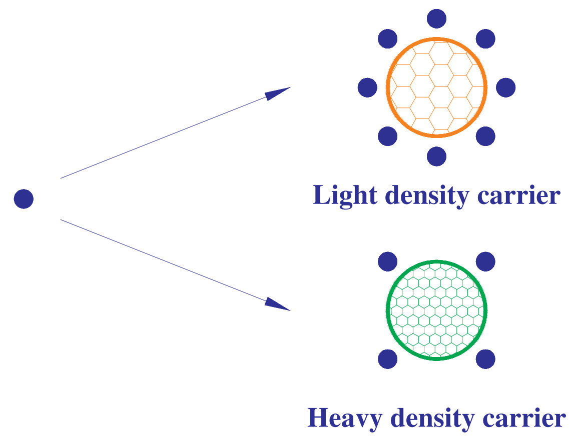


- **Segregation can occur in a cohesive system.**

- **Adherent constitutes a larger percentage by weight on the smaller carrier particles.**

- **If the carrier segregates by size, poor mixture quality will result.**

Segregation Constituent Preference

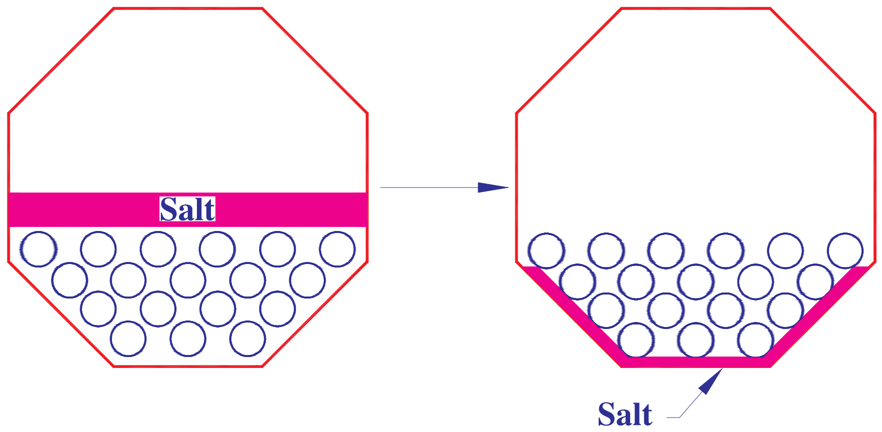


- Adherent prefers a carrier.
- Preferred carrier may strip adherent from another carrier.
- Density differences in carrier may induce segregation.
- Soebago and Stewart (1990) observed a disintegrant depriving a diluent of drug particles.
- Staniforth and Stewart (1987) observed magnesium stearate displacing drug from a binary drug-carrier mixture.

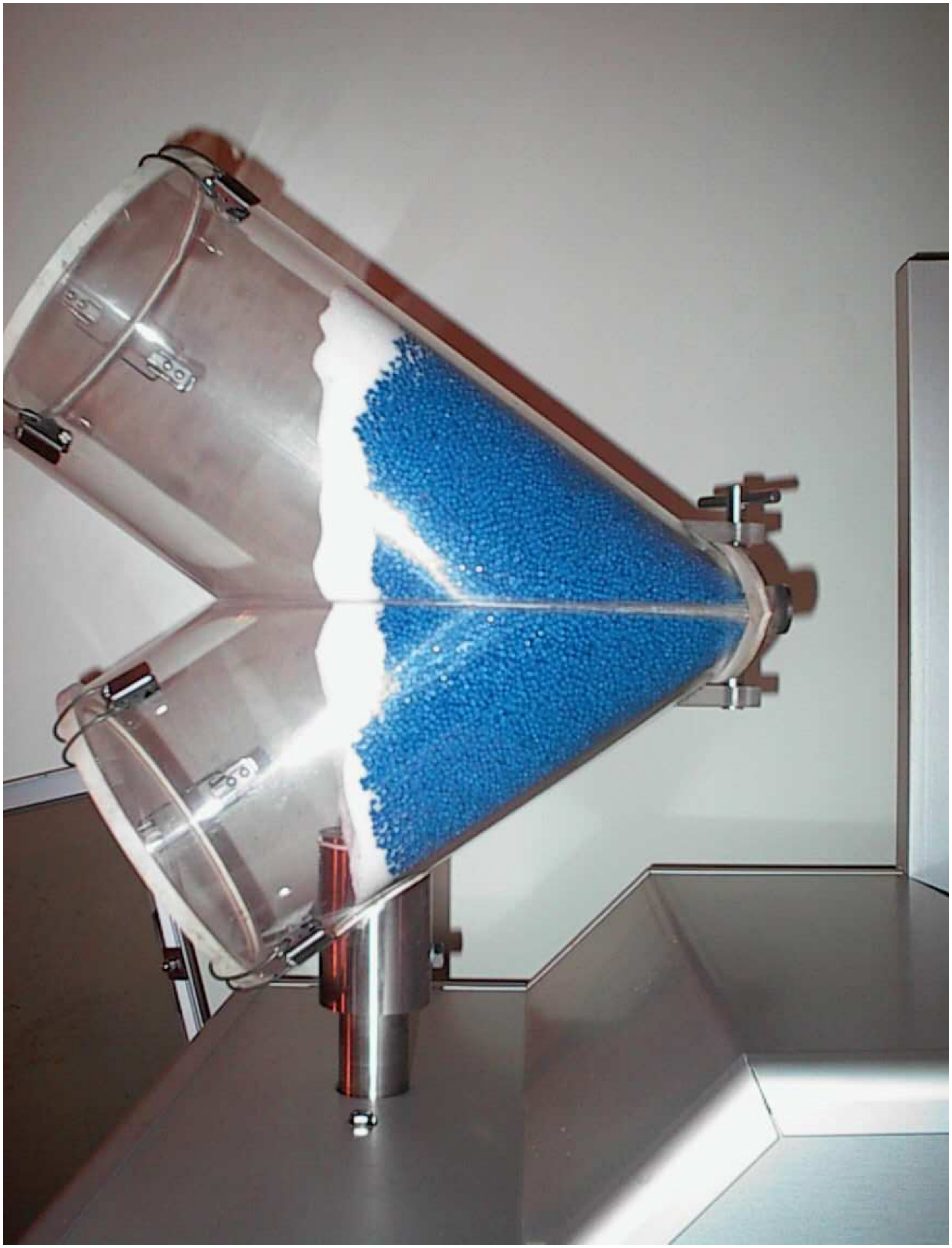
Segregation

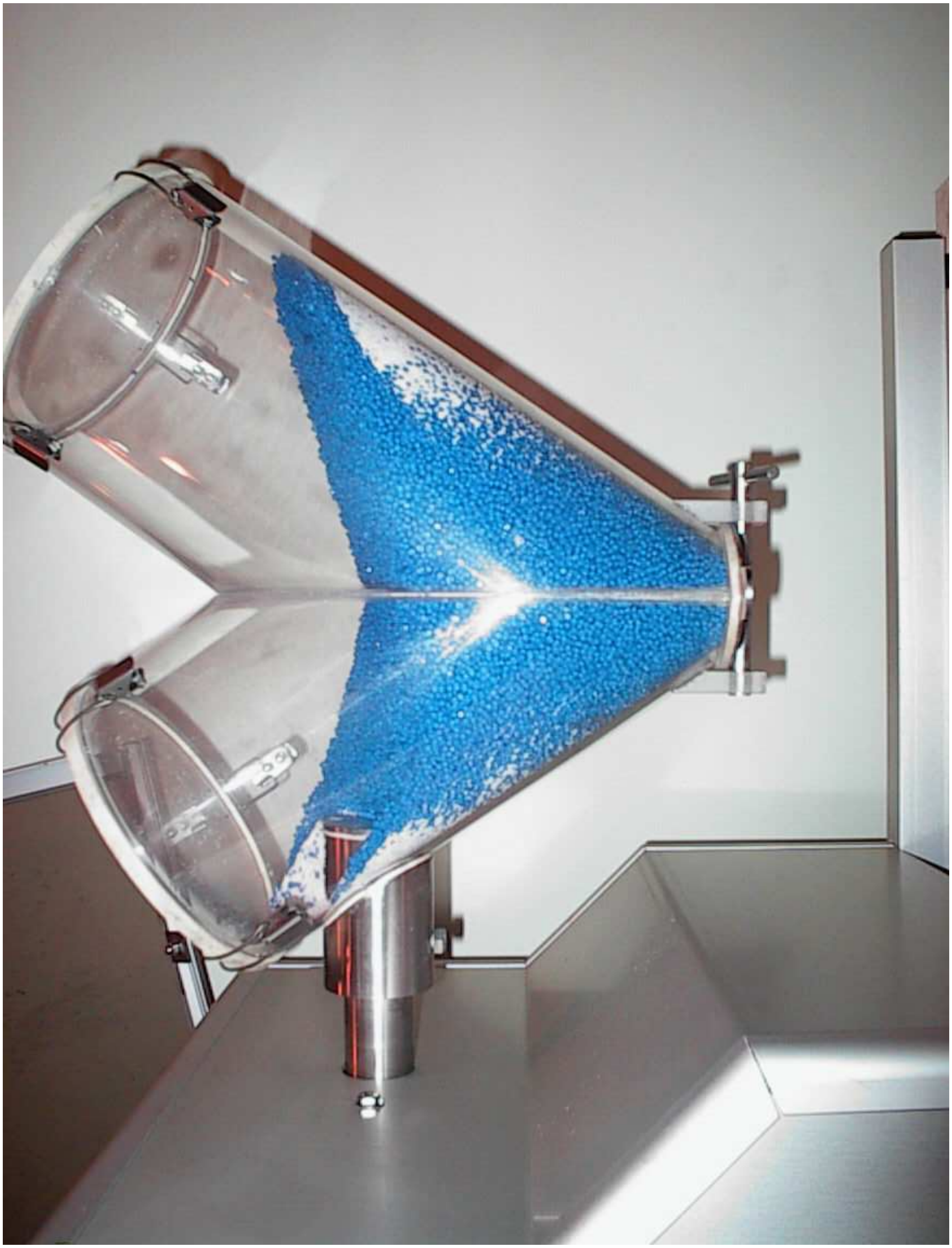
- Particle trajectory
- Percolation(vibratory)
- Percolation(pouring)
- Elutriation

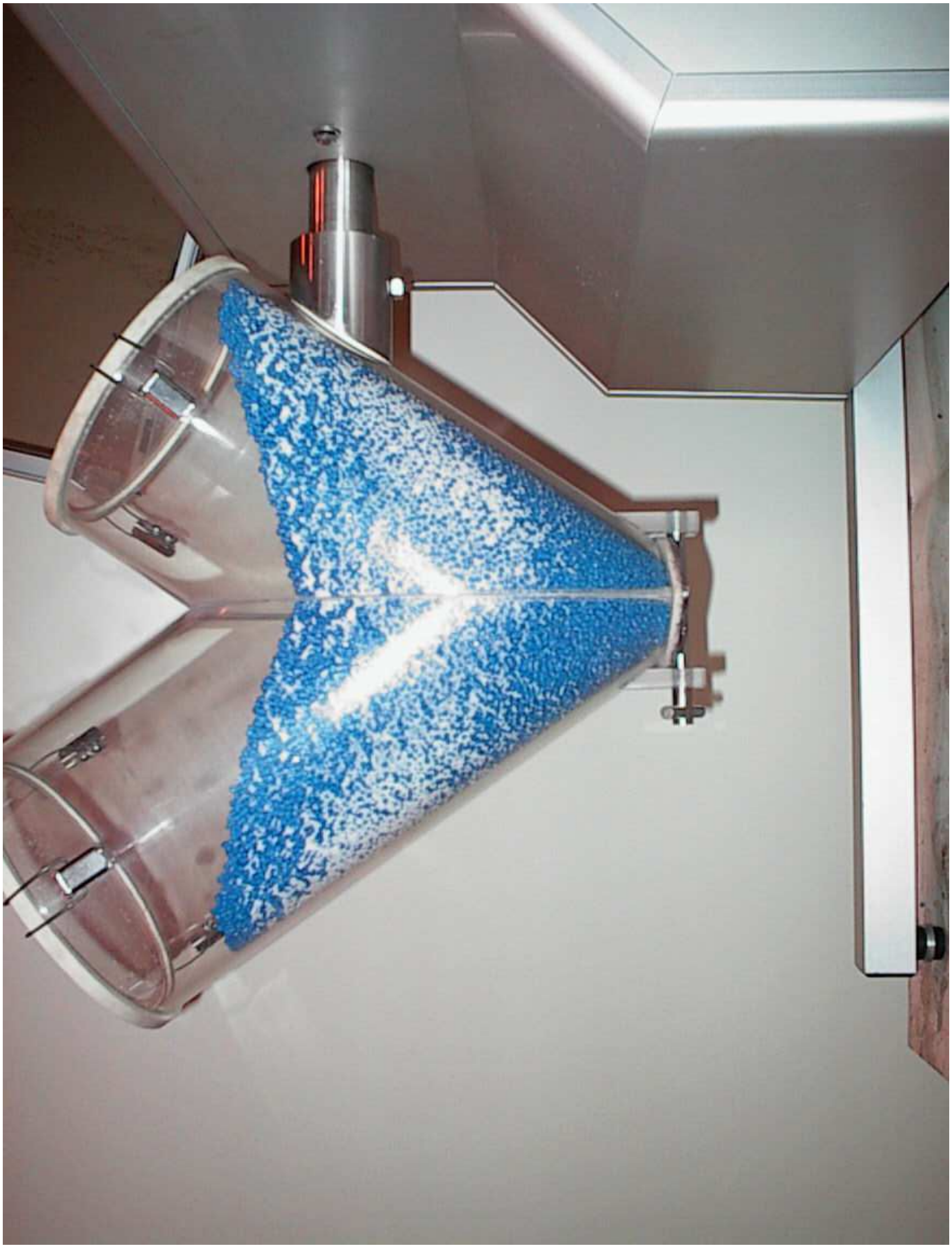
Segregation Percolatory



- System is non-cohesive.
- Salt migrates through spheres and collects near walls.







MEASURING SEGREGATION

-Thiele *et al*. (1986) defined **demixing potential** to predict if tablets made from a mixture would fail content uniformity standards because of segregation.

-Lai (1994) used a **scatter plot** technique and a **tolerance ellipse** to quantify segregation.

-In general, **reducing particle size range**, using a **coating process** or adding a **wet granualtion** step limits segregation potential.

ASSESSING HOMOGENEITY

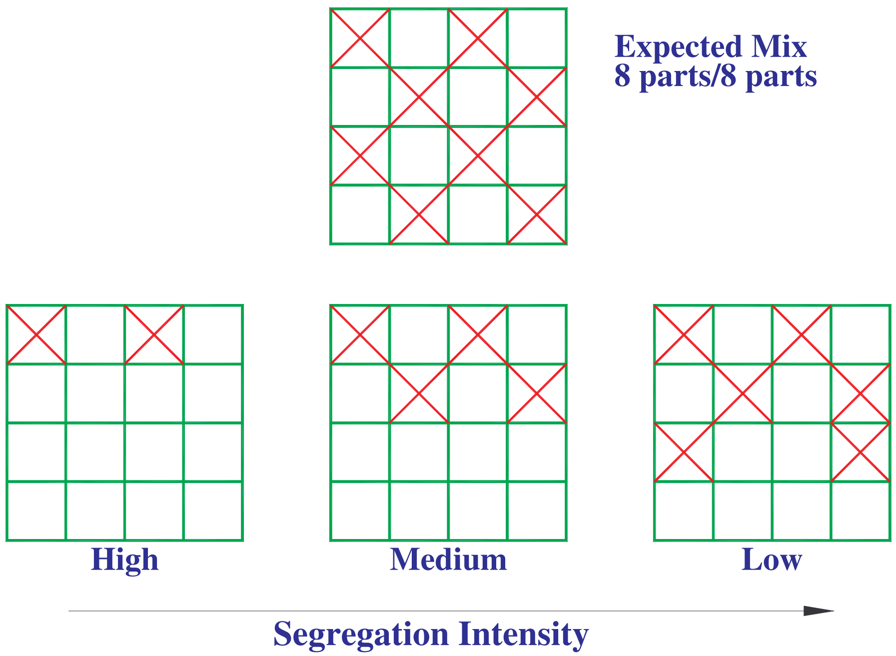
-In broad terms, the mixture is homogenous if it is a suitable state for the next processing step.

-The more removed the mixing step is from the tabletting step, the greater the chance that homogeneity has been influenced.

-Negative influences include discharge segregation or vibratory segregation during transit.

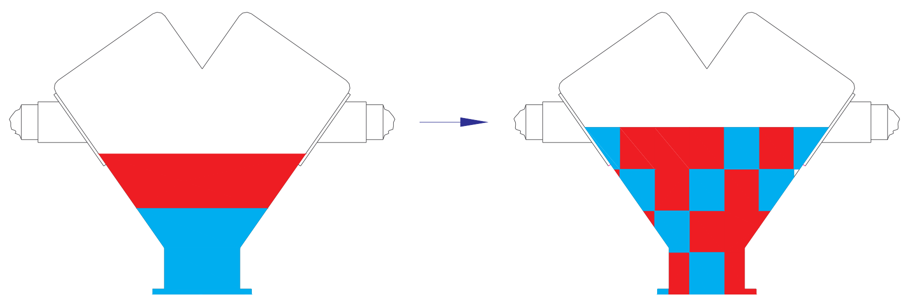
-Positive influences may prevail in subsequent processing steps. Stahl and Langenberger (1981) observed increased homogeneity after the powder exited a rotary tablet press.

Segregation Intensity



- Danckwerts (1953) divided segregation into two components.
- Segregation intensity referred to segregation at the sample level and compared it to the expected value.

Segregation Scale



Total Segregation

Partial Segregation

Segregation scale referred to the physical volume of the segregated region.

MIXING INDICES

-Used to evaluate powder mixing or machine efficiency.

-Standard deviation is a common tool for evaluating when mixing is complete.

-Standard deviation may not be applicable to ordered systems.

-Multi-mechanistic mixing indices may be used to describe the progress toward achieving homogeneity.

SCALE OF SAMPLING SCRUTINY

-Danckwerts (1953) defined scale of scrutiny as the maximum region of segregation constituting an unmixed situation.

-A soft drink formulation may require 25 grams of sample since segregation at the 1 gram level is irrelevant.

-A suitable answer for sampling may be to divide the vessel into a coordinate sysytem and choose **random sampling** sites.

SAMPLING
USING A THIEF

-Inserting the thief through the bed surface draws material down with the probe.

-Powder may be trapped within the inner and outer tubes when the thief is opened.

-Variable flow characteristics of formulation constituents may induce preferential filling.

-Subdividing a **lab sample** into **analytical samples** may introduce more segregation errors.

-Carstensen and Rhodes (1993) advocated taking several different thief sample sizes and analyzing the entire sample to prevent subdivision errors.

-Garcia *et al*. (1995) studied various components of deviation and deemed that about 75 % of variance was due to sampling error.

SAMPLING

-Static, using a thief or freezing the constituents *in situ.*

-Dynamic, sampling outflow or using a probe.

SCALING UP
SIMILARITY CRITERIA

-Geometric

-Kinematic

-Dynamic

GEOMETRIC SIMILARITY

-Ratios of certain linear dimensions are held constant.

-For a V-mixer, it is the ratio of **rotating radius** over the **effective length** (a function of loading).

-Laminar loading has a different effective length than side-by-side loading.

-Minimizing effective length reduces mixing time.

KINEMATIC SIMILARITY

-Maintaining particle velocity ratios at similar points in the vessels.

-Kinematic is a function of the **mobility coefficient** of a powder, the **mixing time** and the **effective length.**

-Maintaining a common tip speed is important.

DYNAMIC SIMILARITY

-Maintaining force ratios at similar locations in the vessels.

-Froude number is part of this criterion as a ratio of **centrifugal** to **gravitational force.**

-Motor size to bed volume ratio does not scale up linearly, so mixing time is extended in the larger vessel.

TYPICAL TORQUE EQUATION

-Complex analysis of torque input to an asymmetrical rotating vessel.

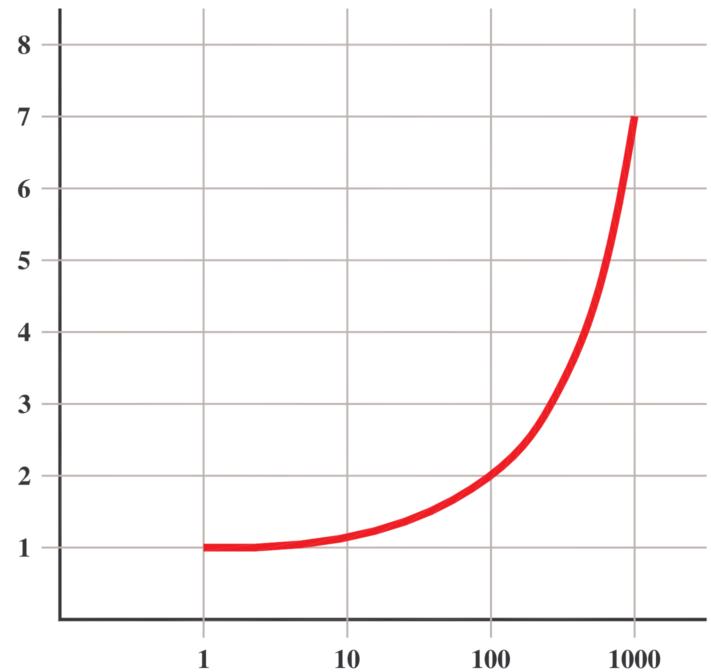
-Consideration is taken of intrinsic factors like density and flow behavior.

-Consideration is taken of extrinsic factors like percentage of fill volume.

-A new torque equation is needed for each change in intrinsic factors.

-Scale up curves are guidelines based on mathematics, empiricism and feedback.

Typical Tumble Mixing Scale-Up Curve



Pilot Lab Vessel

Vessel size = 1 ft^3

Motor Size = 1.5 kW = 1500 J/s = 1500 N-m/s

Mix Time = 30 s

(1500 N-m/s) (30 s) (1/ ft^3) = 45,000 N-m/ft^3

Scale-Up Vessel

Vessel Size = 20 ft^3

Motor Size = 20 kW

Mix Time = ??

(s/20kN-m) (45,000 N-m/ft^3) (20 ft^3) = 45 s

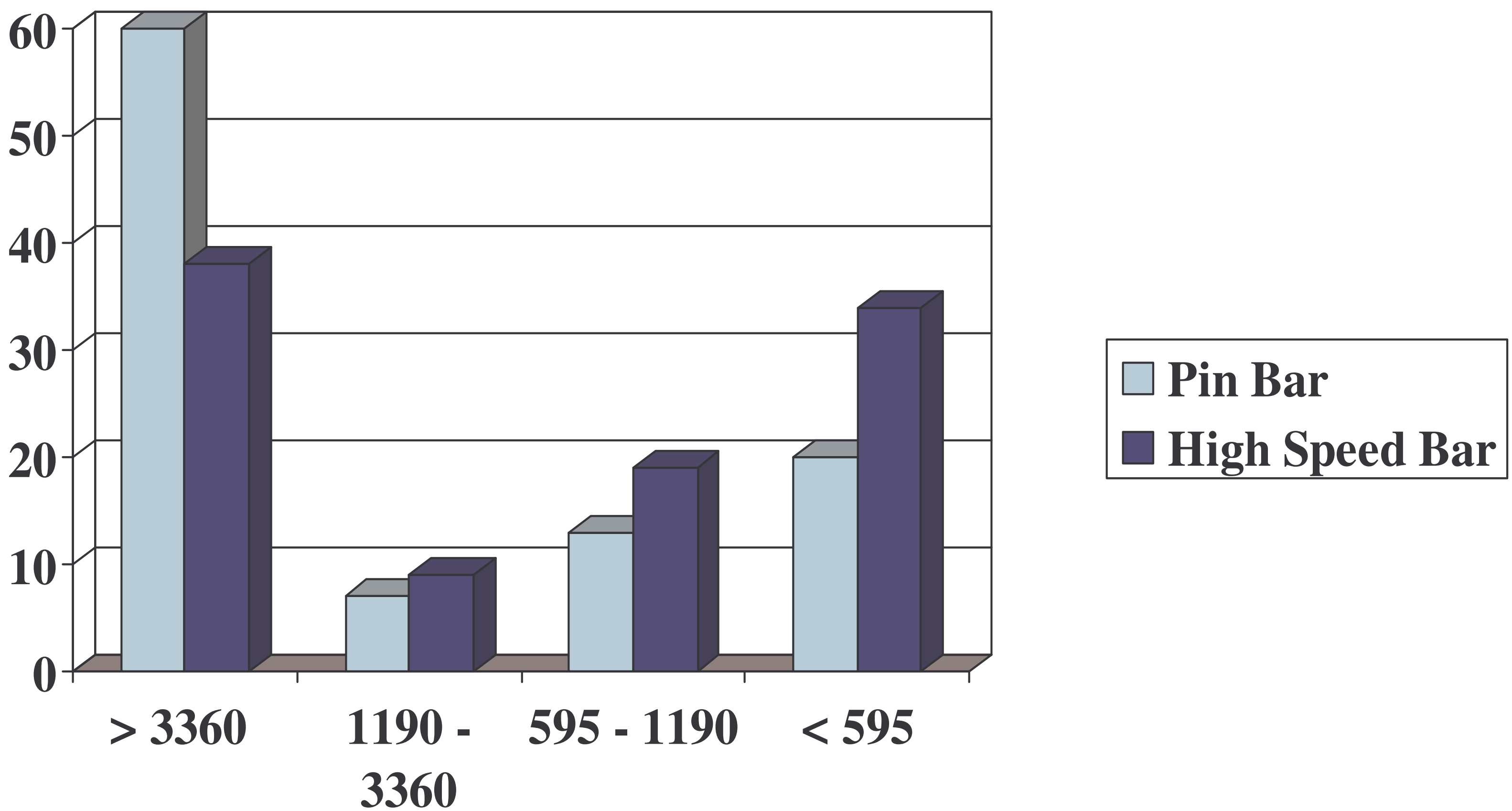
Pin Intensifier Bar

- Next level of energy beyond tumble mixing.
- Tip speed about 8.5 m/s.
- Useful when minor ingredients are < 10%.
- Useful in breaking friable agglomerates.

High Speed Intensifier Bar

- Blades and canted disc provide greater swept volume.
- Typical tip speed about 17 m/s.
- Useful when minor ingredients are < 1%.

Pin vs High Speed Bar



Ultra-High Speed Bar

- Tip speed about 34 m/s.
- Straight disc design.
- Main application in the cosmetics industry.

Liquid/Solids Bar

- High speed bar adapted to liquid addition.
- Controlled atomization for intimacy.

Extended Blade Design

- Increases the loading range capability of high speed and liquid/solids vessels.
- Adequate process results at 60 % of proper working volume.
- Minimizes spray through.

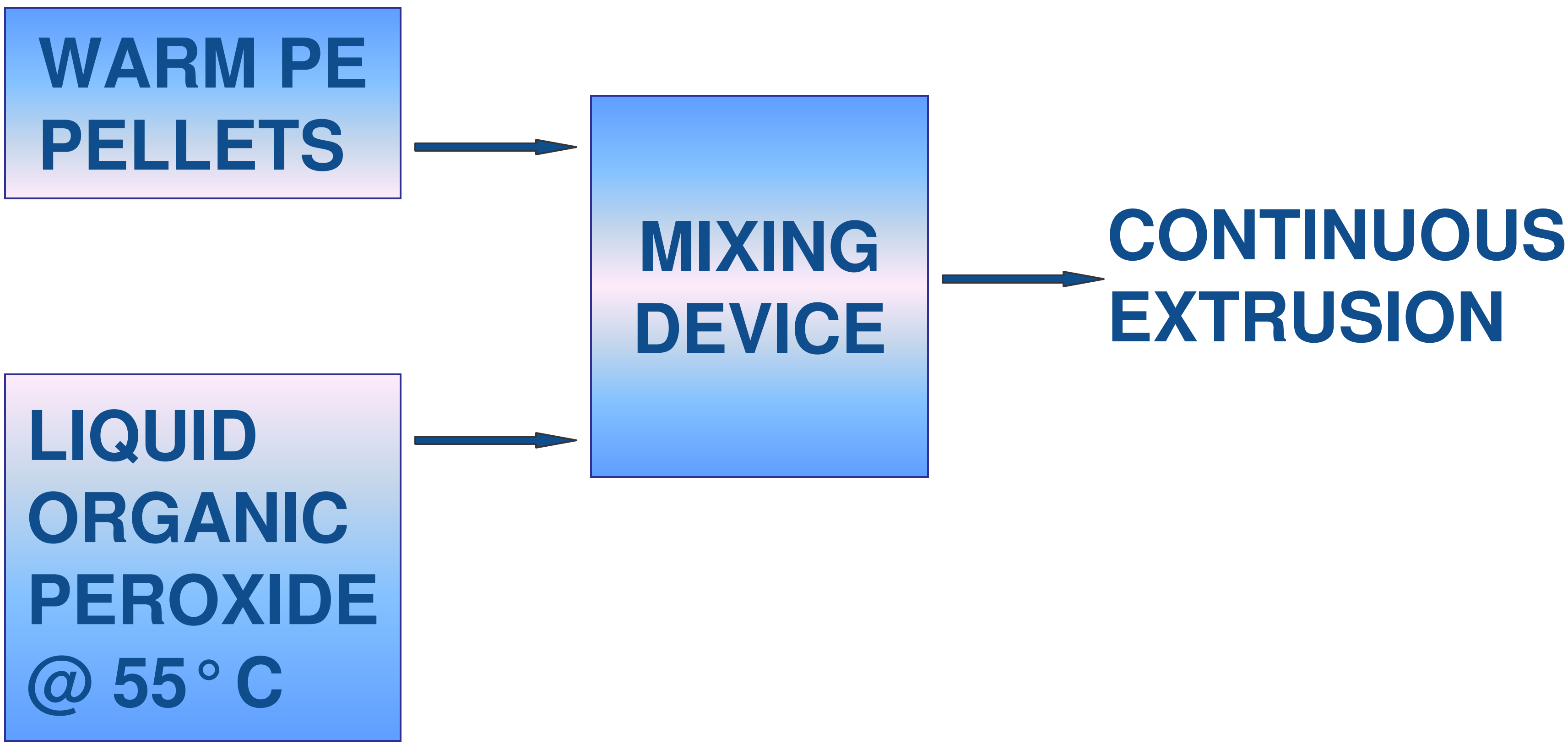
Minimum Attrition Bar

- Liquid addition without particle degradation.
- Flavoring coffee beans.
- Lubricating friable powders.

Non-Pharma Continuous Processing/Crosslinking

- Fine control of minor component (peroxide addition) analogous to API.
- Each pellet must have proper amount, analogous to unit dosage.
- Immediate effluent release to extruder, analogous to tablet press.

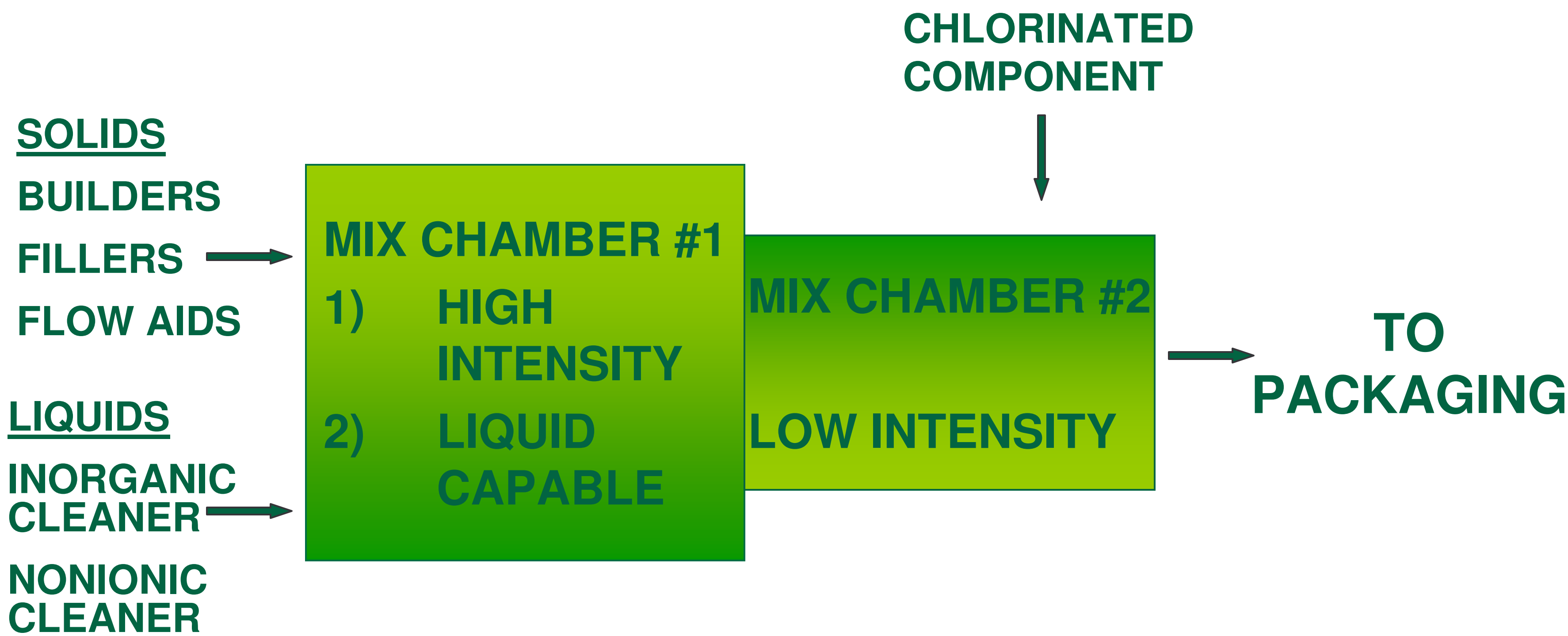
CROSS LINKABLE POLYMERS



Non-Pharma Continuous Processing/Detergents

- Builders analogous to diluents.
- Cleaning agent analogous to API.
- Flow aids analogous to SiO_2.
- Post add chlorine analogous to lube.
- Dual addition of non-miscible liquids.

DETERGENTS



CHLORINATED COMPONENT
SOLIDS
BUILDERS
FILLERS
FLOW AIDS
LIQUIDS
INORGANIC CLEANER
NONIONIC CLEANER
MIX CHAMBER #1
1) HIGH INTENSITY
2) LIQUID CAPABLE
MIX CHAMBER #2
LOW INTENSITY
TO PACKAGING

Utilization Efficiency

- Pharma manufacturing efficiencies are below those of many other industries.
- Continuous processing offers continuous improvement in real time.
- Low risk of cross-contamination with dedicated processing vessels.

Real Time Release

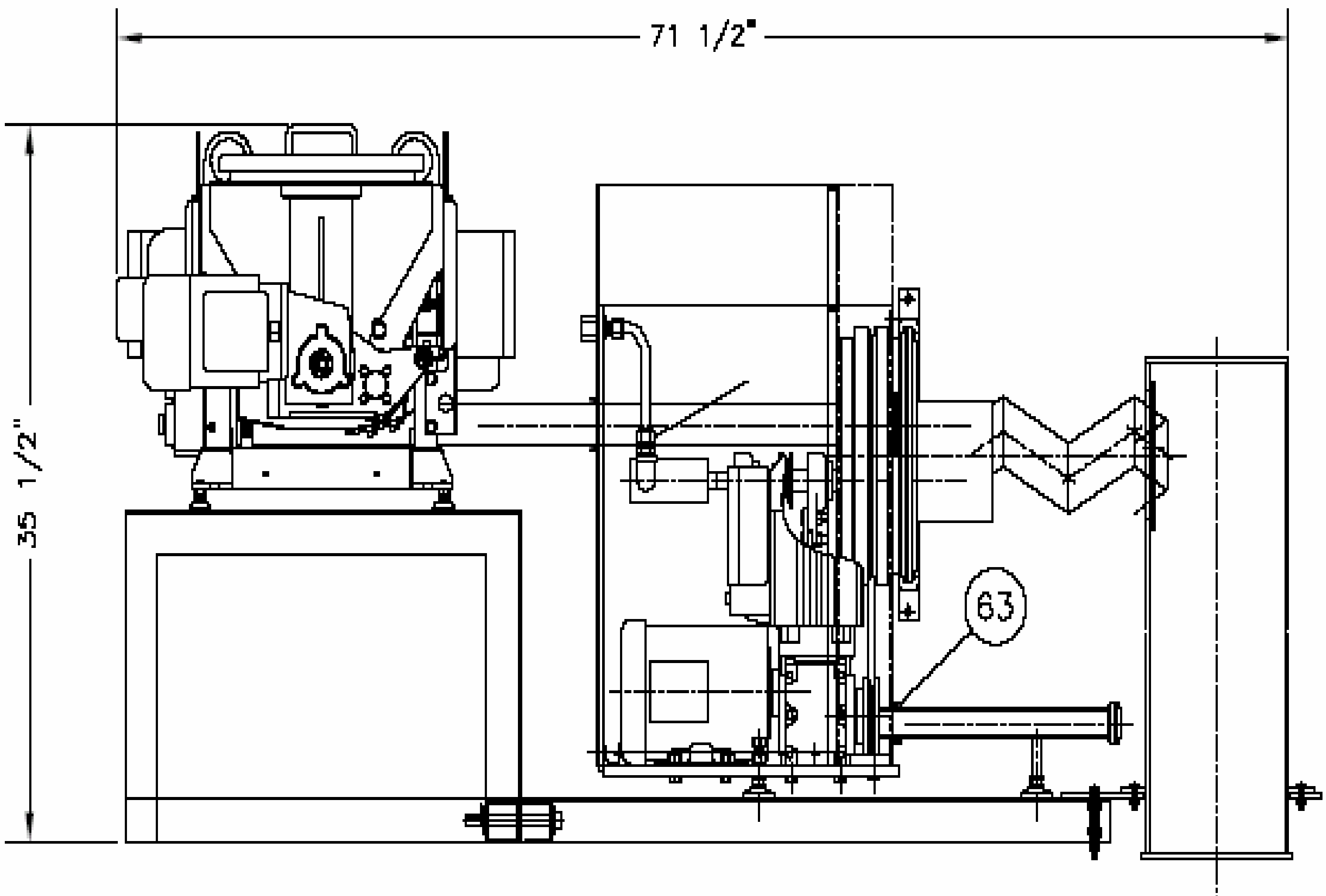
- The ideal for continuous processing.
- Robust process algorithm with feed-forward and feedback capability.
- Multi-chambered mixing device for both intimate mixing and post addition of lube.

Metrics for ROI

- Reduced off-spec material.
- Reduced analytical expenditure.
- Reduced in-process inventory.
- Improved energy usage.
- Improved safety with automation in potent active environment.

Throughput Rates

- 100 kg/hr to < 10 kg/hr in a continuous mode.
- Intermittent mode substantially lowers the rate.
- Intermittent capability is an important consideration.
- Well-suited to custom, low-volume formulations.



71 1/2"
35 1/2"
63

Relating Intrinsic and Extrinsic Factors

$D_Z/(u_Z Z)=0.000562(\varphi^{0.79}/(\gamma^{0.67}n^{1.06}\rho^{0.25})$

D_Z , axial dispersion coefficient, m^2/s

u_Z, mean axial velocity, m/s

Z, drum length, m

Φ, angle of repose, rad

γ, drum angle, deg

n, rotational speed, s^{-1}

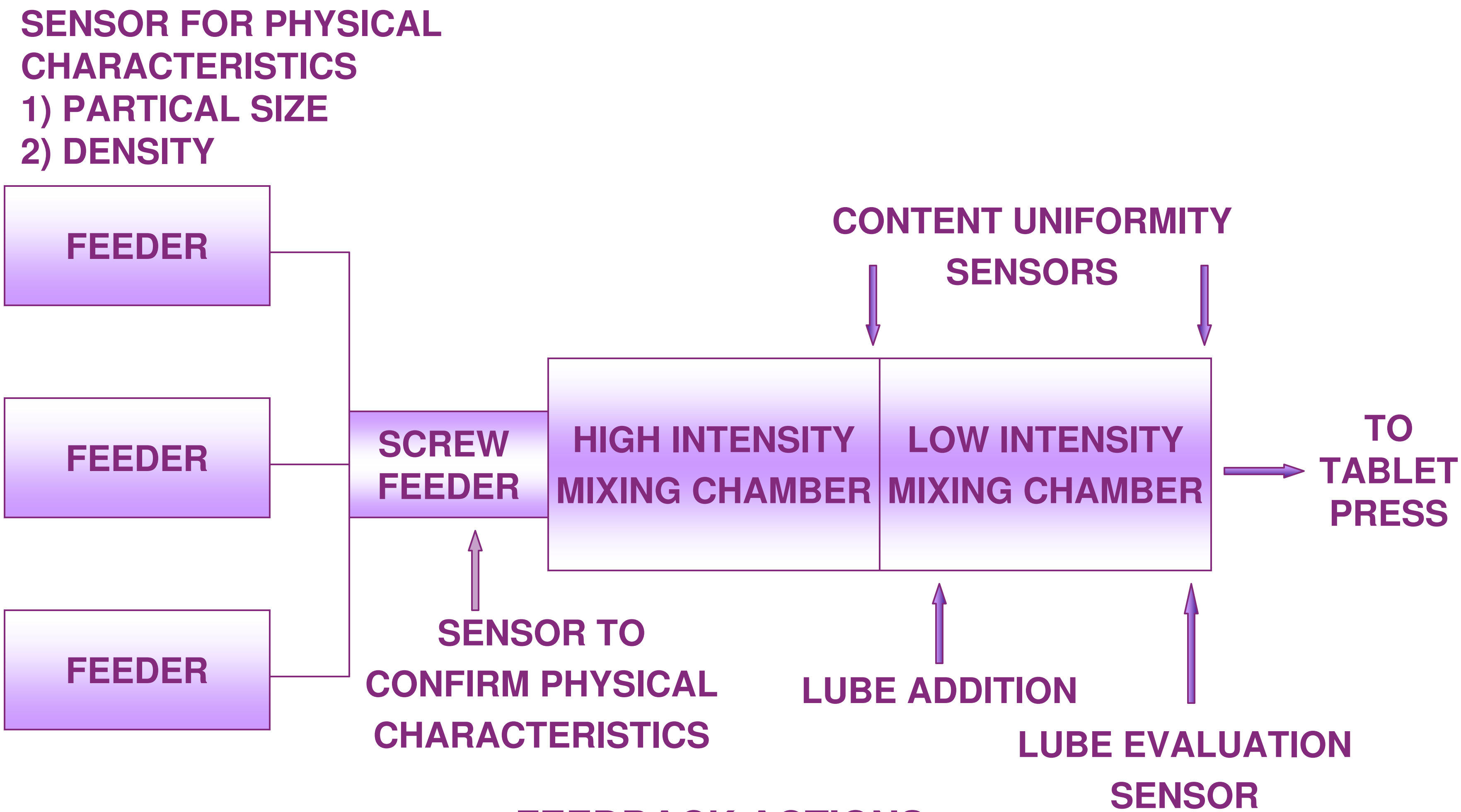
ρ, density, kg/m^3

Sensor Criteria

- Near real time analysis.
- Wireless transmission to data collecting site.
- Non-invasive monitoring.
- Calibration frequency.
- Traceability to known methods.
- Sensor drift in response to environment.

Additional Sensor Considerations

- Maintaining sample point clarity for cohesive formulations.
- Adaptability to an N_2 blast.
- Is too fine a look at uniformity a bad thing?
- Fine sensing may reveal inhomogeneity irrelevant to unit dosage size.



<u>FEEDBACK ACTIONS</u>

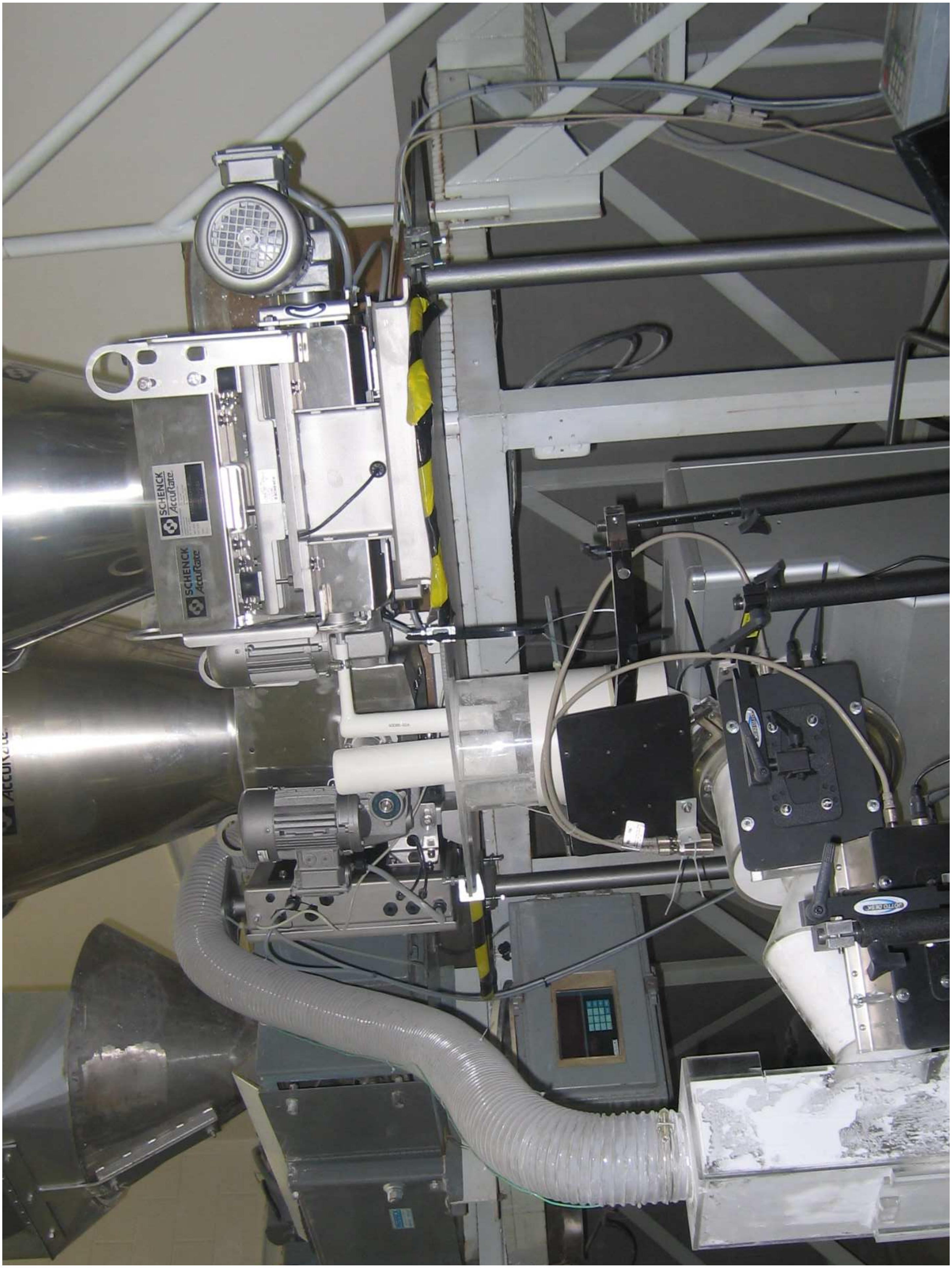
1) INCREASE/DECREASE THROUGHPUT
2) INCREASE/DECREASE AGITATOR SPEED
3) INCREASE/DECREASE SHELL SPEED
4) INCREASE/DECREASE ANGLE
5) INCREASE/DECREASE LUBE

Global Sensor Coverage I

- Process coverage should be complete.
- Sensors prior to feeders may check particle size or density.
- Have these factors changed in a screw feeder?
- Sensors in the mixing device are checking content uniformity.
- Is sensor reading similar for diffusive and convective mixing locations?

Global Sensor Coverage II

- A lube sensitive sensor may be different than the content uniformity sensor.
- How many sites are appropriate for a 1 meter mixing chamber?
- Sensors in various sites must communicate with each other.
- Goal is to compare/contrast/ react in near real time.

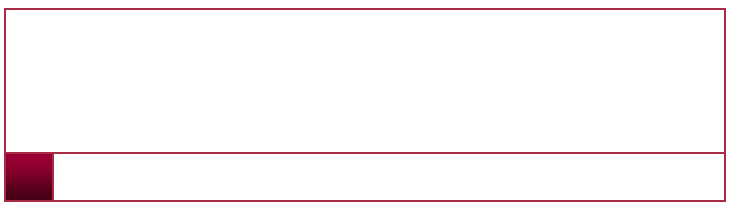

SCHENCK
AccuRate
SCHENCK
AccuRate

BATCH MODELING OF CONTINUOUS PROCESSES

R.G. Sherritt et al I Chemical Engineering Science 58 (2003) 401-415

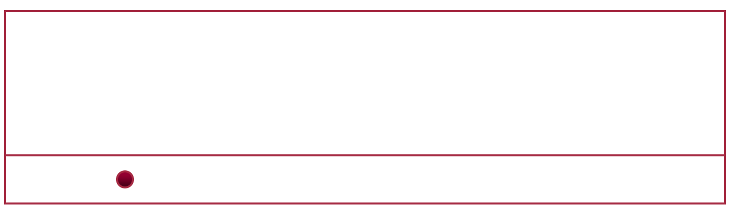
(a) **Half drum**

(b) **Thin slice near centre**



(c) **Thin slice near end**

(d) **Wide band**



(e) **Single particle**

FOR THIN SLICE NEAR END

$$C(0,z) = 0 \qquad (0 \leq z \leq Z)$$

$$C(0,0) = 1$$

$$C(t,z) = \frac{1}{2(\Pi D_2 t)^{1/2}} \exp\left(-\frac{z^2}{4D_2 t}\right)$$

LUBRICATION MONITORING USING THERMAL EFFUSIVITY IN SOLID DOSAGE MANUFACTURE

Patrick Okoye, B.Pharm, M.Sc.
Mathis Instruments Ltd

Presented at the MgSt Workshop at Natoli Engineering, St. Louis, MO, June 2005

Objective

To Evaluate the Use of Thermal Effusivity to Predict Tablet Attributes and Disintegration

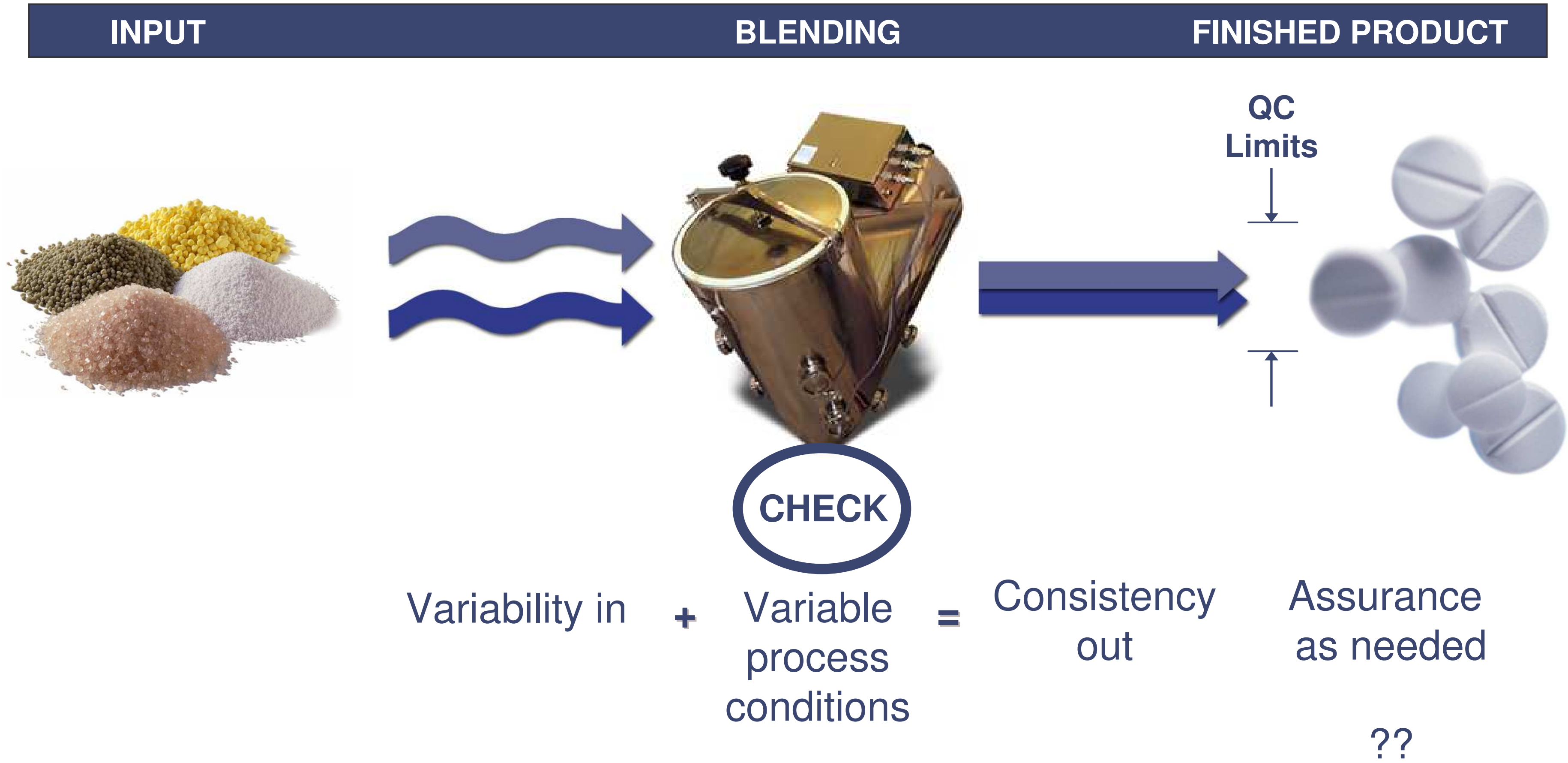
Process Equipment

Equipment	Model	Manufacturer
PK-blender	1 cu. ft	Patterson Kelley
Instrumented Press	10-station press	Natoli Engineering
Friability tester	PTF-20E	Pharma Test
Hardness Tester	PTB-411	Pharma Test
Disintegration Apparatus	VK 7000	VanKel

Protocol

a. Collect adequate samples from the raw material component(s)
b. Charge Avicel PH102 and Anhydrous Lactose, NF in a 1 Cu. ft. V- blender and blend for 10 minutes.
c. Take pre-lubrication samples from three (3) locations in the blender for effusivity measurement.
d. Add magnesium stearate and blend for additional time (as specified).
e. Take post-lubrication samples from three (3) locations in the blender for effusivity measurement.
f. Compress into tablets using 10-station press operated at 20 rpm, 1100 N Compression force.
g. Monitor tablet properties at the press (ejection force, compression force).
h. Sample tablets for tablet weight, friability, disintegration, and hardness.
i. Run offline effusivity measurements and correlate effusivity results to tablet attributes

PAT


INPUT
BLENDING
FINISHED PRODUCT
QC Limits
CHECK
Variability in
+
Variable process conditions
=
Consistency out
Assurance as needed
??

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Factors Affecting Dissolution

1. Solubility of API and Fillers
2. Nature of dissolving medium
3. Particle size
4. Process of mixing
5. Disintegration time

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Dissolution

1. SINGLE POINT

   Time for dissolution, $t_{50\ \%}$ or $t_{90\ \%}$

   Disintegration time > 10 mins may not be problematic.

2. DISSOLUTION PROFILE

   FDA *Guidance For Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997).* There, the similarity factor (f_2) is defined as:

   $f_2 = 50 \text{ x } \log[\ [1 + (1/n)\ {}_{t=1}{}^{n}\ (R_t\text{-}T_t)^2\ ]^{-0.5} \text{ x } 100]$

   An f_2 value between 50 and 100 suggests that two dissolution profiles are similar.

   Disintegration time > 10 mins could be a real problem.

- RESULTS/DISCUSSION

BULK AND TAPPED DENSITIES

BATCH	BULK (g/mL)	TAPPED (g/mL)
A (0.2 % MgSt/ 2 mins)	0.44	0.59
B (0.2 % MgSt/ 20 mins)	0.44	0.61
C (1.1 % MgSt/ 11 mins)	0.51	0.68
D (2.0 % MgSt/ 2 mins)	0.49	0.67
E (2.0 % MgSt/ 20 mins)	0.46	0.57

Carr's indices: A =25.4; B=27.9; C=25.0; D=26.9; E=19.3
More lubricant = better lubrication?
Does level of MgSt influence granular segregation? At what %? How??

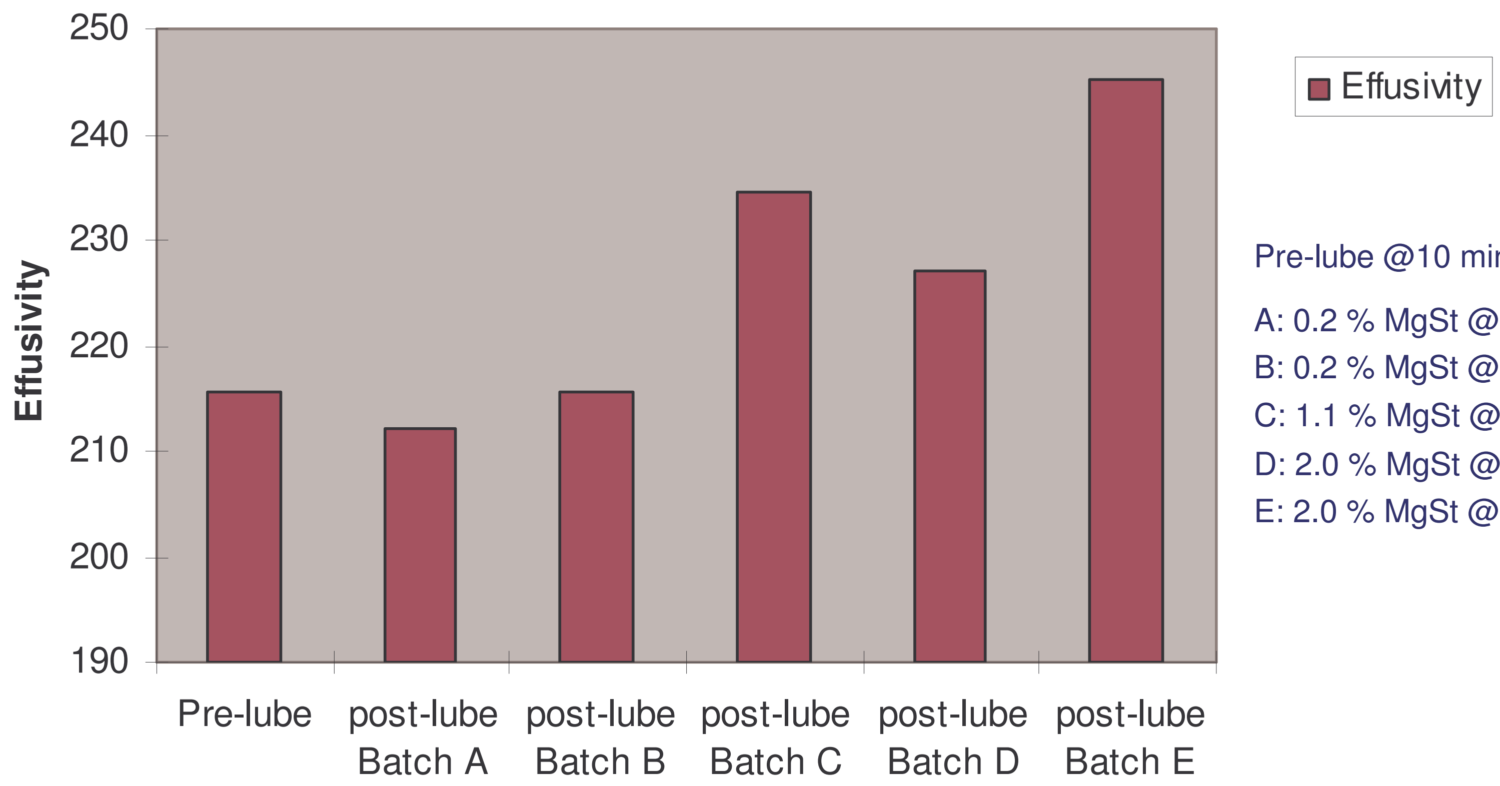
Effusivity of Raw Materials

EFFUSIVITY VALUES			
	AVICEL PH 102	ANHYDROUS LACTOSE	MAGNESIUM ST
1	193.5	242.0	208
2	193.1	244.4	209
3	194.4	243.7	209.6
4	194.9	242.1	207.7
AVE	194.0	243.1	208.6
STD	0.7	1.0	0.8
% RSD	0.4	0.4	0.4

Pre-blending

EFFUSIVITY VALUES FOR PRE-LUBRICATION @ 10 mins			
	TOP	MIDDLE	BOTTOM
1	219.5	219.1	212.1
2	215.9	219.3	211.8
3	216.6	216.6	210.5
Average	217.3	218.3	211.5
Grand Ave	215.6		
STD	1.6	1.2	0.7
% RSD	0.7	0.6	0.3

Effusivity



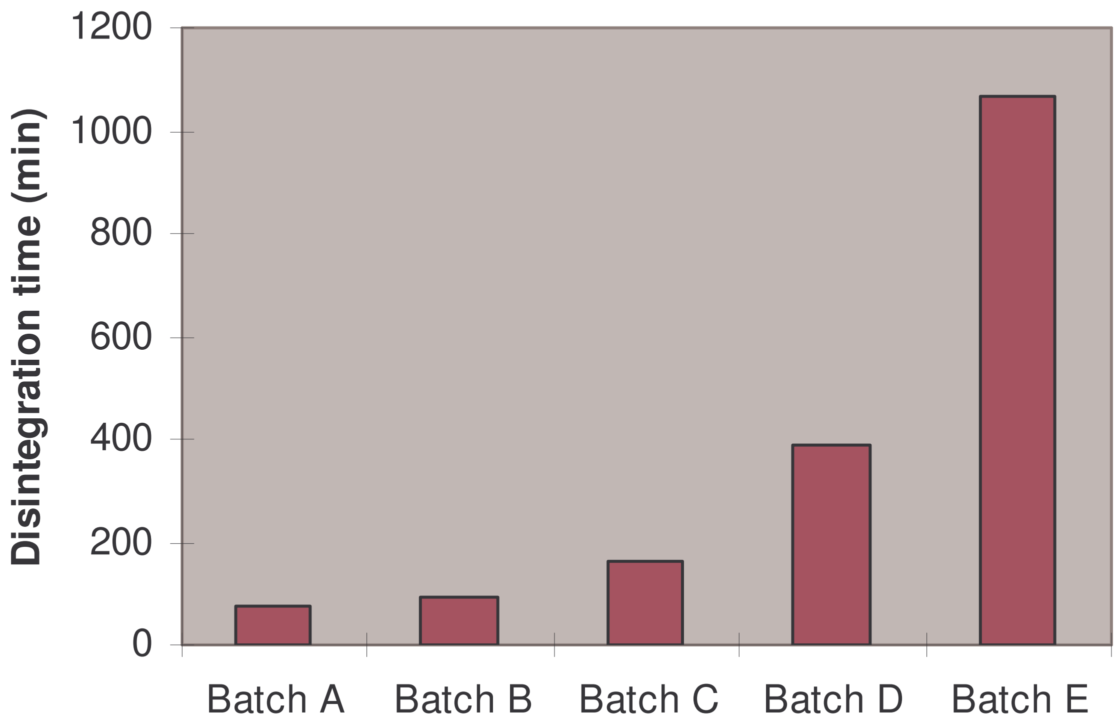
Pre-lube @10 mins

A: 0.2 % MgSt @2 mins
B: 0.2 % MgSt @ 20 mins
C: 1.1 % MgSt @ 11 mins
D: 2.0 % MgSt @ 2 mins
E: 2.0 % MgSt @ 20 mins

DoE Factors and Responses

	Time(min)	MgSt	Ave Effusivity	Ave tab wt	Ave hardness	ave ejection	(%) friability	Disintegration
Batch A:	**2**	**0.2**	**212.2**	**629.9**	**9.17**	**6.76**	**0.16**	**1.25**
Batch B:	**20**	**0.2**	**215.7**	**649.4**	**10.02**	**8.41**	**0.05**	**1.50**
Batch C:	**11**	**1.1**	**234.6**	**628.0**	**5.45**	**10.25**	**0.00**	**2.75**
Batch D:	**2**	**2.0**	**227.2**	**670.2**	**9.47**	**11.63**	**0.00**	**6.50**
Batch E:	**20**	**2.0**	**245.2**	**632.0**	**3.60**	**9.48**	**1.21**	**17.50**

Disintegration Time



A: 0.2 % MgSt @2 mins

B: 0.2 % MgSt @ 20 mins

C: 1.1 % MgSt @ 11 mins

D: 2.0 % MgSt @ 2 mins

E: 2.0 % MgSt @ 20 mins

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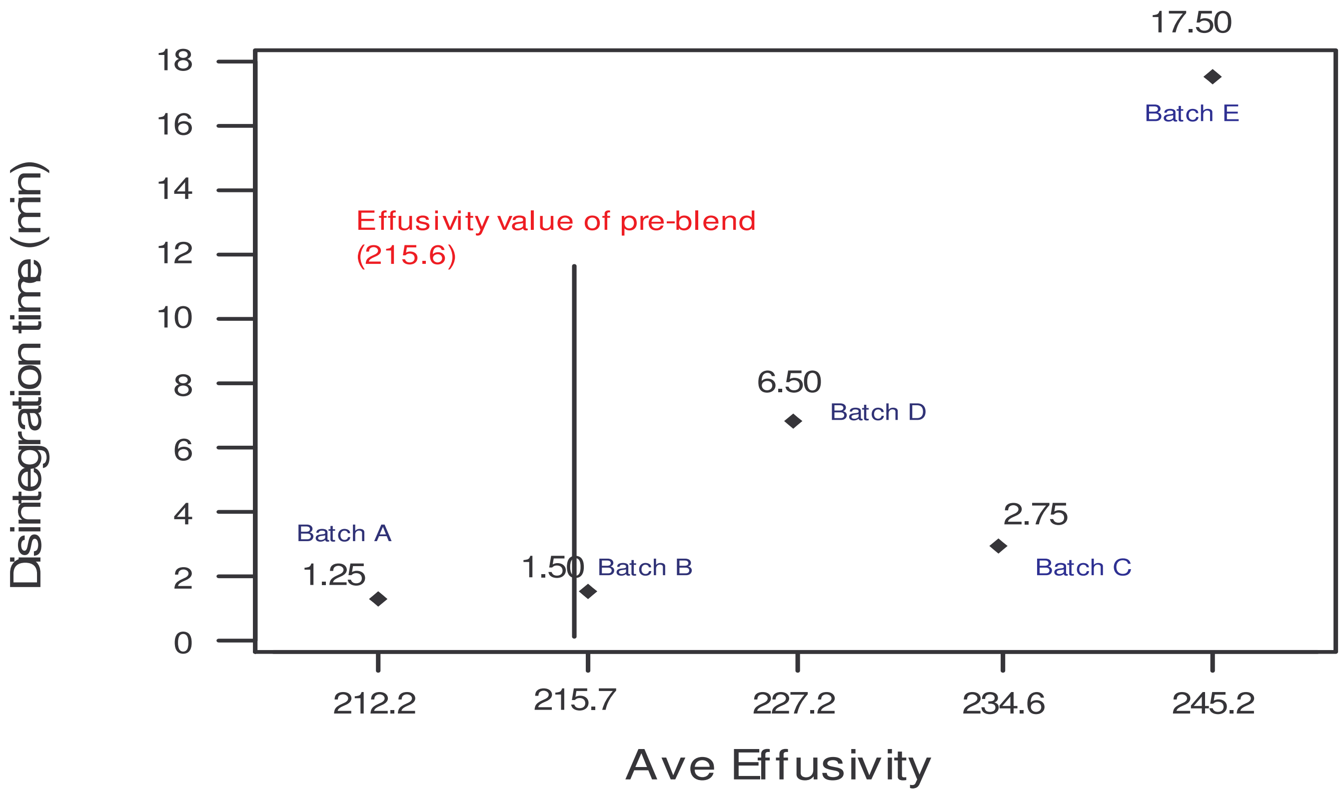
Influence



Post-lubrication blending:

A: 0.2 % MgSt @2 mins

B: 0.2 % MgSt @ 20 mins

C: 1.1 % MgSt @ 11 mins

D: 2.0 % MgSt @ 2 mins

E: 2.0 % MgSt @ 20 mins

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Response Optimization for Ideal Blend

Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
MgSt	is in range	0.2	2.00	1	1	3
Blend Time	is in range	2.0	20.00	1	1	3
hardness	maximize	3.4	11.12	1	1	3
ejection force	minimize	6.1	12.47	1	1	3
Friability	is in range	0.0	0.50	1	1	3
Disintegration	minimize	74.9	1100	1	1	3

Solutions

Number	MgSt	Blend Time	hardness	ejection	Friability	Disintegration	Desirability
• 1	0.20	20.00	10.0	7.5	0.05	85.00	0.86
2	0.22	20.00	9.9	7.6	0.06	88.93	0.85
3	0.20	8.41	9.4	7.5	0.12	78.48	0.84
4	0.20	7.55	9.4	7.5	0.12	78.01	0.84

- **4 Solutions found**

Fused solutions: a) 0.20 % MgSt at ~ 8 mins of blend time

- b) 0.20 % MgSt at ~ 20 mins of blend time

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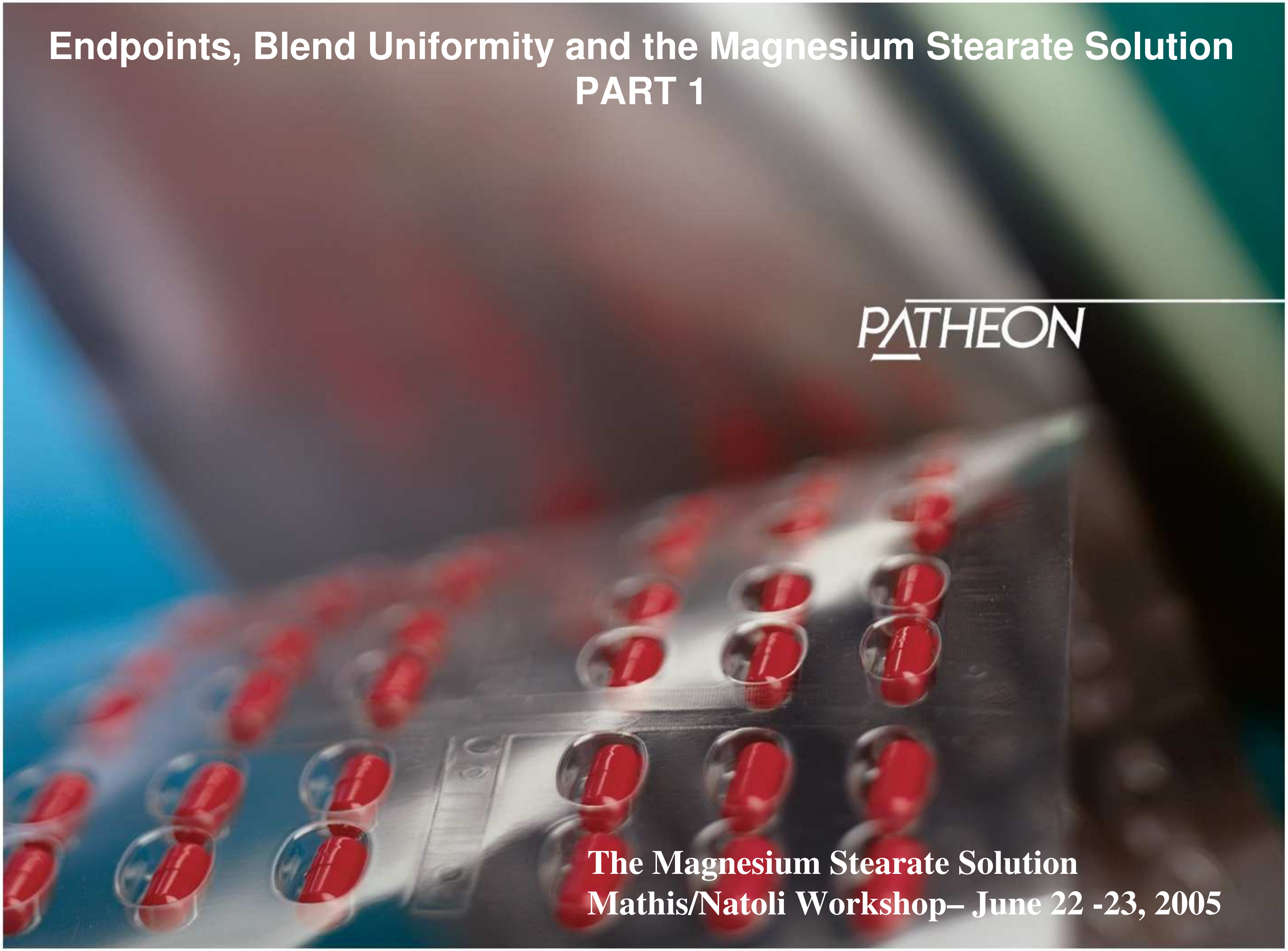
CONCLUSION

- Level of MgSt in the blends appears to influence disintegration time.
- Accurate prediction of optimal level of MgSt in a formulation could minimize or eliminate a major affect on tablet disintegration.
- Optimal lubrication in blend process could be detected by thermal effusivity sensors.

Endpoints, Blend Uniformity and the Magnesium Stearate Solution
PART 1



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The Magnesium Stearate Solution
Mathis/Natoli Workshop– June 22 -23, 2005

Part 1- Presentation Goals

Creating definable endpoints …

Test variation versus product variation (MSA Study)

Blend Applications

Initial applications – bin, lubrication

Process Troubleshooting – case study

Process Development- case study

How low can you go??

Static versus Dynamic

Magnesium Stearate Application

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Creating definable endpoints …

Measuring System Analysis

- Any measurement system will contribute some variation to the observed result - measurement error.
- If the amount of variation is too large relative to the inherent product variation or the specification, the error can lead to incorrect interpretation of results.
- Understand the precision of critical measuring systems and the source(s) of this error is critical
- Measurement System Analysis (MSA) uses statistical techniques to partition the variation into its components

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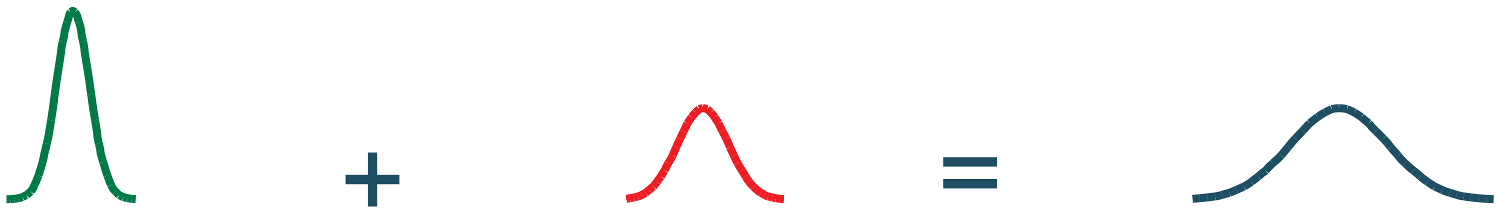
Measurement System Analysis (MSA)

$$\sigma^2_{\text{Product}} + \sigma^2_{\text{Measure}} = \sigma^2_{\text{Total}}$$



True Product Variation + Variation of Measurement System = "Observed" Variation

Variation of Measurement System → Repeatability, Reproducibility

Repeatability - the variation within one sensor

Reproducibility - the variation between multiple sensors

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Preliminary MSA Results

- 5 materials tested individually to ensure content of blender was "homogenous" (Sodium Bicarbonate, Sucrose, Lactose, MCC, and SiO2)
- Effusivity measured by 4 sensors every 2 minutes over a period of 20 minutes

		Time (minutes)										
Excipient	**Sensor**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	
	%RSD	**2.95**	**3.21**	**0.89**	**1.76**	**1.93**	**3.13**	**1.40**	**4.00**	**1.96**	**2.75**	**RSD**
Sodium	**1**	462.0	431.6	443.7	438.8	436.1	428.1	433.5	429.0	429.3	430.2	**2.37**
Bicarbonate	**2**	438.4	449.0	444.9	446.7	445.4	442.2	448.0	437.0	446.1	448.9	**0.74**
	3	442.8	453.1	452.1	441.8	451.5	451.7	443.3	447.1	448.7	443.4	**0.86**
BD=1.12 g/mL	**4**	464.8	466.7	449.5	456.7	456	460.8	439.4	470.1	443.5	459.6	**1.68**

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Preliminary MSA Results

MSA ANOVA Method Results

Source	Variance	Standard Deviation	% Contribution
Total Measurement (Gage)	70.0711533	8.37085141	0.31%
Repeatability	23.7522722	4.873630292	0.10%
Reproducibility	46.3188811	6.80579761	0.20%
Sensor	23.8898875	4.887728256	0.11%
Sensor* Material Interaction	22.4289936	4.735925845	0.10%
Product (Part-to-Part)	22615.9993	150.3861673	99.69%
Total	22686.0705	150.6189579	100.00%

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Preliminary MSA Results

2 Important pieces of Information

Product (Part-to-Part)	22615.9993	150.3861673	99.69%

- Variation due to product is largest %

Source	Variance	Standard Deviation
Total Measurement (Gage)	70.0711533	8.37085141
Repeatability	23.7522722	4.873630292
Reproducibility	46.3188811	6.80579761

- A third of variation is due to repeatability and two thirds is due to reproducibility
- Quantifying measurement error will allow setting meaningful specification for endpoint detection
- Knowing source of variation directs efforts to reduce error and further improve sensitivity

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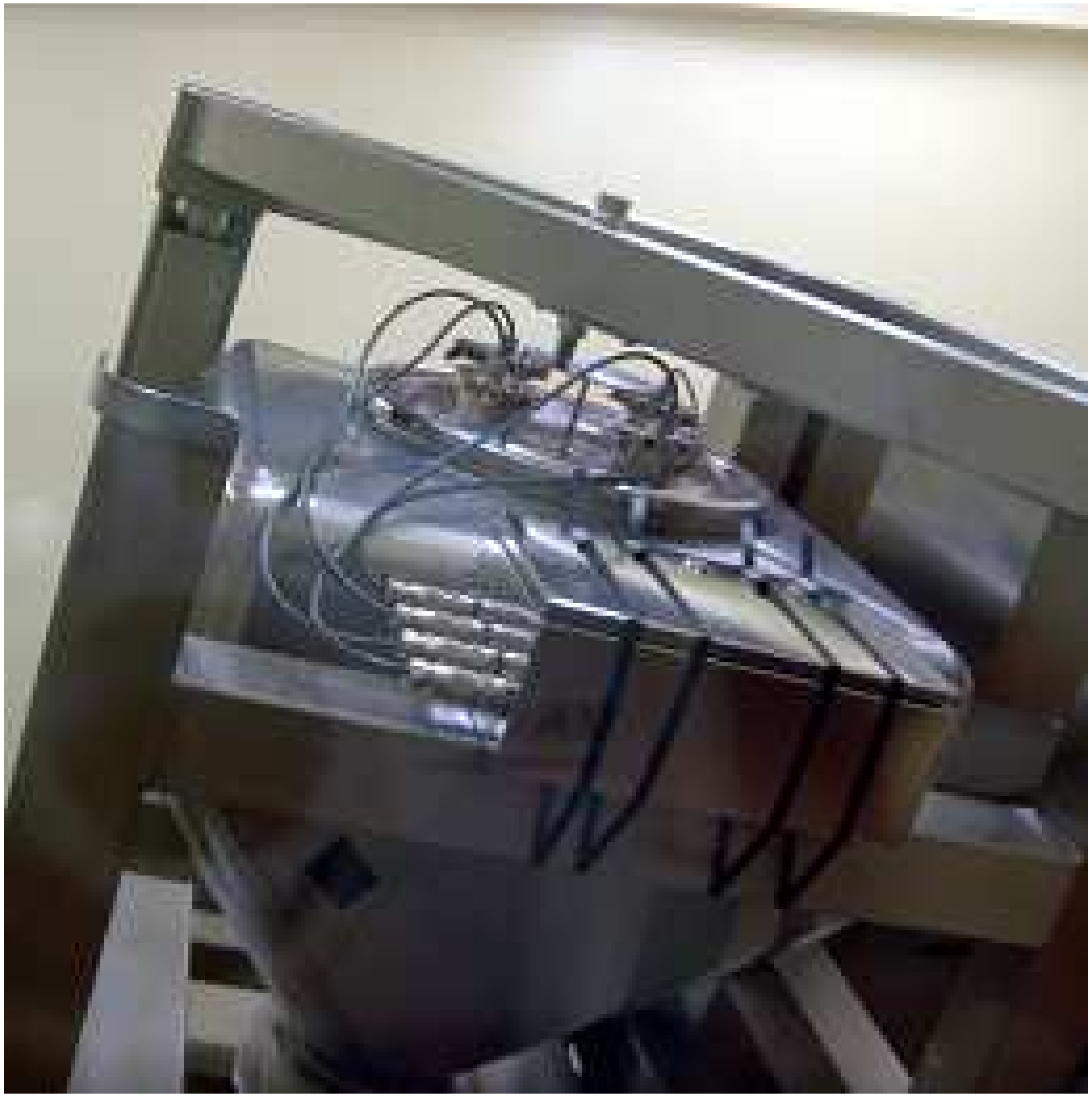
Other Endpoint Considerations

- Scale of scrutiny
- Quantitative or Qualitative endpoints
- Process or Analytical Method Validation

Blend Applications



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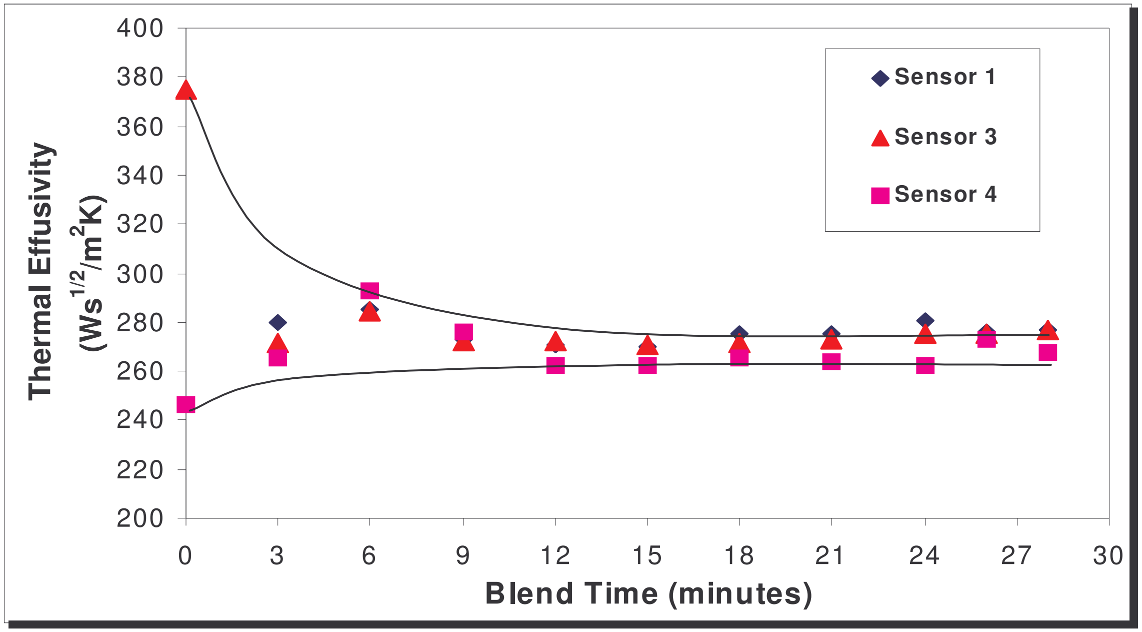
Lactose and Avicel in a 325L Bin

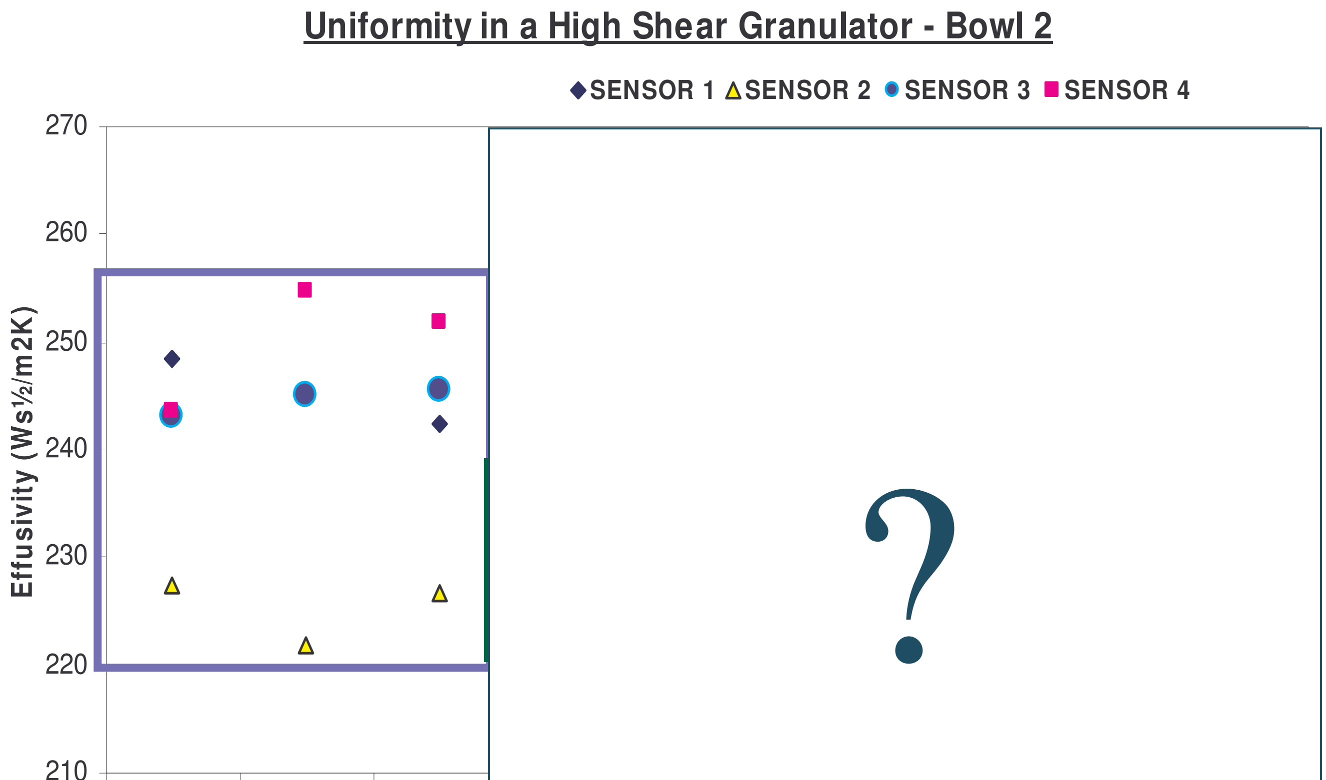


Blend complete in 9 minutes (0.7% RSD)

Blend Uniformity in a High Shear Mixer

Niro PMA 65 with Mathis BT-04 sensors

Blend Uniformity in a High Shear Mixer



Blend Times	0.5	1.0	1.5
%RSD	3.80	5.79	4.40

Blue – Impeller LOW/Chopper OFF

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Blend Process Development

- Define blend process using:
- Traditional BU methods
- Stratified Content Uniformity Testing
- PAT

- Help creatge process “signature”

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Stratified Sampling Draft Guidance…

Involves two critical components

1) Traditional BU testing (sampling thief)

From Blend Sample at least 3 locations with at least 3 replicates at each location

↓

Assay 1 per location*

↓

Blend Sample Criteria:

RSD ≤ 5.0 % and all individuals are within ± 10 % of mean (absolute)

* If test 1 failure then test set 2 and 3

PATHEON

Stratified Sampling Draft Guidance…

2) CU testing on tablets

During filling or compression take 7 dosage unit samples from each of at least 20 locations

↓

Assay 3 per location (weight correct each result)*

↓

RSD of all individuals ≤ 6.0%. Each location mean is within 90.0 – 110.0 % of target potency, and all individuals are within 75 – 125 % of target potency.

(Individuals are not weight corrected)

* If test 1 fails then re-perform with at least 7 dosage units from each location

PATHEON

Stratified Sampling Draft Guidance…

Pitfalls and shortcomings

- Still relies on traditional BU sampling as representative of batch uniformity
- Blend sampling using a sampling thief is flawed (sampling bias)
- Expensive (60 to 200 tablets tested for CU)
- Confusing

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Stratified Sampling Draft Guidance…

How PAT technologies can help

- Another set of data to back-up or refute thief sampling data
- Still have confidence from weight averaged CU data that blend does not segregate post blend
- Ties PAT data in with known and accepted analytical test methods (i.e. HPLC)

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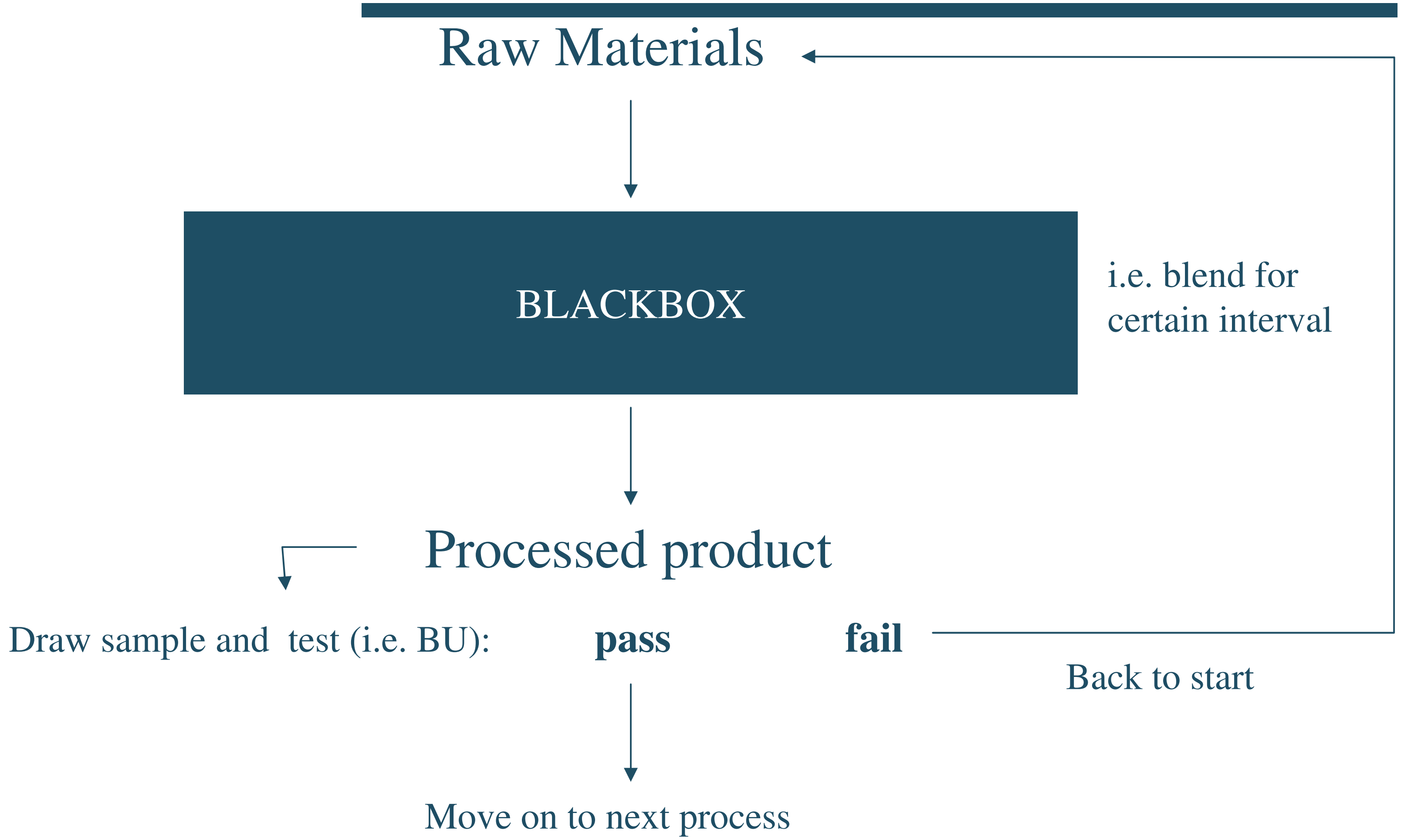
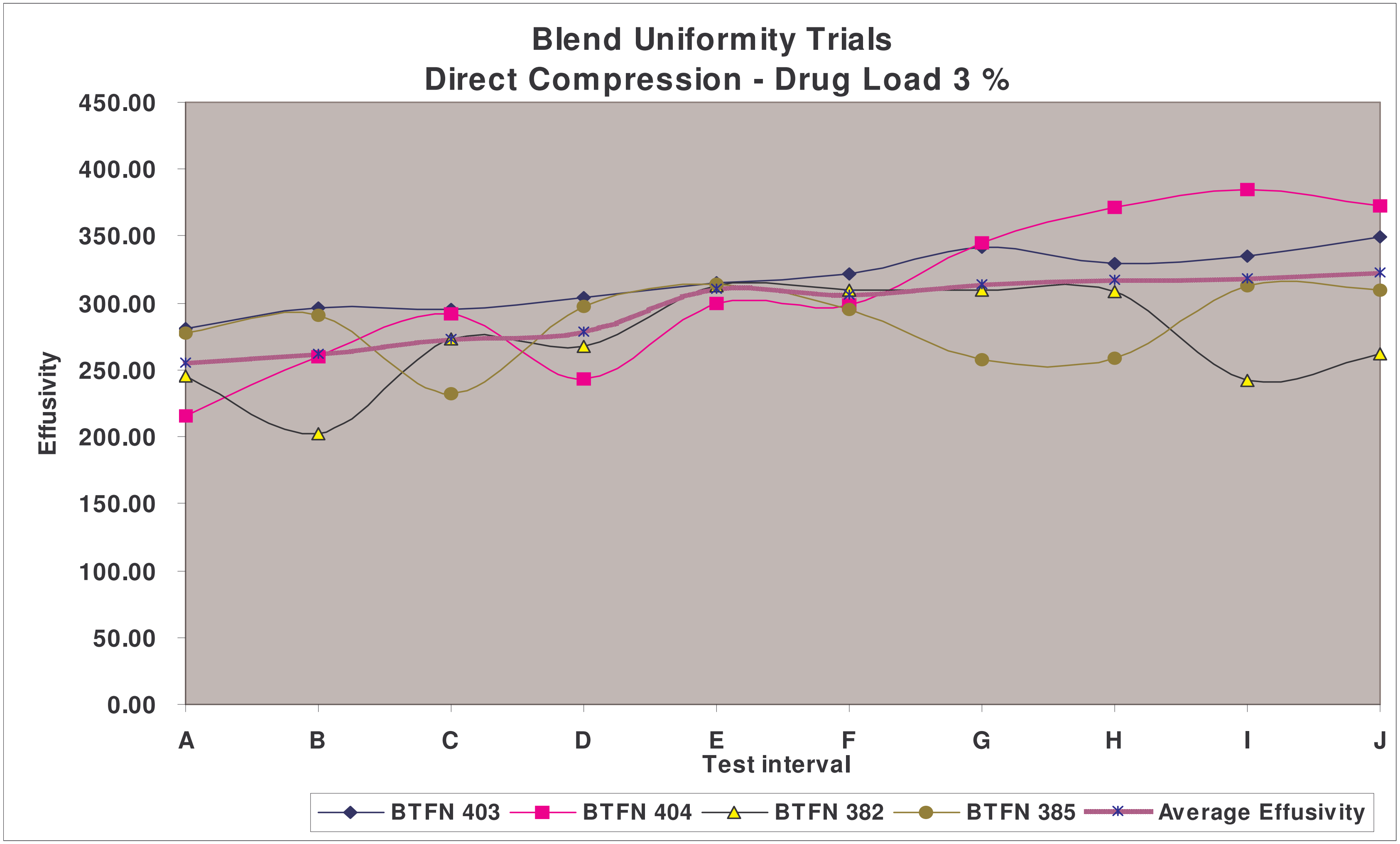
Traditional "Blackbox" Process Development Scenario



Blend Process Development Case Study



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Blend Process Development Case Study

- Blend Interval 1 (BU Data)

Mean	99.0	96.3
Min	86.8	93.8
Max	107.2	99.2
RSD	5.9	1.7

- Blend Interval 2 (BU Data)

Mean	99.9	98.7
Min	95.9	94.4
Max	105.1	101.7
RSD	2.4	2.1

- Blend Interval 3 (BU Data)

Mean	102.4	100.7
Min	97.9	66.0
Max	102.4	125.5
RSD	2.1	14.5

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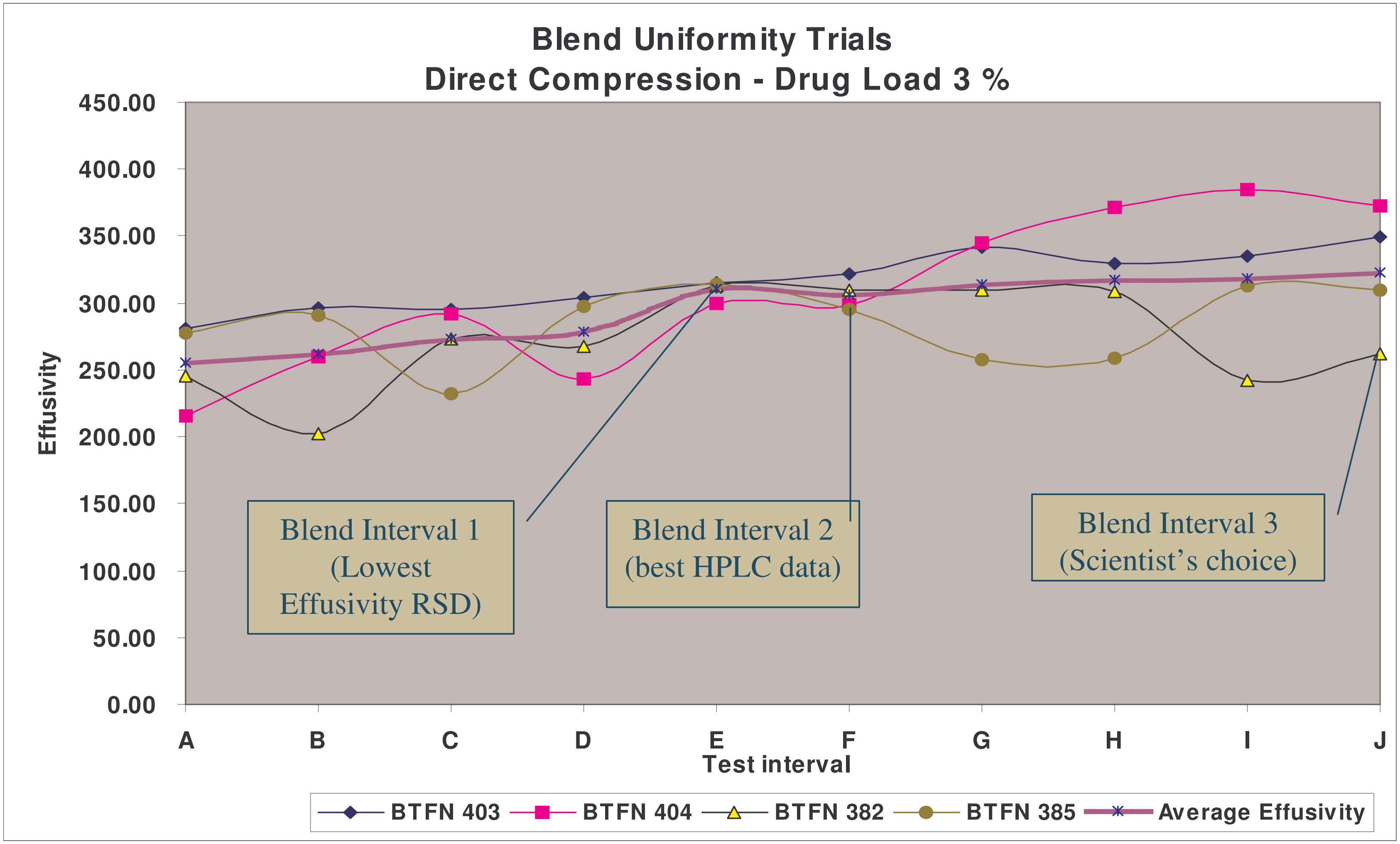
Blend Process Development Case Study



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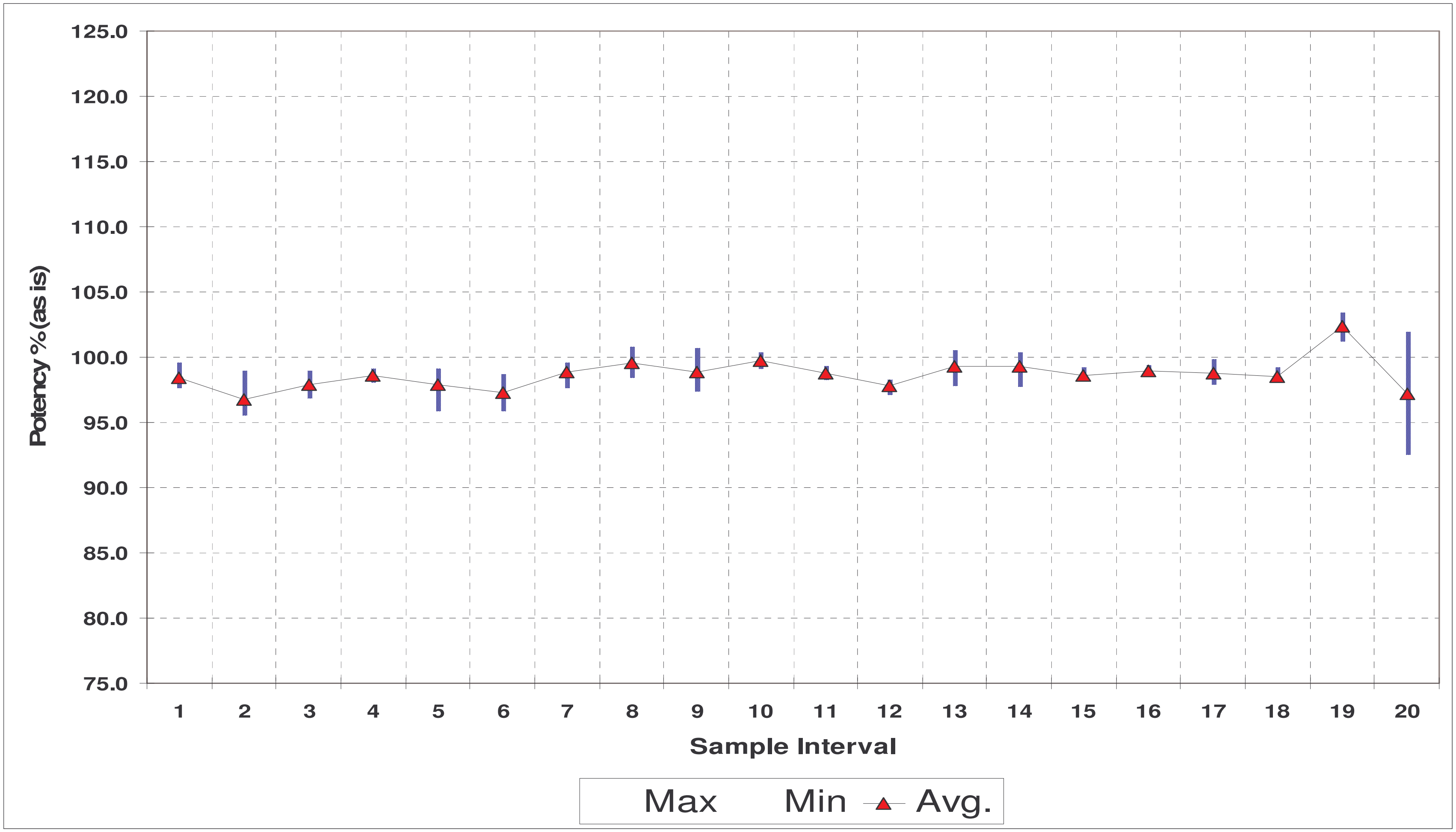
Blend Process Development Case Study

Stratified Sampling Data – Blend Interval 1 (Weight Uncorrected – 75 – 125 % individual limits)



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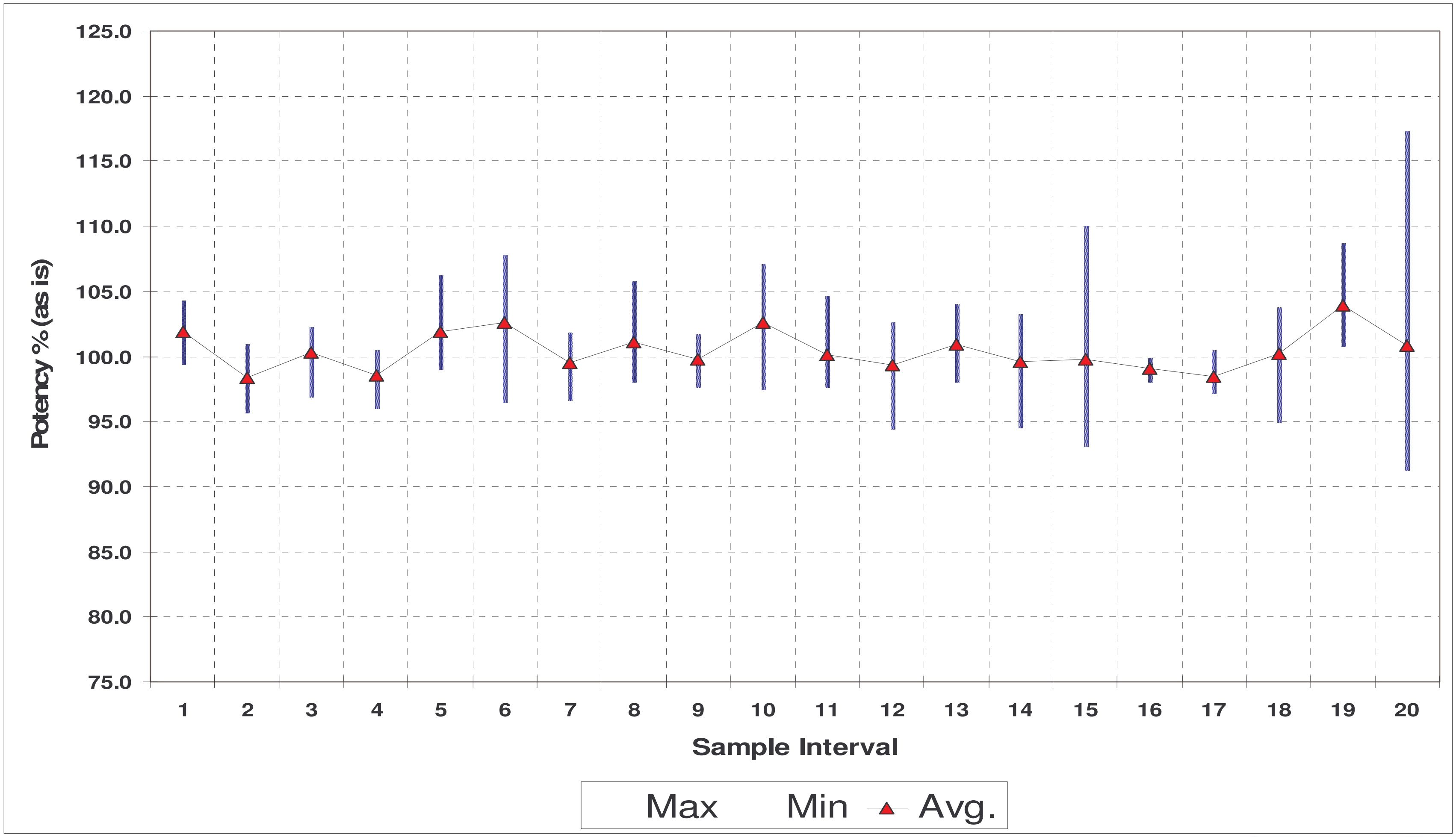
Blend Process Development Case Study

Stratified Sampling Data – Blend Interval 2 (Weight Uncorrected – 75 – 125 % individual limits)



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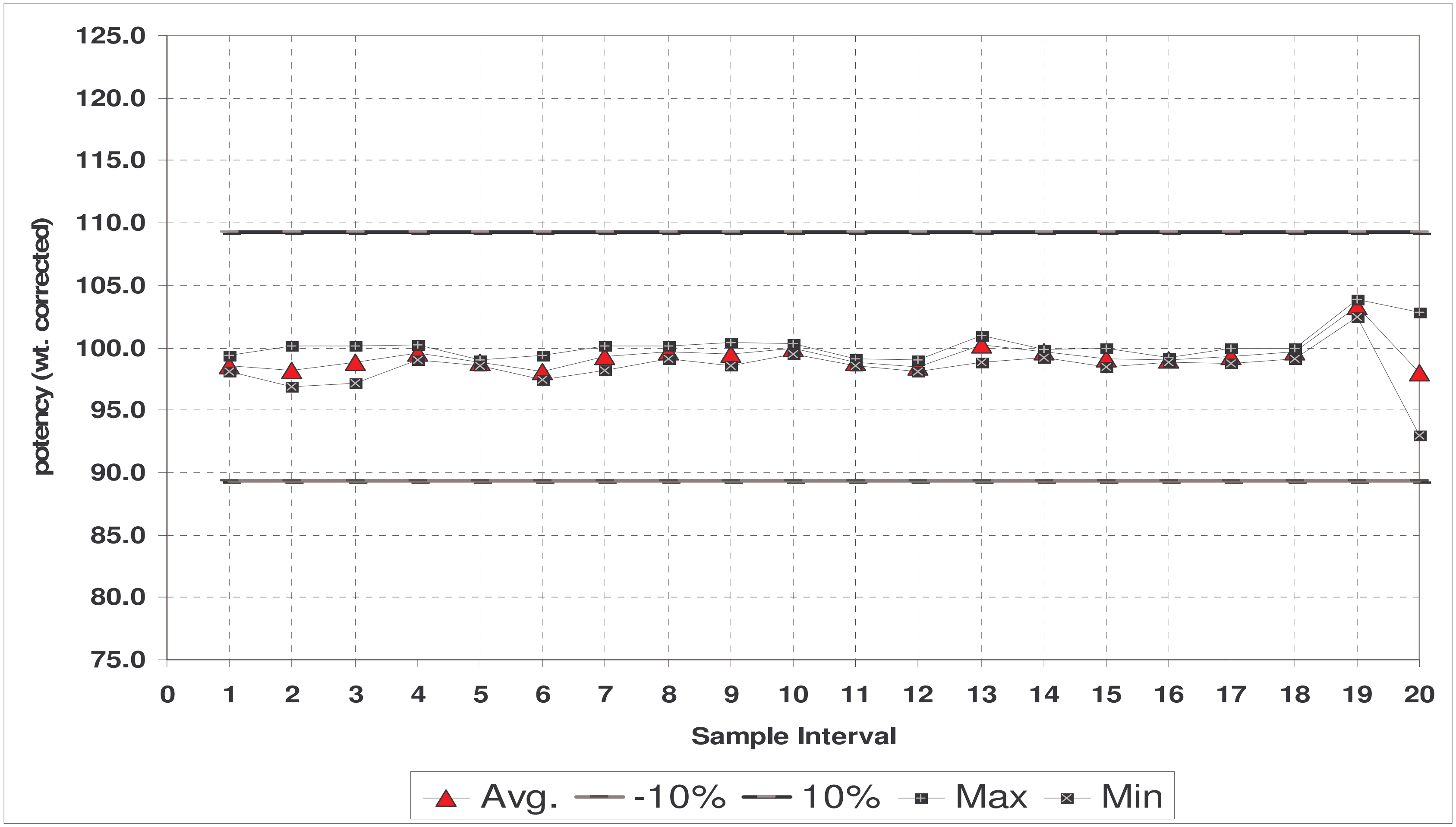
Blend Process Development Case Study

Stratified Sampling Data – Blend Interval 1 (Weight Corrected: 90 – 110% mean limit)



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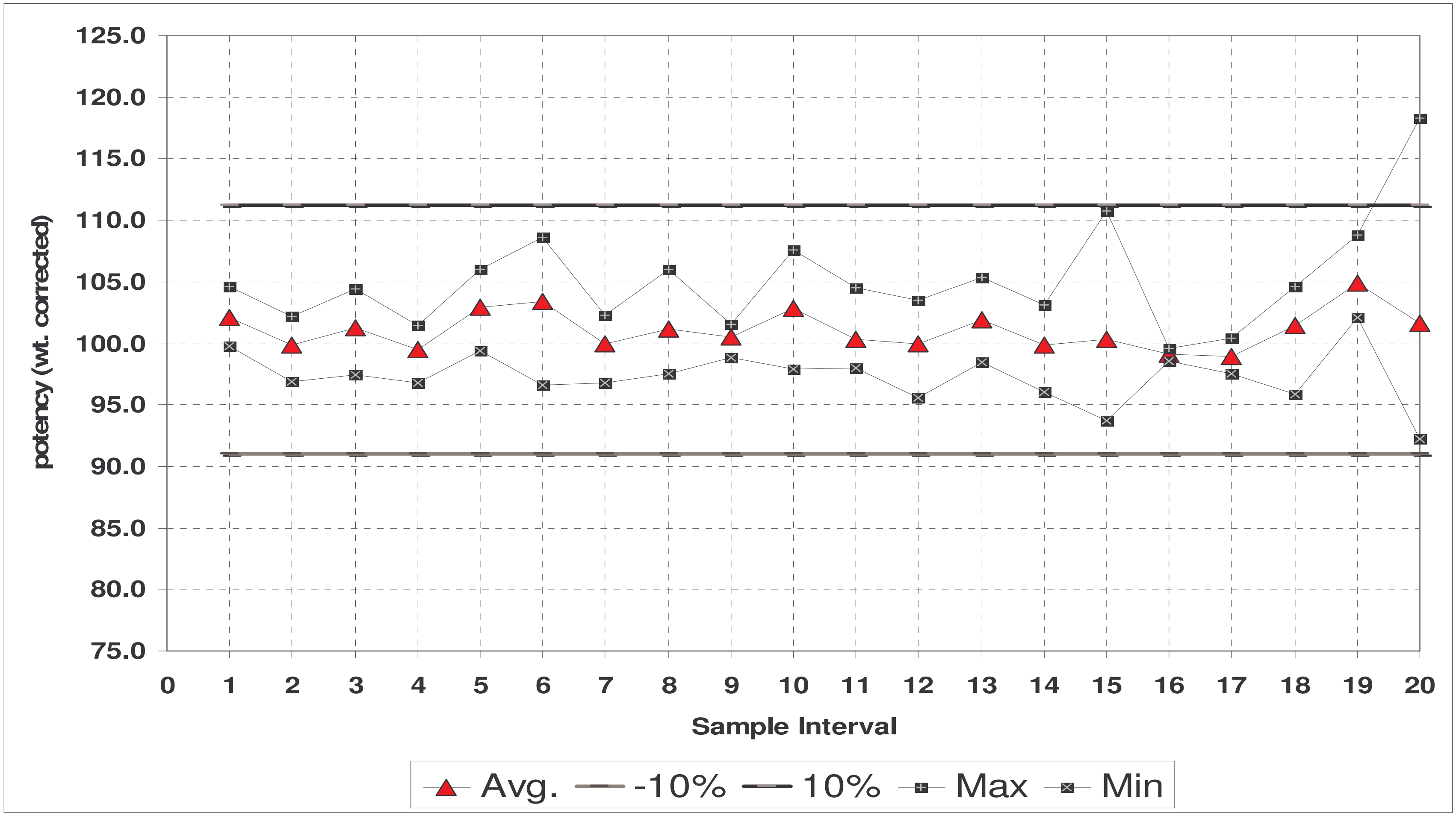
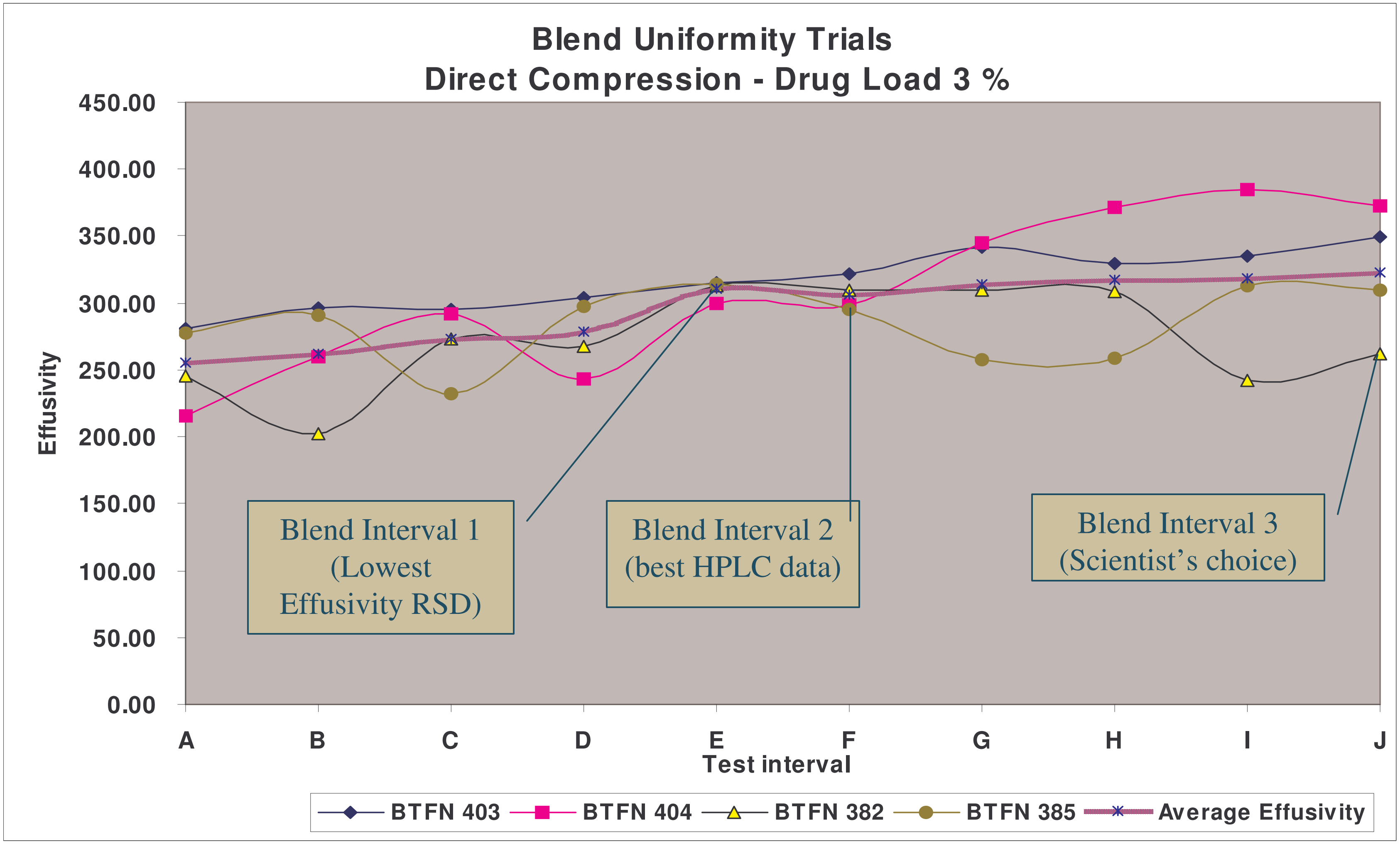
Blend Process Development Case Study

Stratified Sampling Data – Blend Interval 2 (Weight Corrected: 90 – 110% mean limit)



PATHEON

Blend Process Development Case Study



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Process Analytical Method Development

…Using both static and dynamic systems

Phases 1 and 2 (Static system)

Phase 1 -Binary mixtures:

-Sodium Bicarbonate: effusivity 446 Ws½/m2K
-Methyl Paraben (marker compound – API) : effusivity 235 Ws½/m2K

Phase 2 -Ternary mixtures:

-Sodium Bicarbonate: effusivity 446 Ws½/m2K
-Methyl Paraben (marker compound – API) : effusivity 235 Ws½/m2K
-Avicel Ph 102: effusivity 227 Ws½/m2K

-Endpoint Criteria based on MSA studies:
1 - the RSD between 2 sensors < 1.5% AND
2 – the change in average effusivity between two consecutive readings < 1

- At that point, sample 4 locations for HPLC (Top Right Centre Bottom)
- Evaluate effusivity as a predictive method of endpoint

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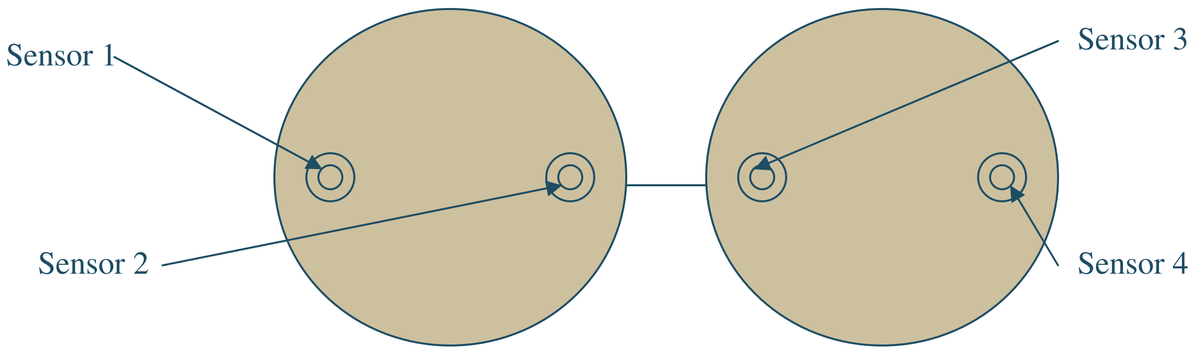
Phases 1 and 2 (Static system)

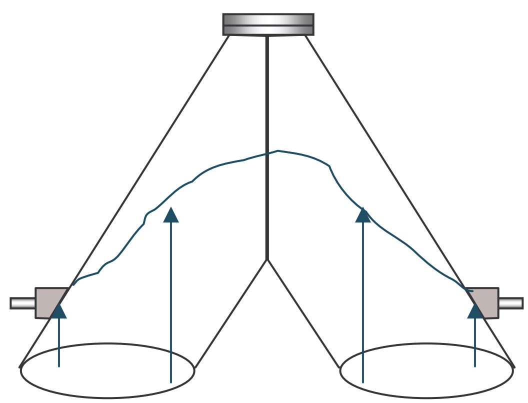
- Why only 2 sensors???

V-blender (top view- left and right lids)



Data from MSA indicates sensor bias (lowest RSD for sensor 2 and sensor 3 locations)??

Why?



Differential pressure between inner and outer locations??

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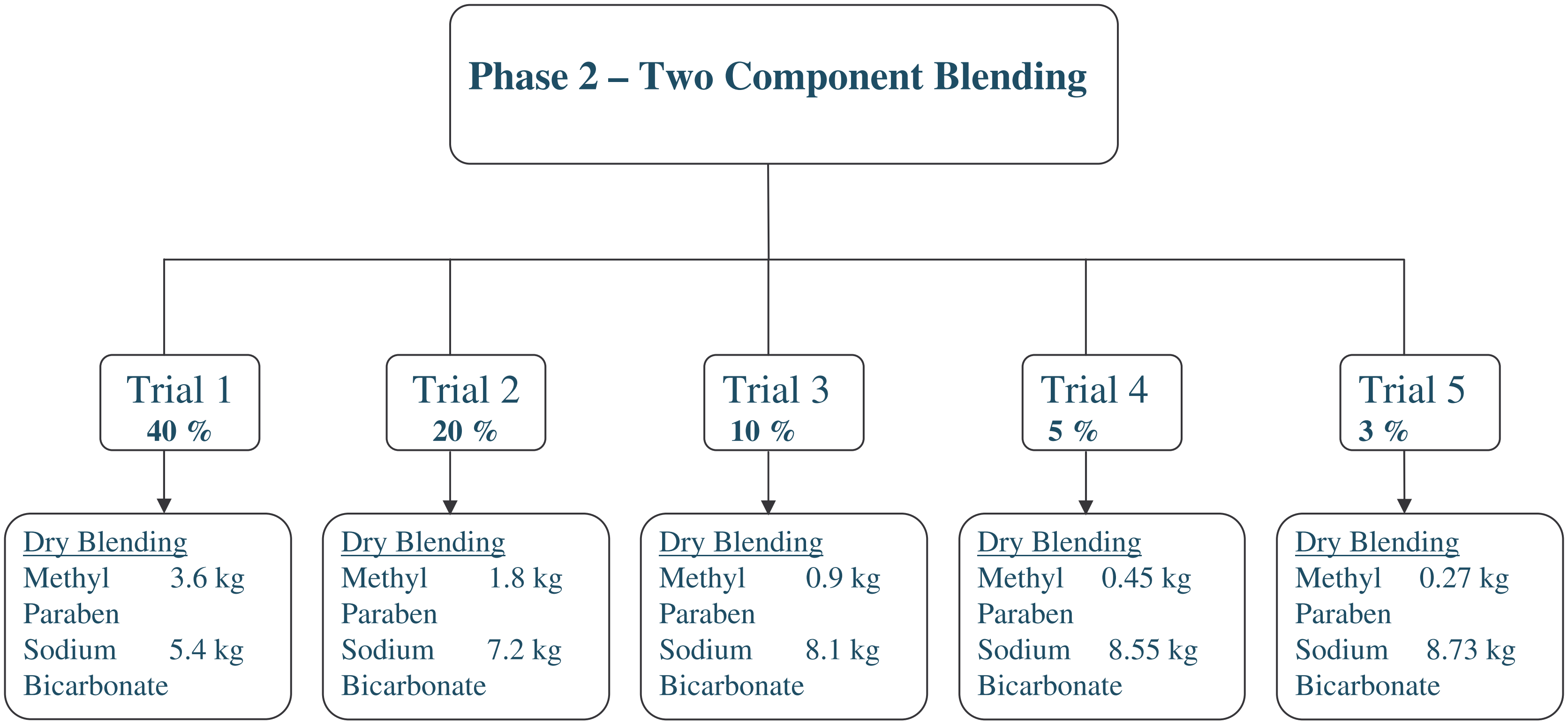
Phase 1 Flow Diagram



2 types of distinctive endpoint profiles were obtained

Rapid and "fish" profiles

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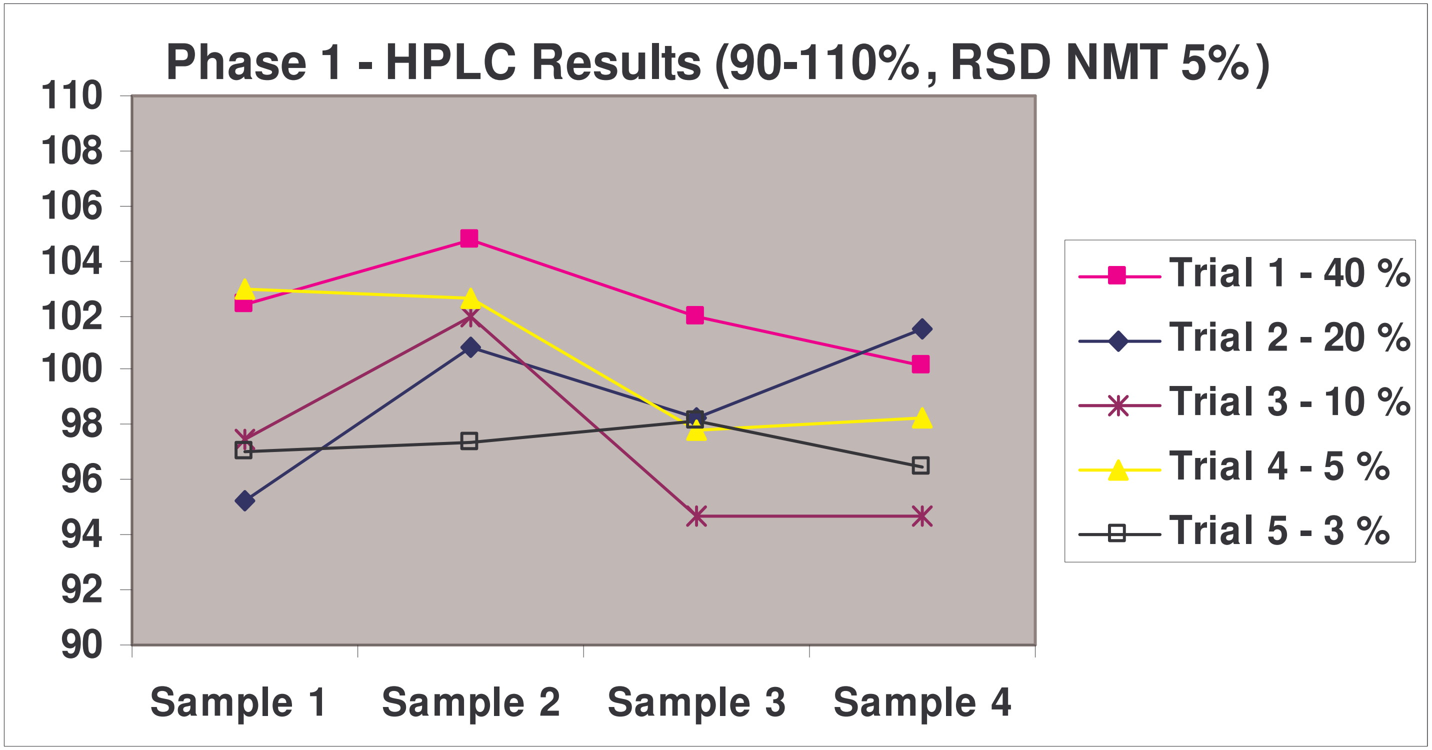
Phase 1 Results

HOW LOW CAN YOU GO???????

As low as 3 % marker compound in a binary mixture



RSD
1.97
3.23
3.26
3.04
1.15

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Phase 2 Flow Diagram

Phase 3 – Three Component Blending

Trial 1 — 5%

Dry Blending

Methyl Paraben	0.4 kg
Sodium Bicarbonate	3.8 kg
Avicel	3.8 kg

Trial 2 — 3 %

Dry Blending

Methyl Paraben	0.24 kg
Sodium Bicarbonate	3.88 kg
Avicel	3.88 kg

Trial 3 — 1%

Dry Blending

Methyl Paraben	0.08 kg
Sodium Bicarbonate	3.96 kg
Avicel	3.96 kg

Trial 4 — 0.5 %

Dry Blending

Methyl Paraben	0.04 kg
Sodium Bicarbonate	3.98 kg
Avicel	3.98 kg

2 types of endpoint profiles were again obtained
Rapid and "fish" profiles

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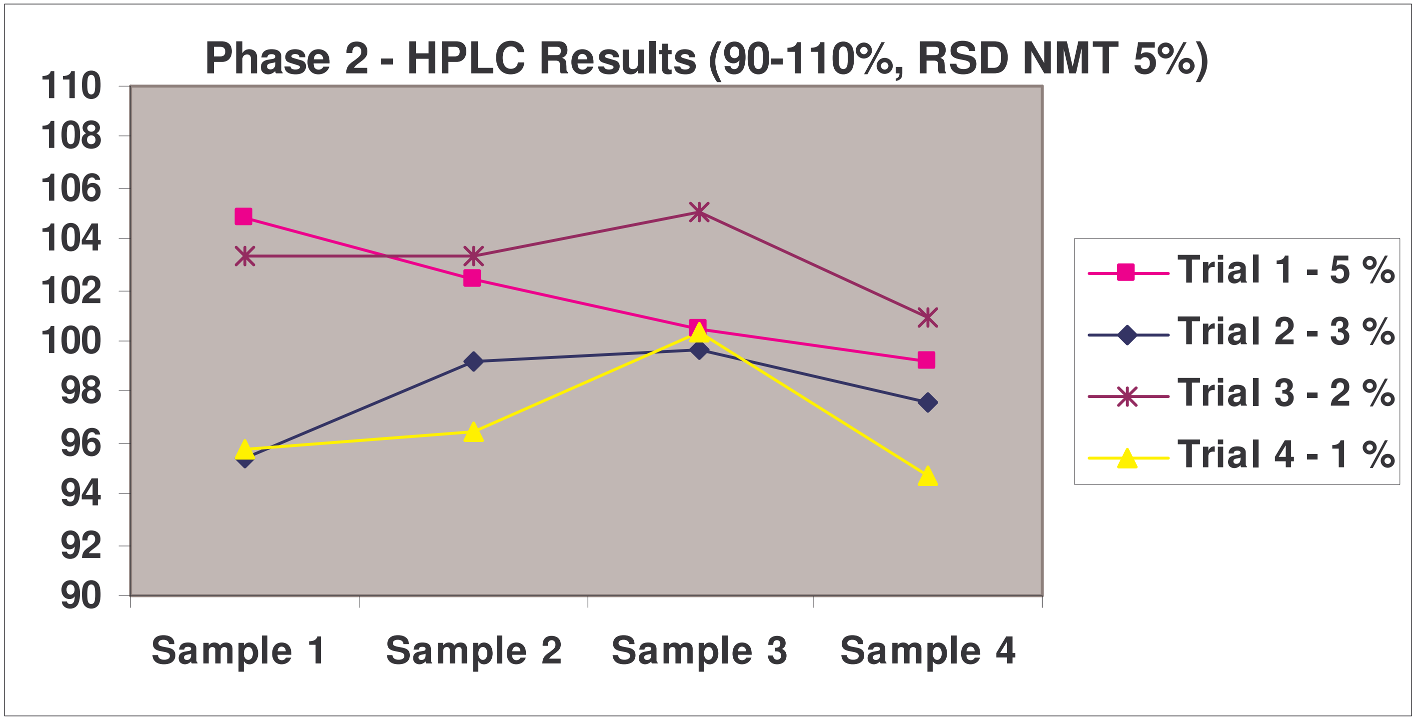
Phase 2 Results

HOW LOW CAN YOU GO???????

As low as 0.5 % marker compound in a ternary mixture



RSD
2.39
1.98
1.67
2.52

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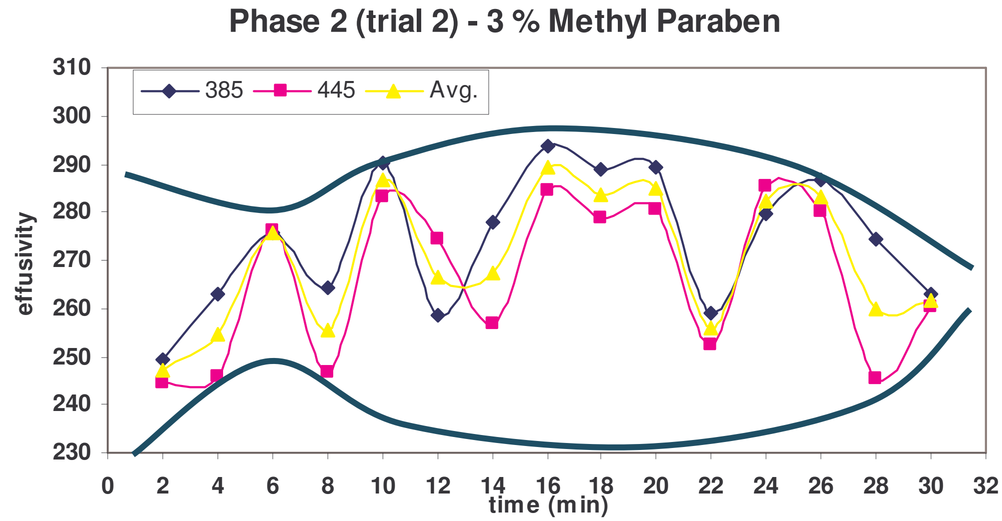
Phase 2 Results – “fish”



HPLC Data
Mean = 98.0%
Min = 95.4%
Max = 99.7%
RSD% = 1.98

	Time (min)														
Sensor	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**
385	249.28	263.07	275.56	264.44	290.07	258.45	277.74	293.93	288.87	289.36	259.19	279.5	286.6	274.6	262.95
445	244.63	245.95	276.15	246.5	283.24	274.24	256.6	284.62	278.71	280.52	252.61	285.2	280.01	245.39	260.2
Avg.	246.96	254.51	275.86	255.47	286.66	266.34	267.17	289.27	283.79	284.94	255.9	282.4	283.31	259.99	261.58
%RSD	**1.33**	**4.76**	**0.15**	**4.96**	**1.68**	**4.19**	**5.6**	**2.28**	**2.53**	**2.19**	**1.82**	**1.43**	**1.65**	**7.94**	**0.74**

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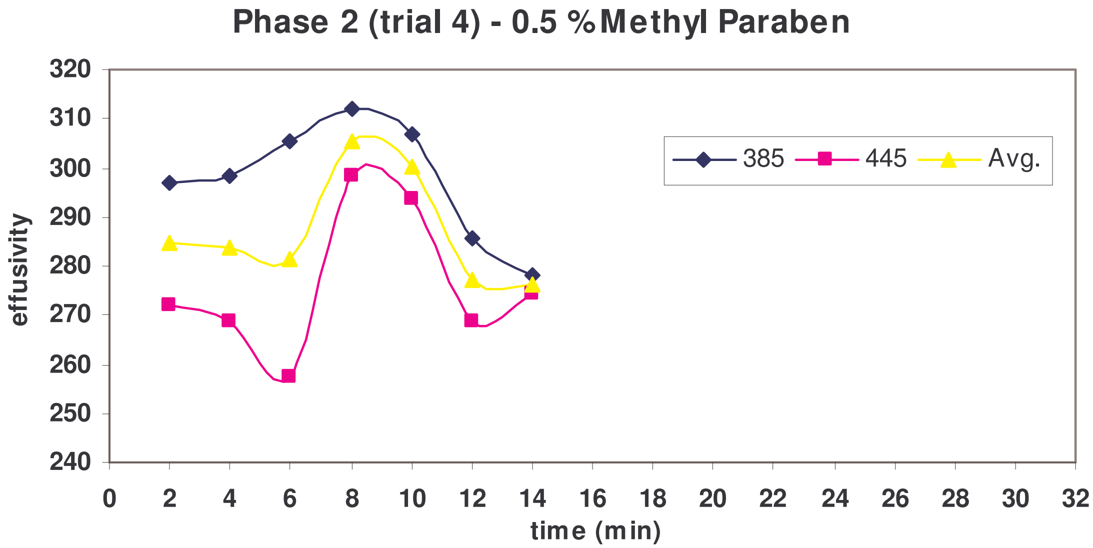
Phase 2 Results – Rapid



HPLC Data
Mean = 96.8%
Min = 94.7%
Max = 100.3%
RSD% = 2.52

Phase 3 Trial 4							
	Time (min)						
Sensor	**2**	**4**	**6**	**8**	**10**	**12**	**14**
385	297	298.26	305.59	312.2	306.82	285.49	278.32
445	272.08	268.86	257.34	298.32	293.85	268.79	274.51
Avg.	284.54	283.56	281.46	305.26	300.33	277.14	276.41
%RSD	**6.19**	**7.33**	**12.12**	**3.22**	**3.05**	**4.26**	**0.97**

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Conclusion – Static Study

In all cases, HPLC confirmed the indication of uniformity by effusivity, down to 0.5% active.

Blend times varied from 6 – 30 minutes, with a "fish" profile clearly indicated in the longer blend times.

The variation in blend time demonstrates the need for routine online measurement of endpoint based on material properties vs adherence to a time based endpoint.

"Fish" profile demonstrates the existence of blending/deblending phenomenon (different mechanism for blend homogeneity).

PATHEON

Dynamic (Wireless) Study - (Phase 1)

With dynamic, wireless, in-line systems we've added a new dimension

.....TIME!

Design of Experiments - CCD (Central Composite Design)

- Able to see main effects, interactions, quadratics and axial points
- Effusivity of each sensor is measured response (single component)
- Trial consists of 36 randomized runs (each run = 6 data points for all sensors) = 216 data points
- Data will be used to generate optimal sensor synchronization map

FACTOR A B18	FACTOR B B19	FACTOR C B23	FACTOR D B25	Y1 – Y6	Y-BAR	S
1.0 – 2.0 SEC	1.2 – 2.4 SEC	1.2 – 2.4 SEC	1.4 – 2.4 SEC	6 replicates	?	?

PATHEON

Dynamic (Wireless) Study - (Phase 2)

Wireless Blend Uniformity Trial

- Will perform confirmation run using ternary mixture to test sensor performance in detecting uniformity of blend
- BU Trial to be executed in the 16L bin
- Materials to consist of marker compound (Methyl Paraben) and 2 excipients
- “Synchronization Map” based on data from DOE

Material	Manufacturer	% w/w
Sodium Bicarbonate	Church and Dwight	44
Avicel PH 102	FMC Corporation	34
Methyl Paraben	Clariant industries	22

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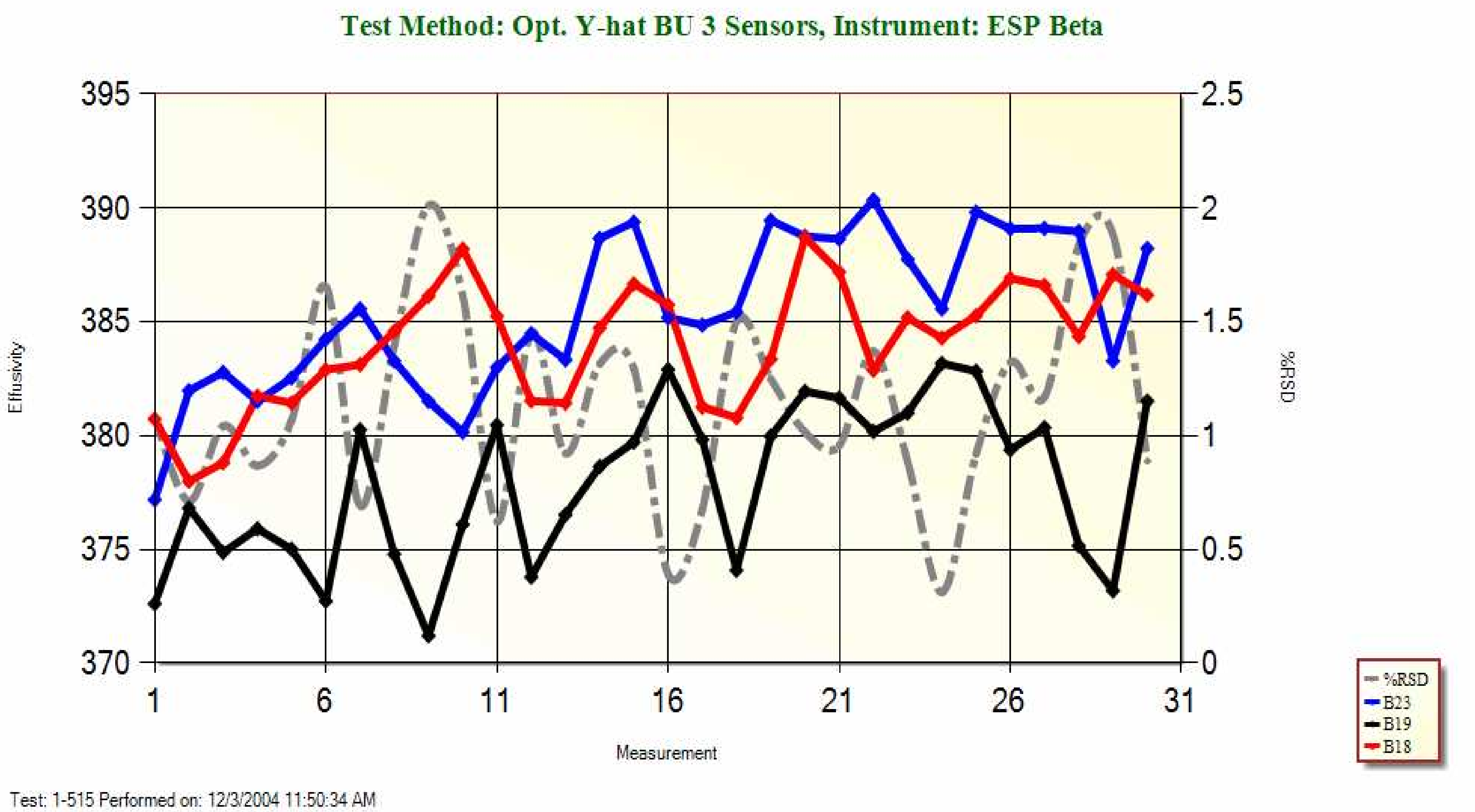
Screen Capture from Friday Dec 3rd



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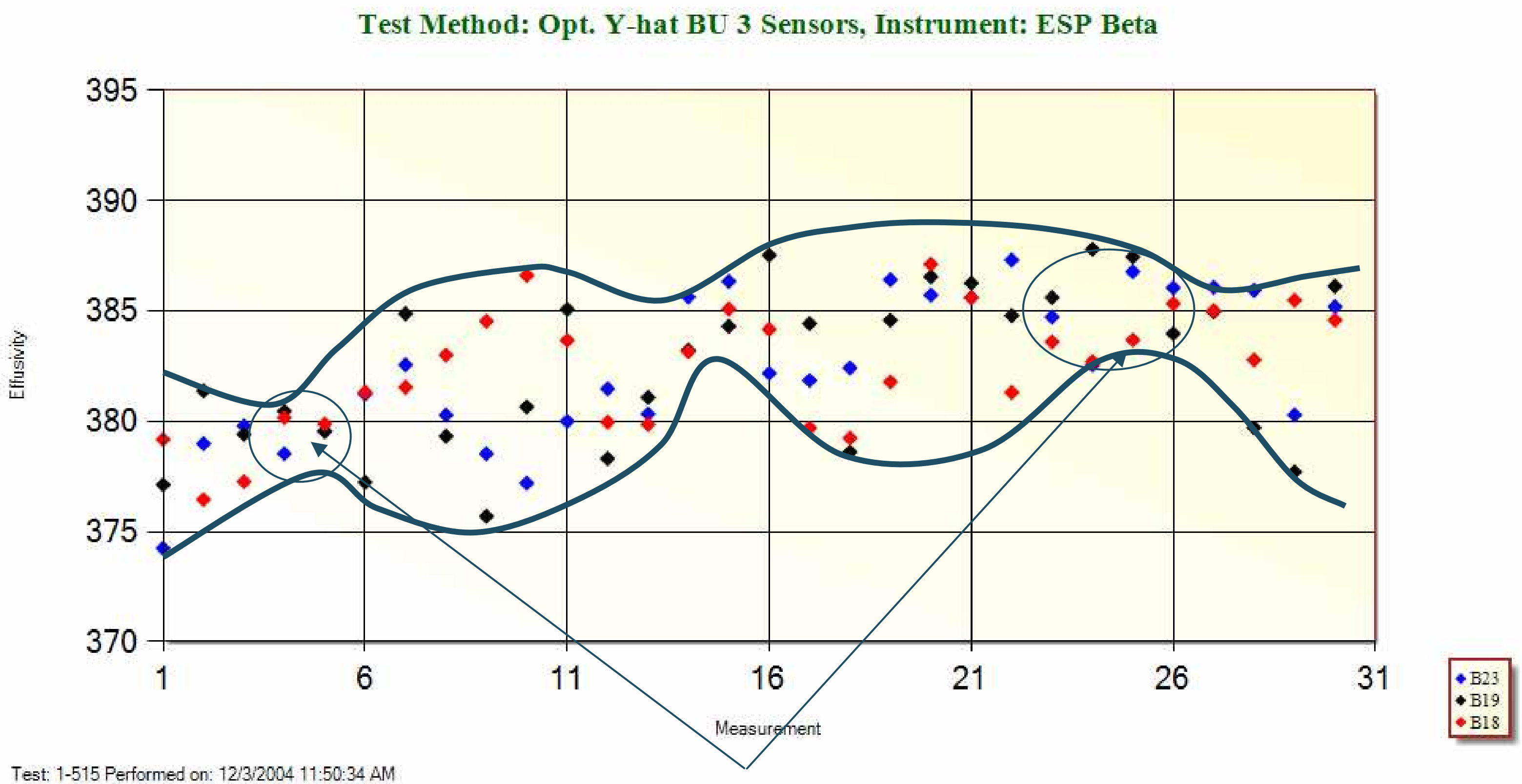
Interpretation????



Uniformity achieved with less than 1% change in average effusivity and RSD< 1.0%

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Magnesium Stearate Solution

- Magnesium Stearate does not do what it is suppose to do!

- Or does it??

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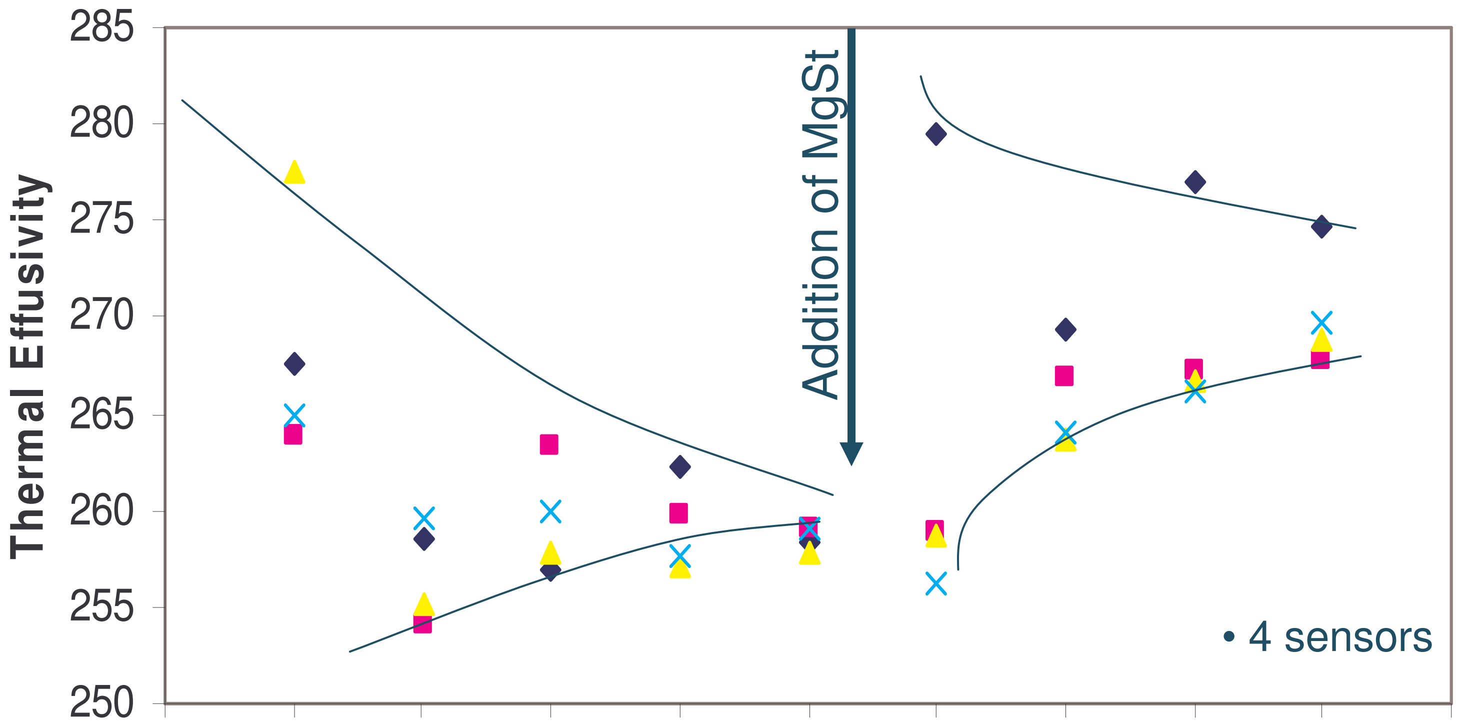
Magnesium Stearate effect



Average	268.52	256.85	259.53	259.15	258.57	263.33	266.03	269.29	270.26
%RSD	2.3%	1.0%	1.1%	0.9%	0.2%	4.1%	1.0%	1.9%	1.1%

Blend Time (minutes)

The blend is complete at 5 min at 0.2% RSD. MgSt addition causes an initial level of variation before uniformity again at 9 minutes (1.1% RSD).

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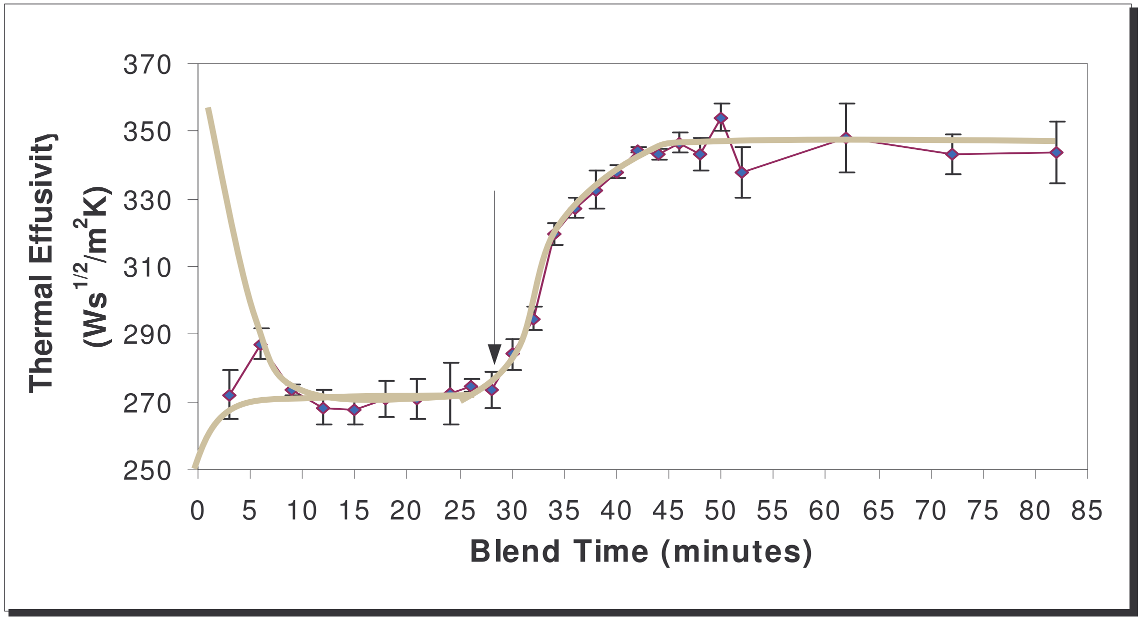
Lubricant Influence



Effusivity climbed post addition and then hit a plateau

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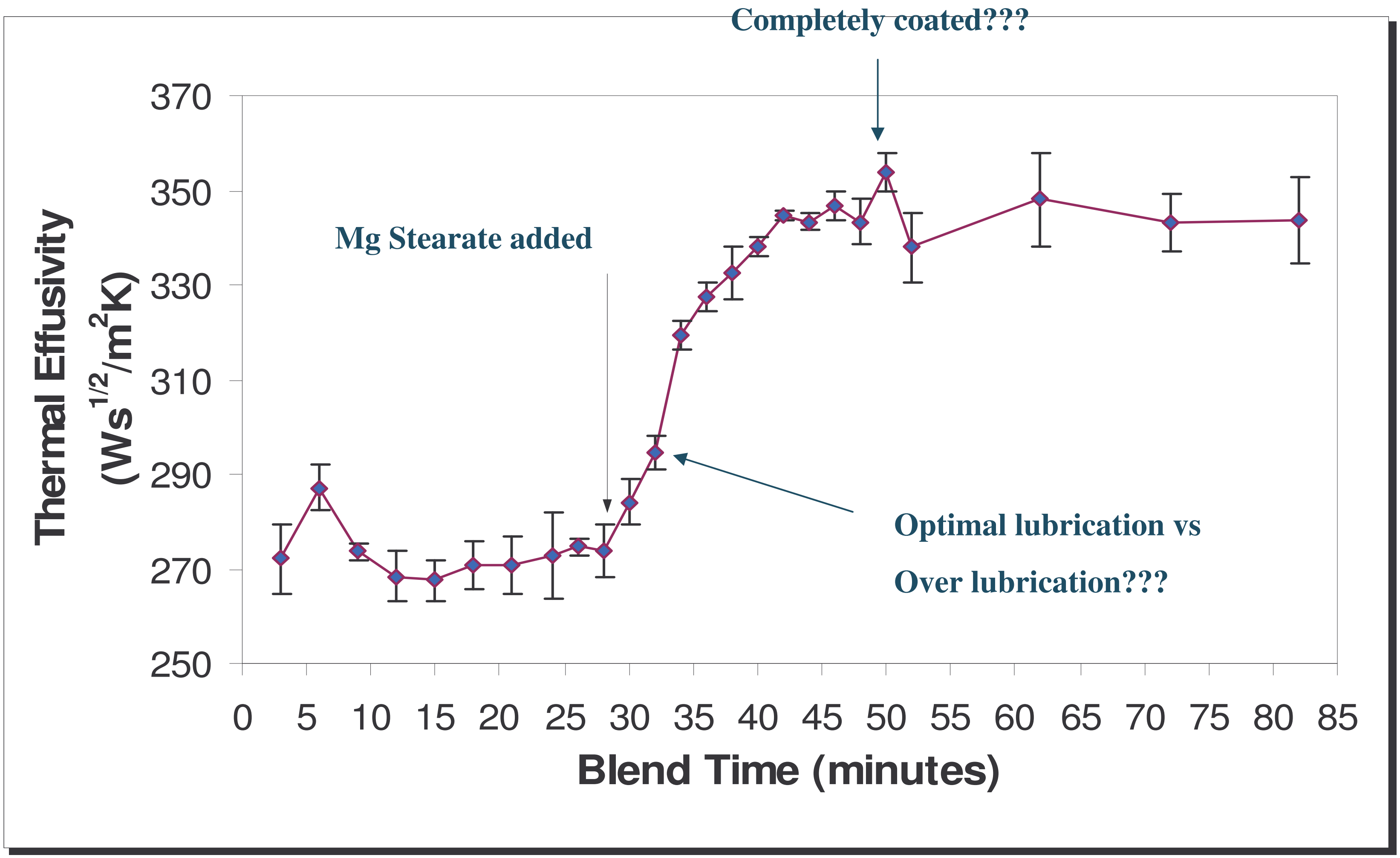
Magnesium Stearate Mapping??



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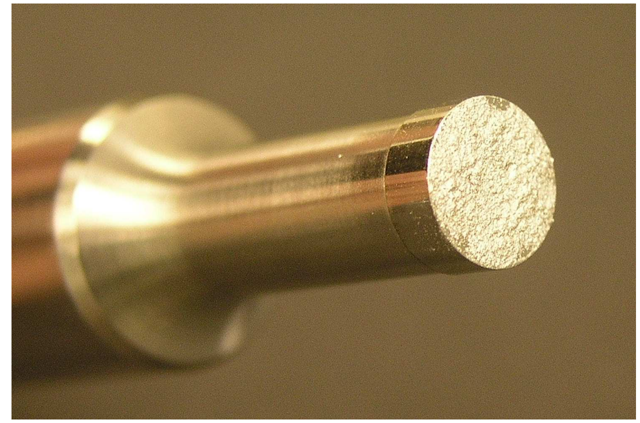
Mathis



?

EFFU......WHAT?

NATOLI

A BRIEF HISTORY

OF

TABLET MANUFACTURING

CIRCA 1840 TABLETING MACHINE

DWELL TIME AND HEAT BUILD UP WOULD NOT BE A PROBLEM WITH THIS 1920'S HAND OPERATED TABLET PRESS.

OPERATORS COULD JUST CRANK IT SLOWER.

IF ONLY IT WAS THAT EASY NOW!

THIS STOKES B1 DOES NOT HAVE A MOTOR MOUNT BECAUSE IT WAS ORIGINALLY DESIGNED TO RUN OFF A STEAM POWERED OVERHEAD DRIVE LINE.

WOW, A STEAM DRIVEN TABLET PRESS!

CHECK OUT THE HIGH TECH OVERLOAD SYSTEM!

THE STOKES BB2 WAS THE FIRST "MODERN HIGH SPEED" TABLET PRESS

INTRODUCED IN THE '30'S, MANY OF THESE PRESSES ARE STILL IN OPERATION.

THE 60’S INTRODUCE MANY NEW CONCEPTS WHICH AID IN BETTER TABLET QUALITY AND CONSISTANCY.

ROTARY FORCE FEEDERS

ADJUSTABLE UPPER PUNCH PENETRATION

HYDRAULIC OVERLOAD SYSTEMS

LOWER PUNCH RETAINERS AND SCRAPER SEALS

ROTARY TABLET PRESSES HAVE COME A LONG WAY.

NEW SYSTEMS HAVE TAKEN MUCH OF THE GUESS WORK OUT OF TABLETING.

DIRECT COMPRESSION

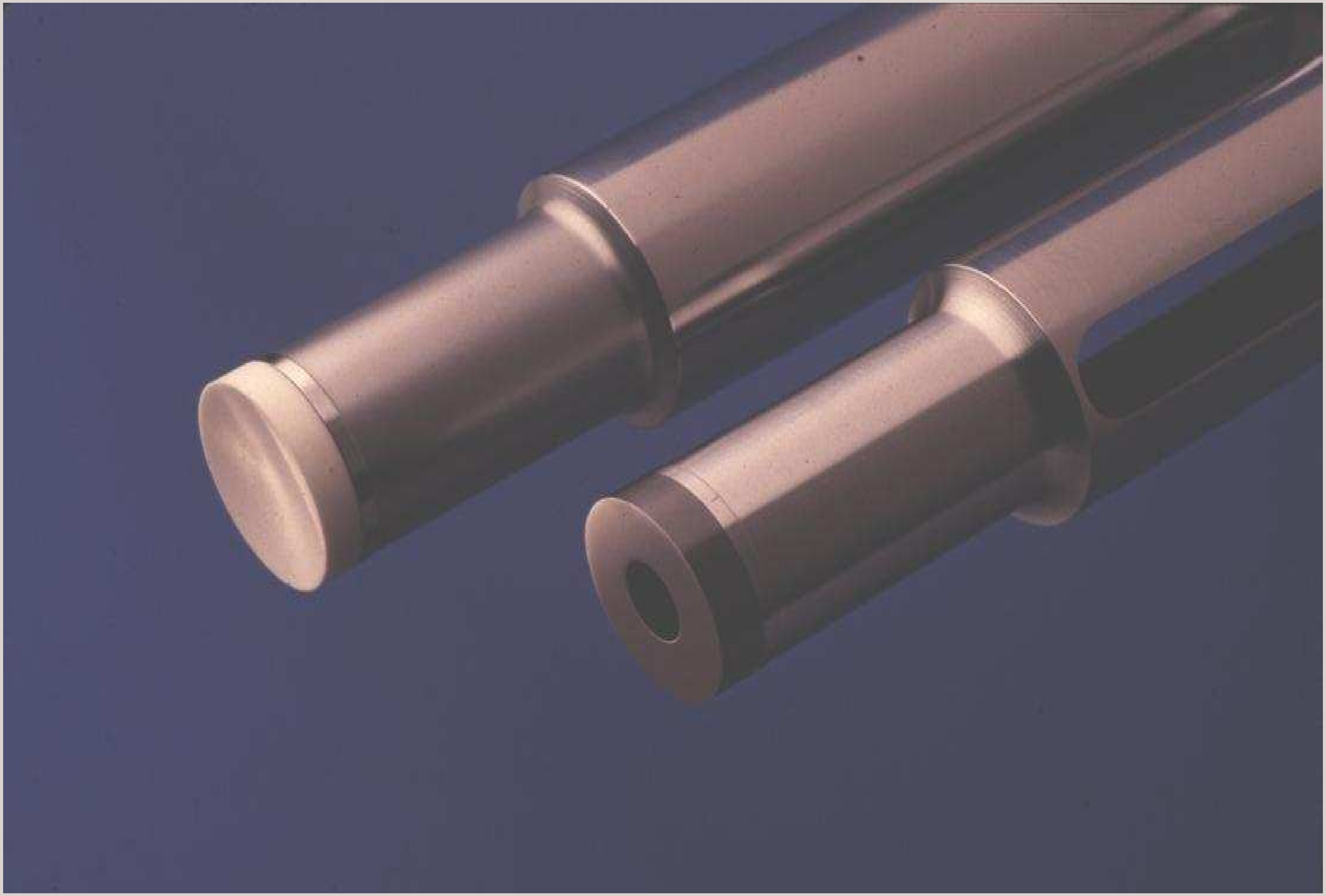
DIRECT COMPRESSION, INTRODUCED IN THE 80’S, WAS MEANT TO INCREASE EFFICIENCY.

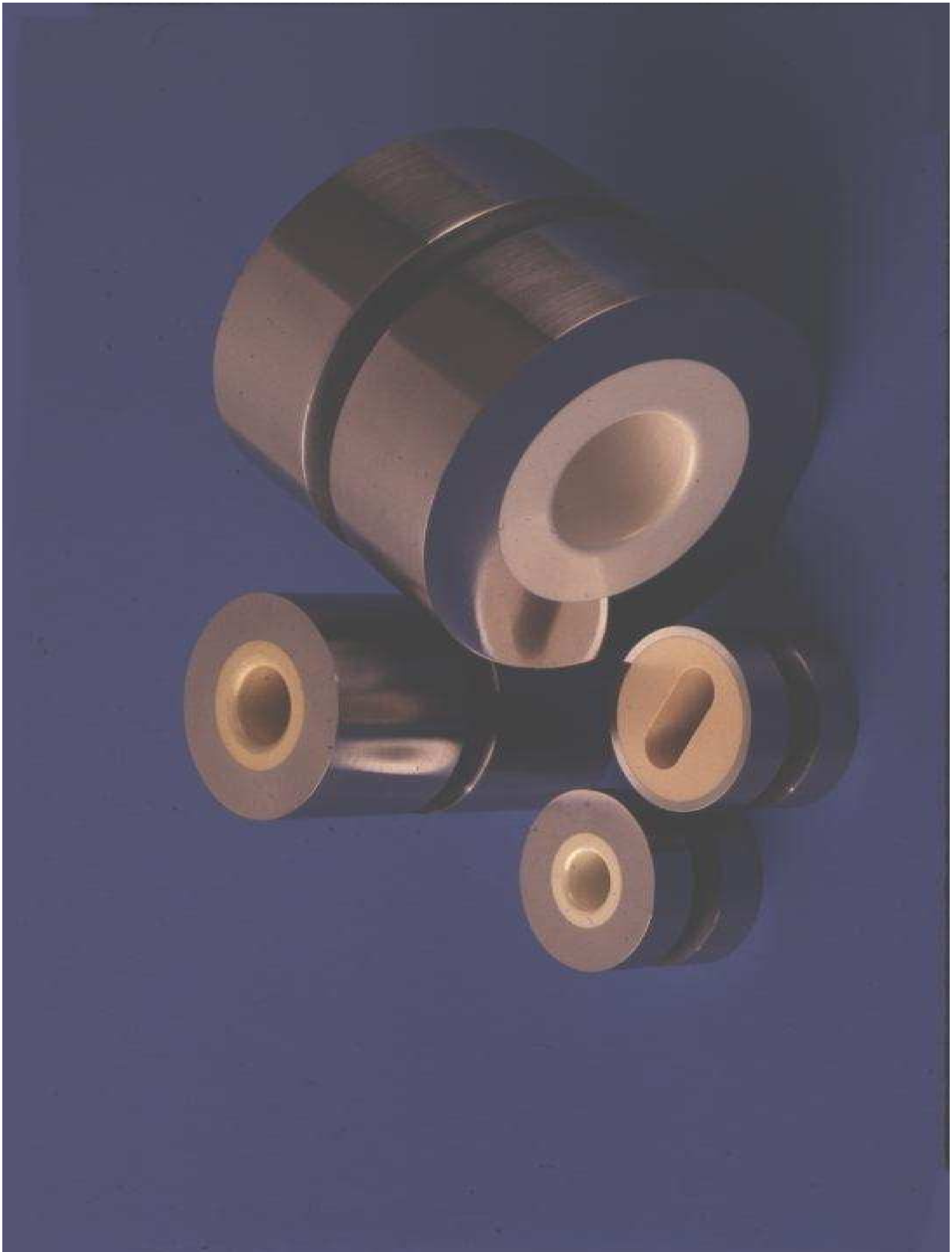
DO YOU BELIEVE IT HAS ?

STICKING AND PICKING

A NIGHTMARE TO THE TABLET COMPRESSION INDUSTRY

CERAMIC TIP PUNCHES LOOKED LIKE A SOLUTION … UNTIL THE SUBJECT OF METAL DETECTORS WAS BROUGHT UP. CERAMIC TOOLS ARE NOW USED FOR INDUSTRIAL TABLETS.





TABLET QUALITY

MANY FACTORS AFFECT TABLET QUALITY

- GRANULATION
- PRESS TYPE
- PRESS SPEED
- PRESS CONDITION
- TOOL CONFIGURATION
- TOOL CONDITION
- TOOL STEEL TYPE
- TOOL STEEL QUALITY
- FEEDER DESIGN
- FEEDER CONDITION
- FEEDER SPEED
- PADDLE CONFIGURATION
- PROPER FILL CAMS
- PUNCH PENETRATION
- PRODUCT RECIRCULATION
- HOPPER DESIGN
- PUNCH CONTROL
- SCRAPERS & TAKE- OFFS
- HUMIDITY
- TEMPERATURE
- OPERATOR SKILLS!
- AND MORE

HERE ARE TWO IDENTITCAL PUNCHES MADE BY THE SAME VENDOR. THESE TOOLS WERE USED BY THE SAME COMPANY, MAKING THE SAME PRODUCT, ON THE SAME TYPE PRESS, BUT AT DIFFERENT LOCATIONS.

ONE SET DID NOT ACHIEVE THE REQUIRED HARDNESS.

WHY?

ARE THEY REALLY IDENTICAL?

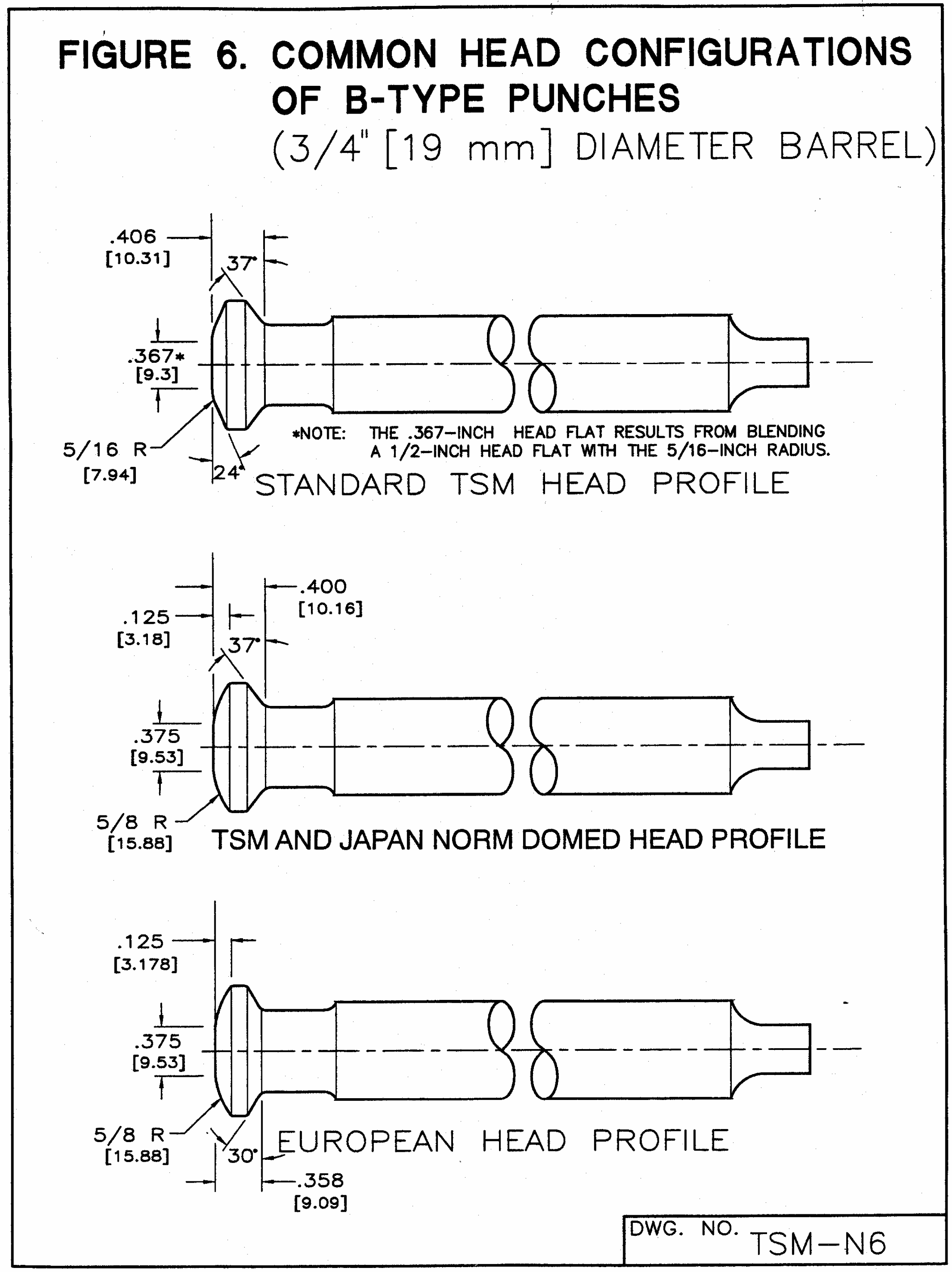
NO

NOTE THE TIP WEAR ON THE PUNCH TO THE LEFT.
THIS WILL ALLOW AIR TO ESCAPE FASTER BUT WILL CAUSE FLASHING.
LESS AIR ENTRAPMENT WILL PRODUCE A HARDER TABLET

AGAIN…..NO

THE PUNCH ON THE LEFT IS CONFIGURED WITH A DOMED HEAD.
THIS WILL CAUSE THE PUNCH TO ENTER THE DIE AT A SLOWER RATE
ALLOWING MORE AIR TO ESCAPE.

THE DOMED HEAD CONFIGURATION INCREASES DWELL TIME AND PUT LESS STRESS ON TOOLING AND PRESSES.
IT DISTRIBUTES HEAVY EJECTION LOADS OVER A LARGER SURFACE AREA.

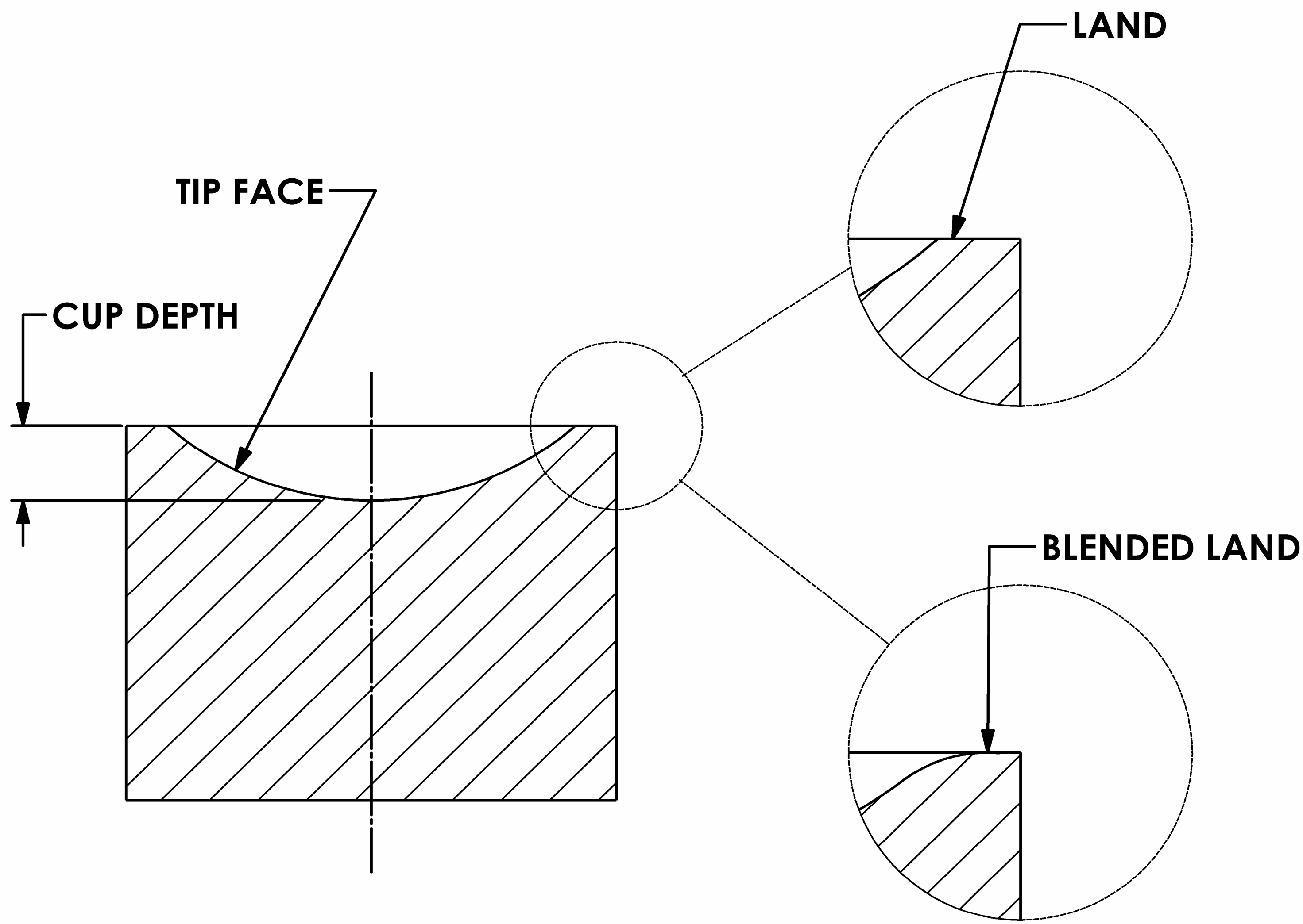


THE END RESULTS

THE COMPANY INVOLVED WITH THIS SITUATION WAS PLEASED TO FIND THEY COULD ACHIEVE THE SAME HARDNESS BY TAPERING THEIR DIES AND HAVING THE PUNCHES REWORKED TO THE DOMED HEAD CONFIGURATION

LAND EROSION

NO, WE AIN’T TALKIN’
‘BOUT THE BACK 40!


LAND
TIP FACE
CUP DEPTH
BLENDED LAND

TYPICAL LAND ERODED PUNCH CUP

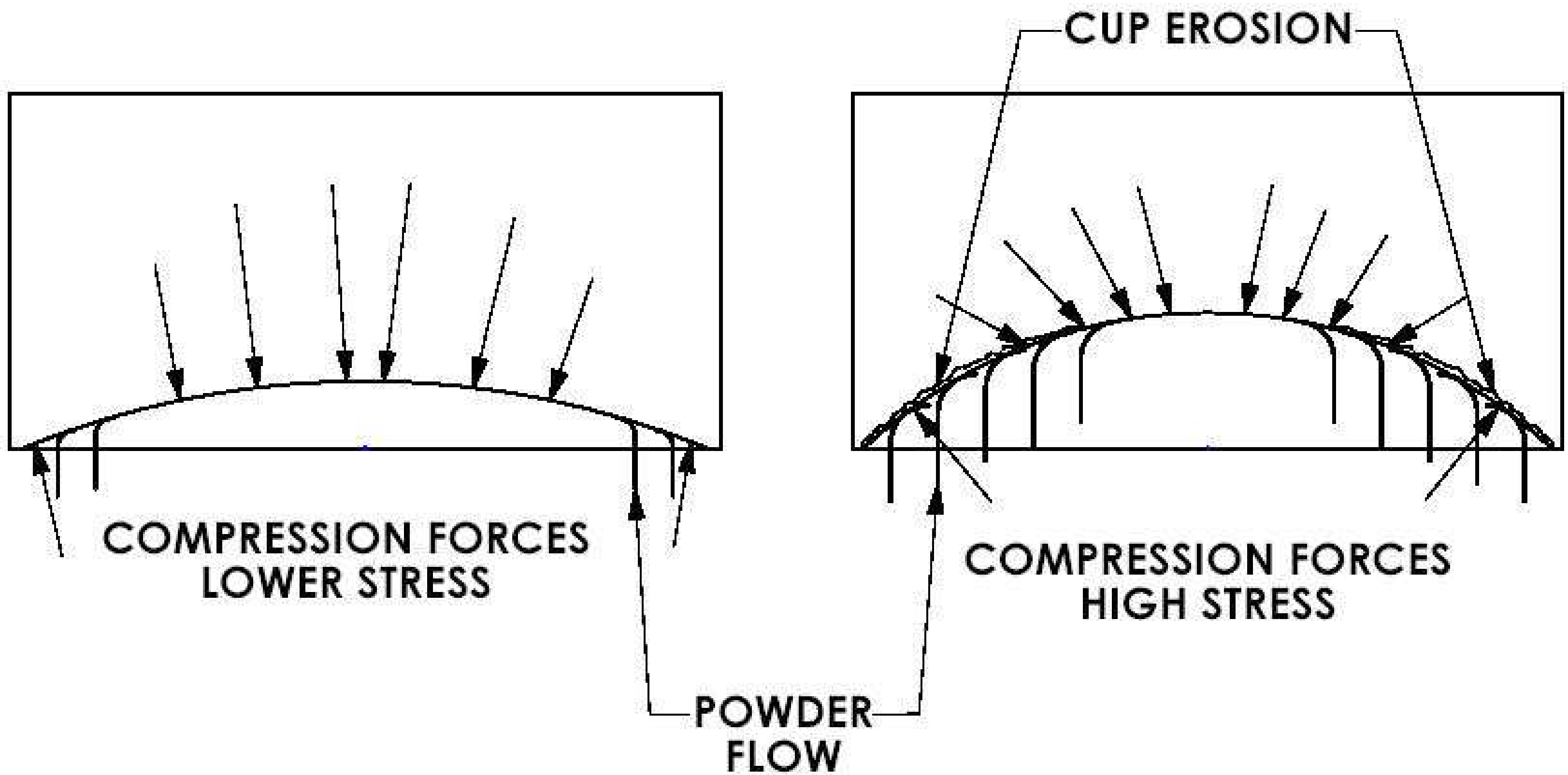
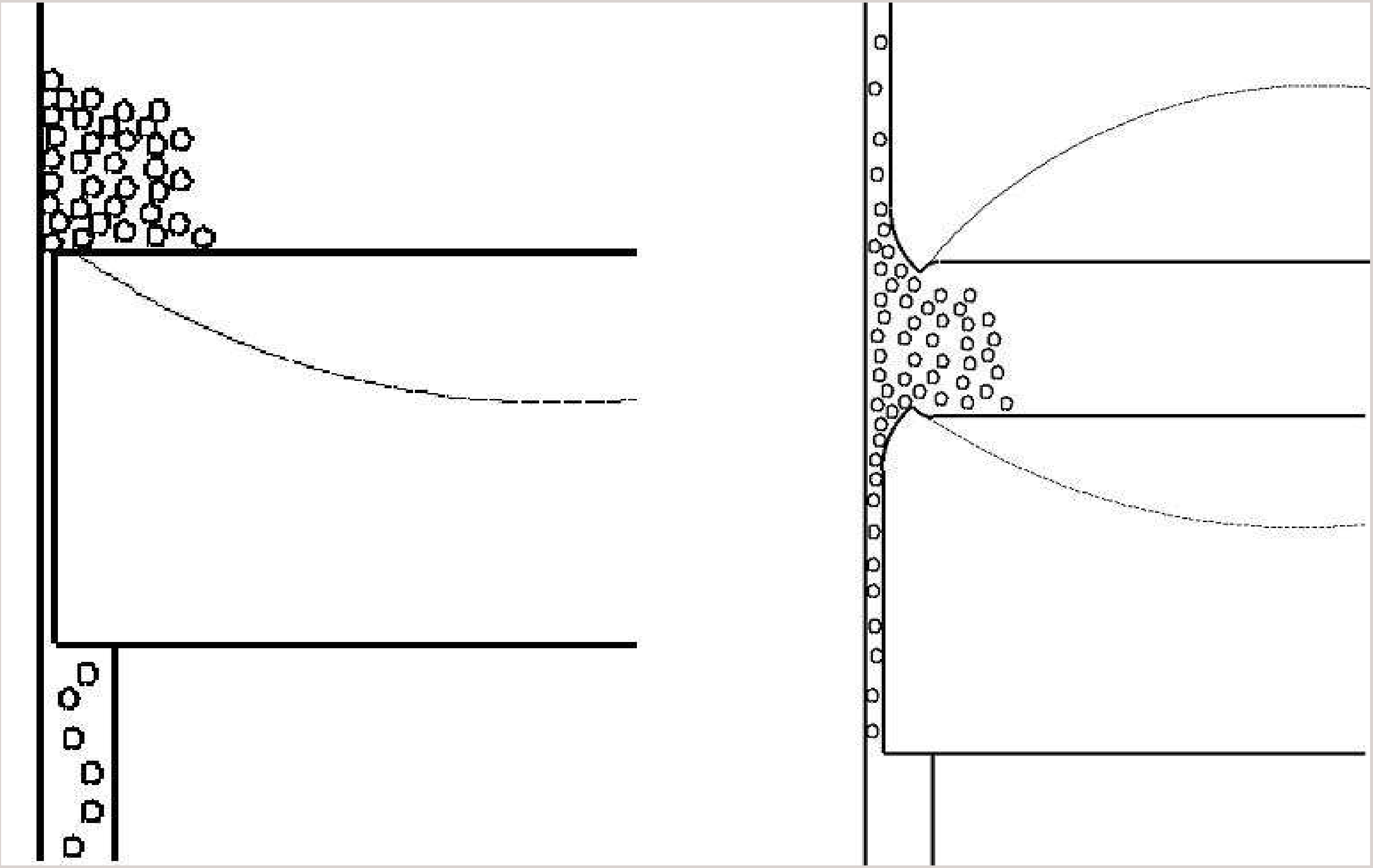

CUP EROSION
COMPRESSION FORCES
LOWER STRESS
COMPRESSION FORCES
HIGH STRESS
POWDER
FLOW

FIGURE 3.

A TRUE “RULE OF THUMB”

YOUR THUMB NAIL IS ONE OF THE BEST METHODS TO CONFIRM LAND EROSION OR “J HOOKING”

SHARP EDGES ON PUNCHES ARE CRITICAL TO MAINTAIN TABLET QUALITY AND MAXIMUM RUN TIME



ANOTHER " RULE OF THUMB"

IF YOU DRAG THE RELIEF OF THE LOWER PUNCH ACROSS YOUR THUMB NAIL AND IT DOES NOT SHAVE IT, THE RELIEF IS TOO DULL TO CLEAN THE DIE BORE.

BUFFING WILL HELP WITH STICKING AND PICKING PROBLEMS.
IS THIS THE ONLY SOLUTION FOR ERODED TOOLS ?
YES …. BUT WHAT IF THEY ARE NOT ERODED ?

REMEDIES FOR STICKING AND PICKING

- TABLET DESIGN
- PUNCH STEEL TYPES
- PUNCH STEEL QUALITY
- PUNCH STEEL COATINGS
- POLISHING COMPOUNDS
- MACHINE ADJUSTMENTS
- GOOD GRANULATION

NEW SOLUTIONS TO OLD PROBLEMS

COMPOSITE PUNCH TIPS HAVE BEEN VERY SUCCESSFUL IN CERTAIN APPLICATIONS.
NEW FORMULAS SHOULD ENHANCE PERFORMANCE

THE ROTA-TAB IS A PROTOTYPE TABLET PRESS.

THE TOOLING IS CONTAINED IN A CONSTANT FLOW OIL BATH. THE INITIAL INTENT WAS TO CONTAIN THE TOOLS FROM PRODUCT CONTAMINATION.

THEN THE LIGHTS WENT ON! WHAT IF AN OIL CHILLER WERE ADDED TO KEEP THE PUNCHES COOL?…COOL!…LESS HEAT… LESS STICKING AND PICKING!

EVALUATION IS PENDING.

MATHIS INSTRUMENTS FINDS AN ANSWER TO REAL TIME PRODUCT BLENDING DATA

MANUFACTURING

IMPROVE YOUR PRODUCTIVITY BY ELIMINATING DEFECTIVE BATCHES

Real Time Information for Process Improvement

Mathis ESP™ (Effusivity Sensor Package) can integrate with your existing or new equipment and offers an additional 'window into your processes.' ESP also provides trending data that can help you refine your production in response to changes in batch size, use of different equipment, and variations in environmental and ingredient characteristics.

Optimized Lubrication & Improved Tableting

Mathis ESP can 'see' magnesium stearate in your blender and provide an invaluable measure of its effectiveness in your formulation. It provides real time information so you can prevent over-lubing, and anticipate and prevent problems at your tablet press – reducing the amount of discarded tablets.

Replace LOD for Fluid Bed Drying

Mathis effusivity sensors are extremely sensitive to variations in moisture content. Our ESP can be integrated with your fluid bed dryers to provide on-line measurements to help you determine drying end points – and reduce or eliminate the number of time-consuming LOD tests.

Obtain Comprehensive Blend Profiles

ESP shows you what is going on inside your blender and pinpoints when optimal physical uniformity has been reached – without stopping your blending, thieving samples, and compromising containment. Profile when de-blending, attrition and particle shearing start to impact homogeneity. Mathis ESP supplements your batch records with effusivity profiles, and invaluable reference points for accurately running smaller or larger batches.

EFFUSIVITY SENSOR PACKAGE

Mathis

A Revolutionary Window Into Your Processes.

Mathis ESP is a powerful, new tool for manufacturers that can supplement your release protocols or replace them. It provides critical information at key production stages to improve your productivity and enhance efficiency by eliminating defective batches.

The ROI of Real Time Knowledge

By providing you with instantaneous information, Mathis ESP gives you batch-specific knowledge that can help you identify subtle variations in your formulations and magnesium stearate lubrication levels, so you can adjust your tablet press accordingly. It offers rapid return on investment through savings from faster validation, streamlined processes, and fewer lost production batches. The system price can be fully recovered by preventing one lost batch – based only on ingredient costs and the time-consuming requirements of tracing, investigating and documenting the cause.

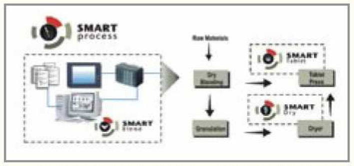
Robust and Ready for Your Production Environment

Mathis ESP is built for the realities of manufacturing facilities:

- Sensors on your blending and drying equipment provide uninterrupted data
- Open architecture platform can integrate with all brands of controllers, PLCs and plant SCADA systems
- System software allows 21CFRpart 11 compliance
- Operator-friendly HMI screens provide clear, concise status information
- Data tracking and reporting provide supervisory and QA personnel with batch specific information and trending analysis over time
- OEM version available on new equipment
- Durable sensors can tolerate hot water washdown
- Excellent reliability - MTBF 3500 hours for sensors
- Retrofitting, installation, integration, validation and training are provided as a simple, one-stop bundled solution.

Operator-Friendly Interface with Multiple Access Levels

Mathis ESP provides need-to-know information quickly and clearly through its operator-friendly Human/Machine Interface (HMI). System status and alarm conditions can be determined at a glance. For supervisory and QA personnel, additional, password-protected access levels provide batch-specific historical effusivity data. This can be used for trending analysis as well as correlation to your other processes to improve efficiency and isolate production problems.



Industrial configuration for effusivity in a solid dose manufacturing site © 2005 Brock Solutions Inc.

Optimize Lubrication & Reduce Losses at Your Tablet Press

When tablets fail dissolution testing, the problem can frequently be traced back to over-lubing with magnesium stearate in the blender. Mathis ESP quantifies the lubrication levels of your blends in process, before they reach your tablet press – allowing you to reduce the time to establish your press settings, and ensure hardness and dissolution specifications are maintained. Mathis ESP also gives you the blend uniformity information to demonstrate functional equivalency for SUPAC when you are running variations to standard batch sizes – or have to use different blending equipment for a formulation.

Courtesy of Tote

Courtesy of Natoli

Reduce or Eliminate LOD Testing Requirements

An on-line effusivity sensor on your fluid bed dryer provides quantification of moisture content on a minute-by-minute basis – while it's operating – and without compromising containment. No more stopping the dryer repeatedly to do time-consuming Loss On Drying (LOD) tests. With sensitivity down to 0.25% moisture content, Mathis ESP determines the precise endpoint for drying, allowing you to run your equipment until the specific moisture content is reached. SOP requirements can be maintained by performing one LOD test at the conclusion of drying as confirmation of specification compliance.

Invensys integrates Mathis effusivity sensor at Confab Laboratories on an O'Hara FBD. © Invensys Systems Inc.

Demo.

Contact us to schedule a live demonstration or to find out how Mathis ESP can improve your manufacturing quality and efficiency.

1-866-425-3637 www.MathisInstruments.com

Mathis

WHAT CAN A SYSTEM LIKE THIS DO ?

- PAT
- GIVES AN OPERATOR A NEW TOOL
- REDUCES SCRAP
- INCREASES PRODUCTION
- PRODUCES CONSISTANT TABLETS
- INCREASES TOOL LIFE

SCALE UP

FROM R&D TO PRODUCTION

WILL IT BE

RESEARCH AND DEVELOPMENT

OR

REWORK AND DESTROY?

CAN YOU REALLY MAKE TABLETS FROM PARAKEET GRAVEL ?

STORY TIME

TABLET PRESS SET UP

BASIC PRESS SET UP

SPECIFIC TOOLS - TABLET PRESSES CANNOT BE SET UP PROPERLY WITHOUT THE CORRECT TOOLS. SOME INEXPENSIVE TOOLS WILL EXTEND THE LIFE OF AN EXPENSIVE PRESS.

CAM ALIGNMENT- A MUST TO INCREASE PRESS AND TOOL LIFE. MISALIGNED CAMS CAUSE PREMATURE WEAR AND HEAT BUILD UP .

TOOL INSTALLATION- SIMPLE PROCEEDURES TO INSURE PROPER SET UP.

CLEANLINESS- ONE OF THE MAJOR CAUSES OF PRESS AND TOOL FAILURE IS EXCESS GRANULATION. CONTAMINATION OF LUBRICANTS AND THE PRESS WILL DECREASE RUN TIME AND CAUSE DAMAGE TO IT AND THE TOOLING.


NATOLI ENGINEERING CO. INC
TABLET PRESS TOOLING
AND REPLACEMENT PARTS
ST CHARLES, MISSOURI (314) 926 8900
NATOLI
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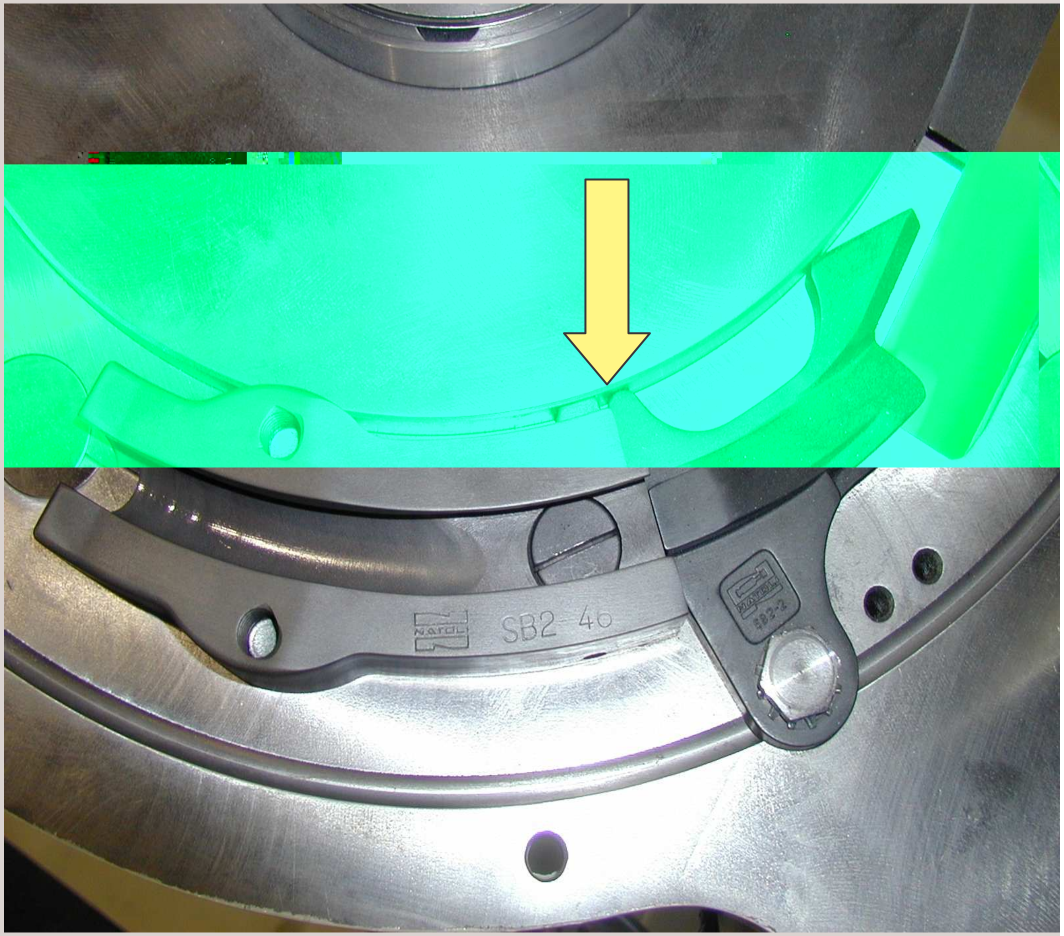
NATOLI
D126

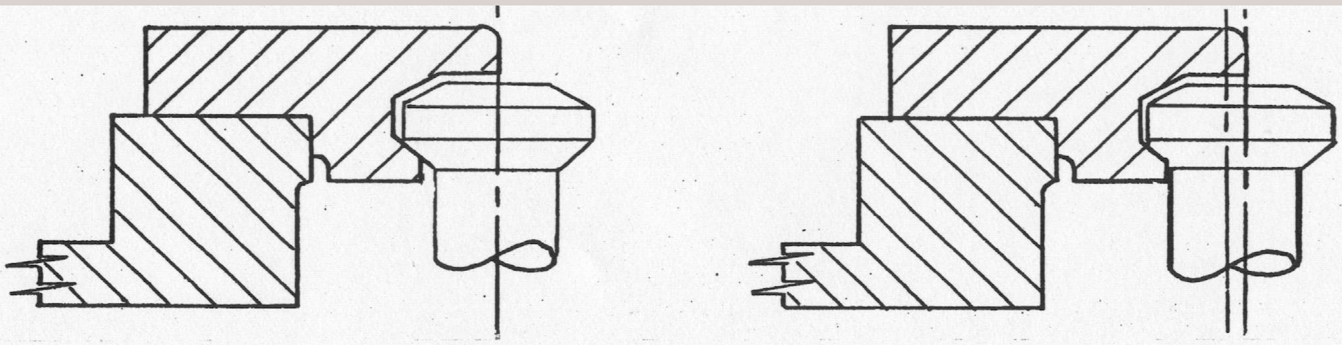
THIS IS WHY A PRESET TORQUE WRENCH IS RECOMMENDED

CAM ALIGNMENT

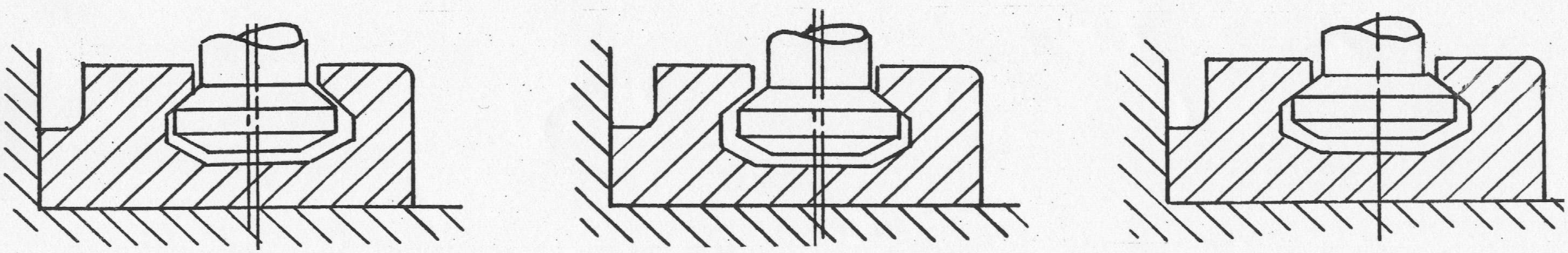
- CAM ALIGNMENT ON MOST TABLET PRESSES IS DETERMINED BY A RADIAL CONTACT SURFACE. IT MUST BE CLEAN AND FREE OF DAMAGE OR PROPER ALIGNMENT WILL NOT BE ACHIEVED



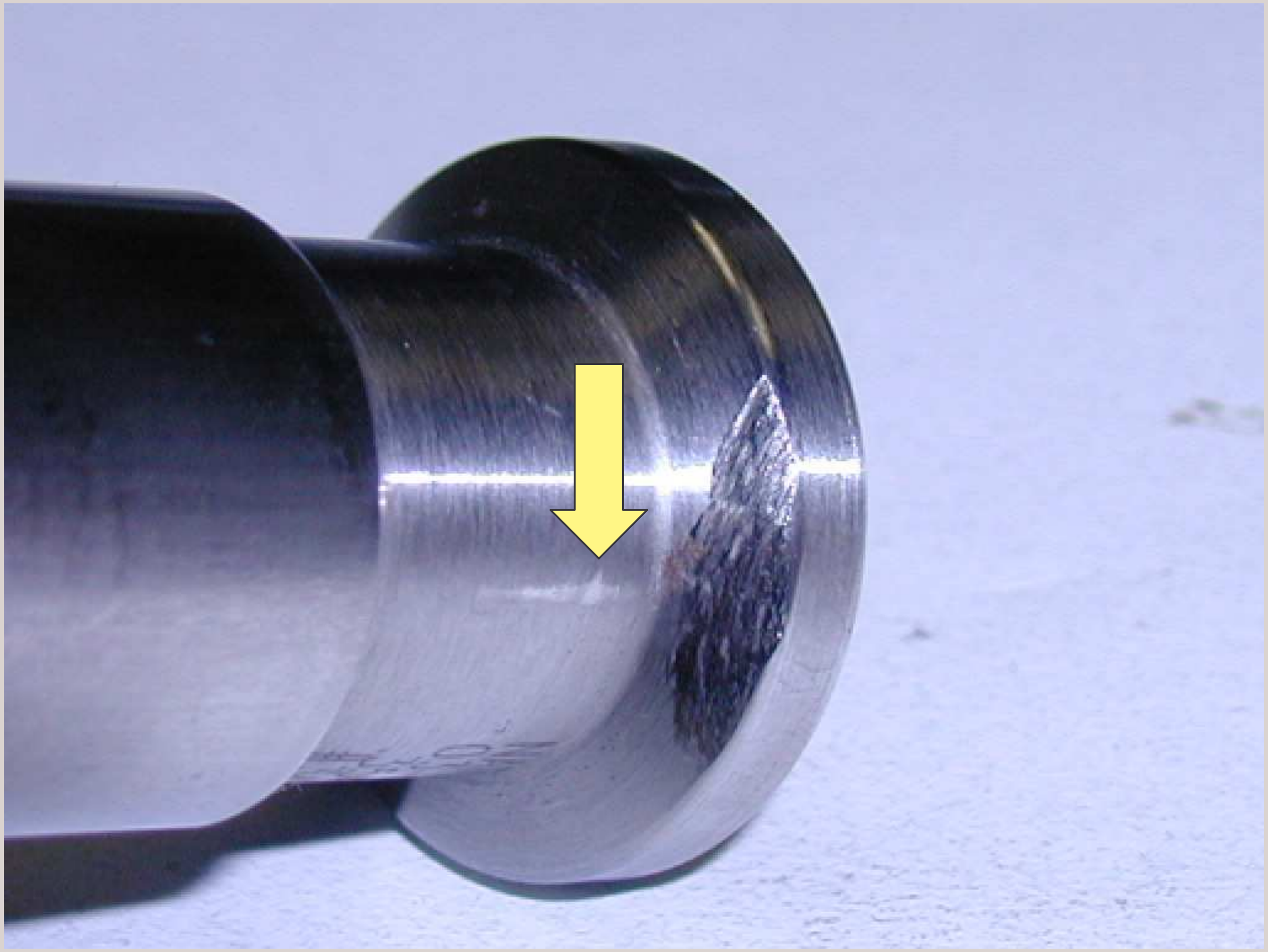
CORRECT

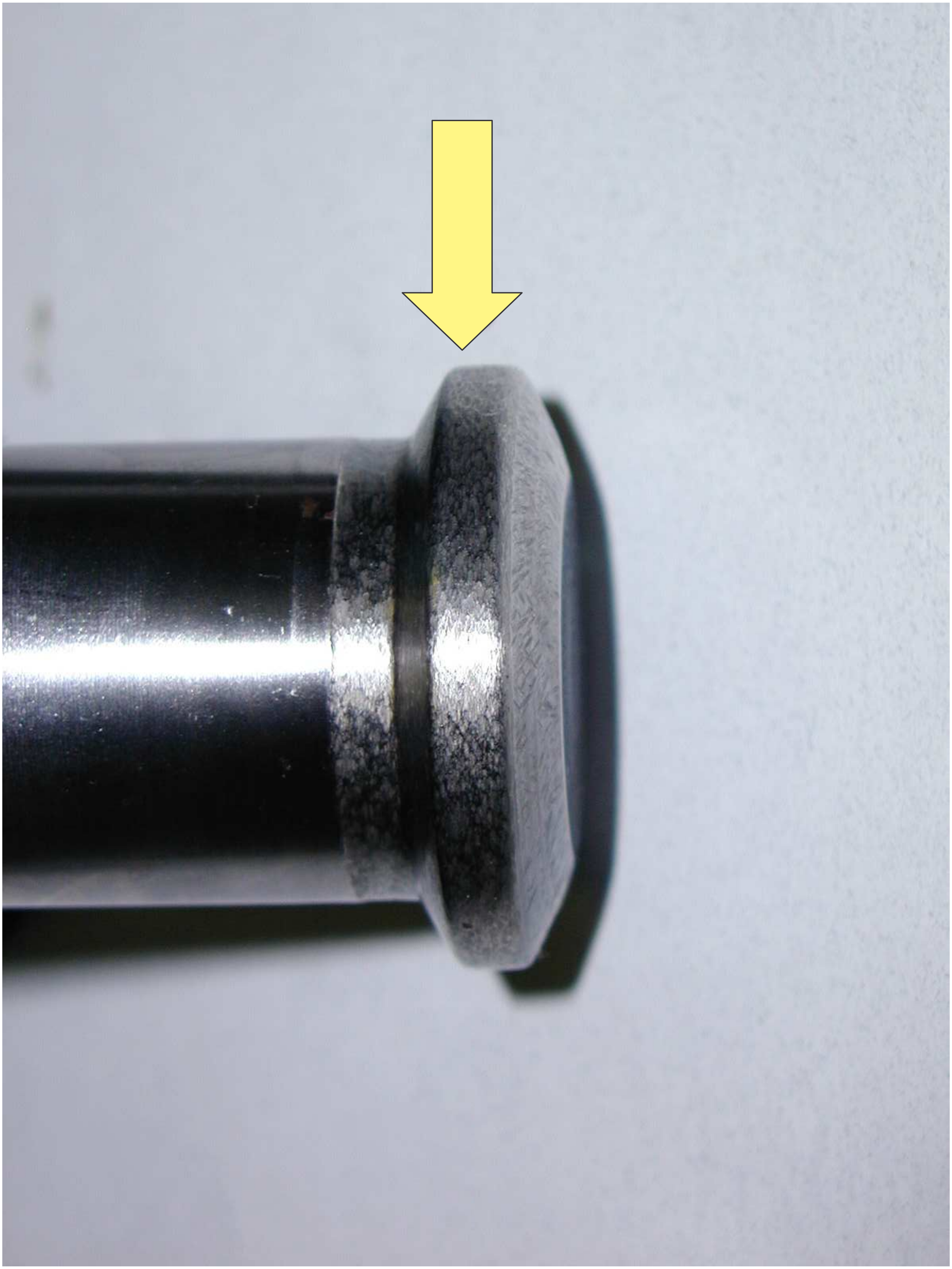


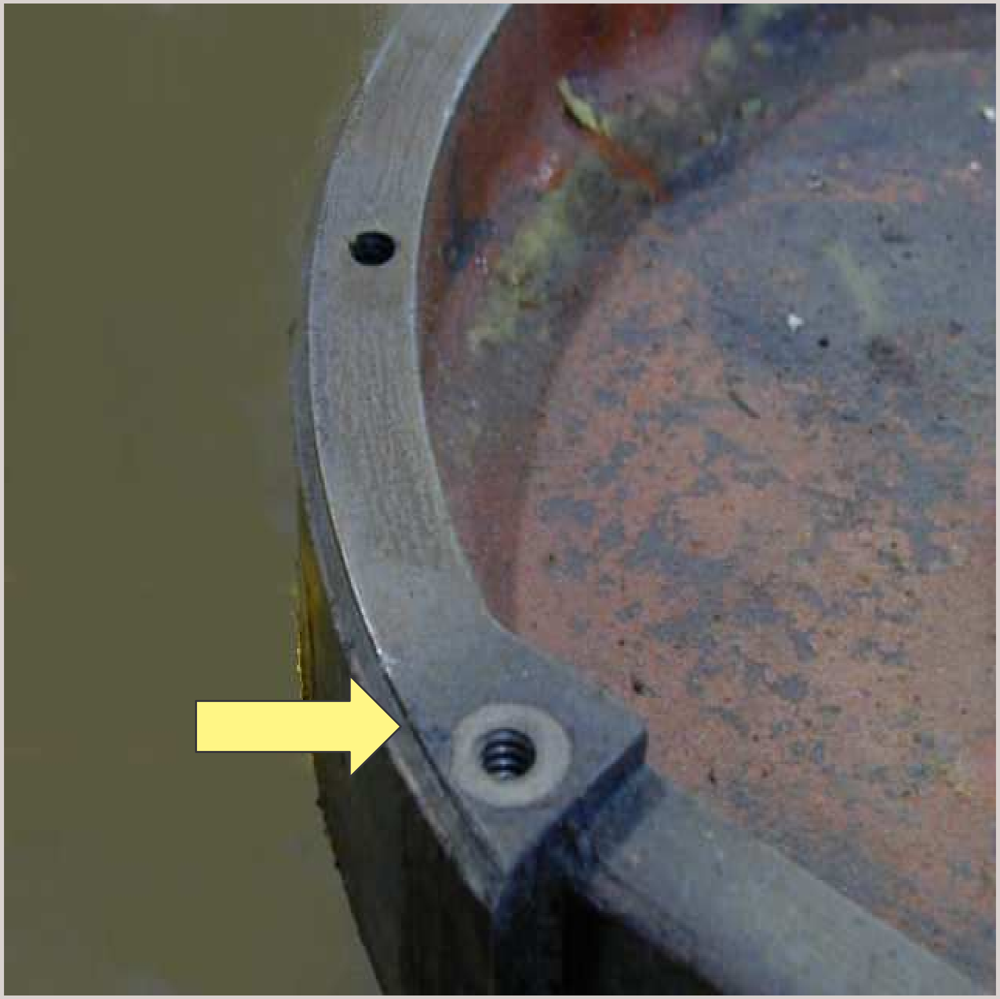
CORRECT



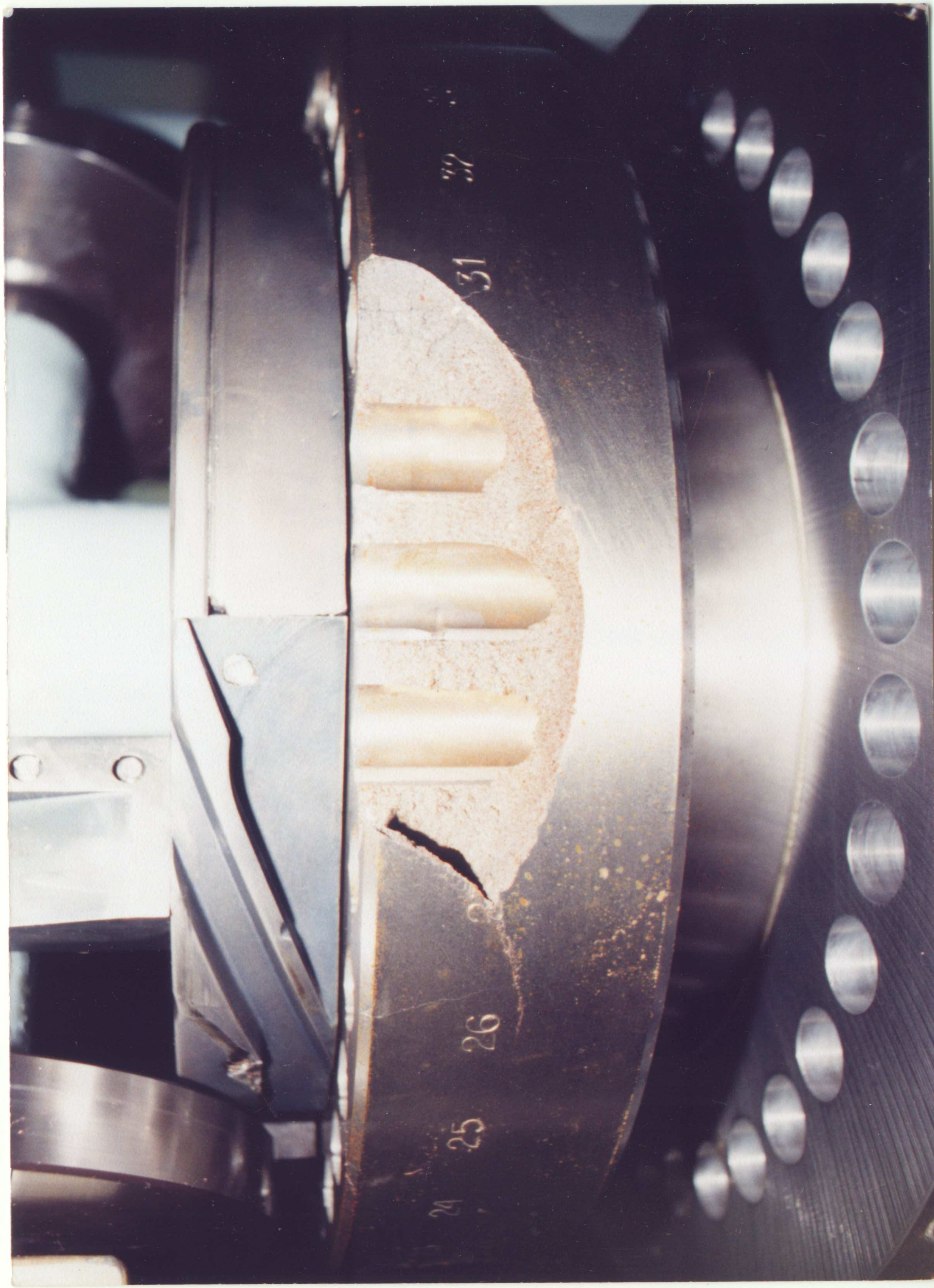
- PUNCH DAMAGE DUE TO IMPROPER CAM ALIGNMENT.







METAL PARTICLES FROM CAM BODY WILL FALL BETWEEN THE PUNCH BARREL AND GUIDE. THE RESULTS MAY VARY FROM MINOR BINDING TO SEVERE MICROWELDING TO A TOTAL SIEZURE AND PRESS FAILURE.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31
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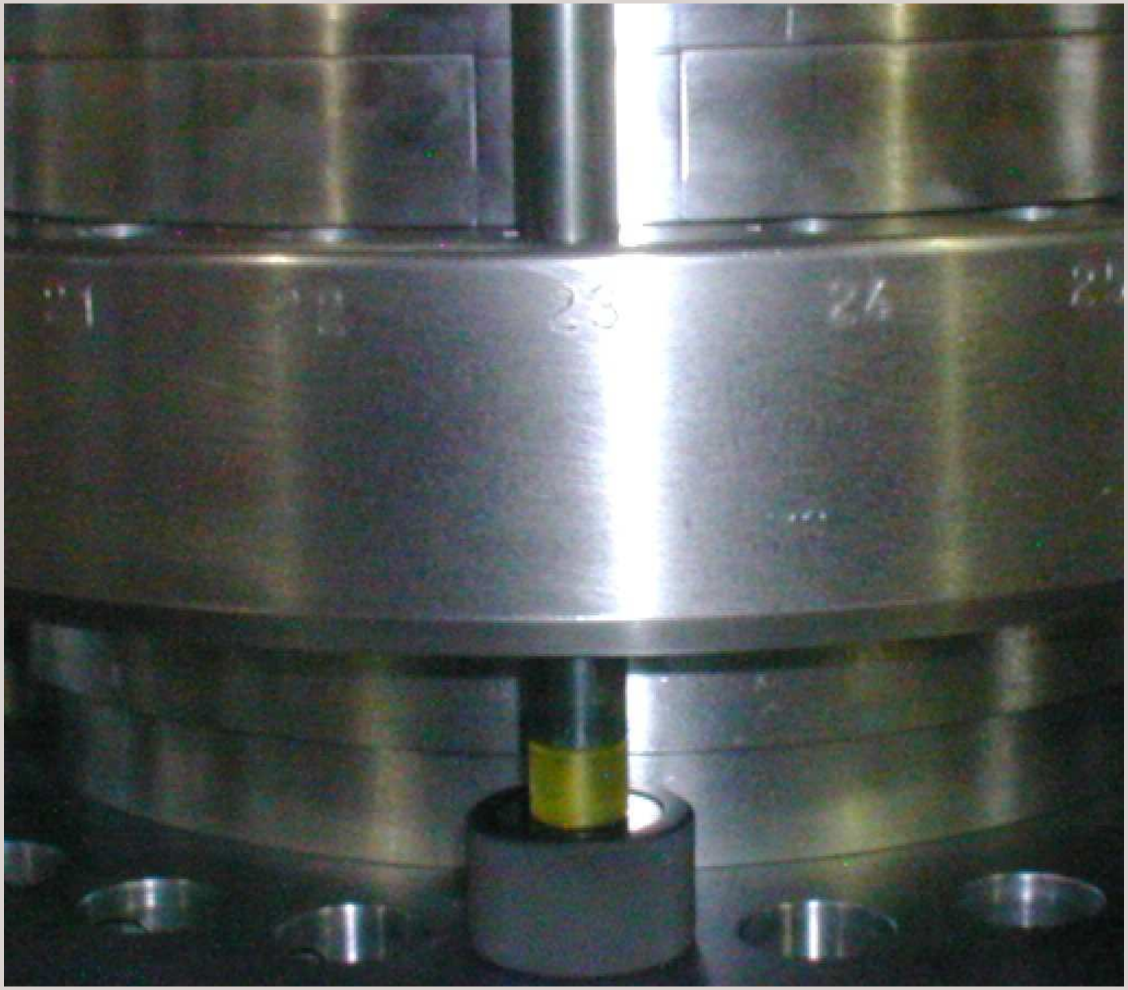
24

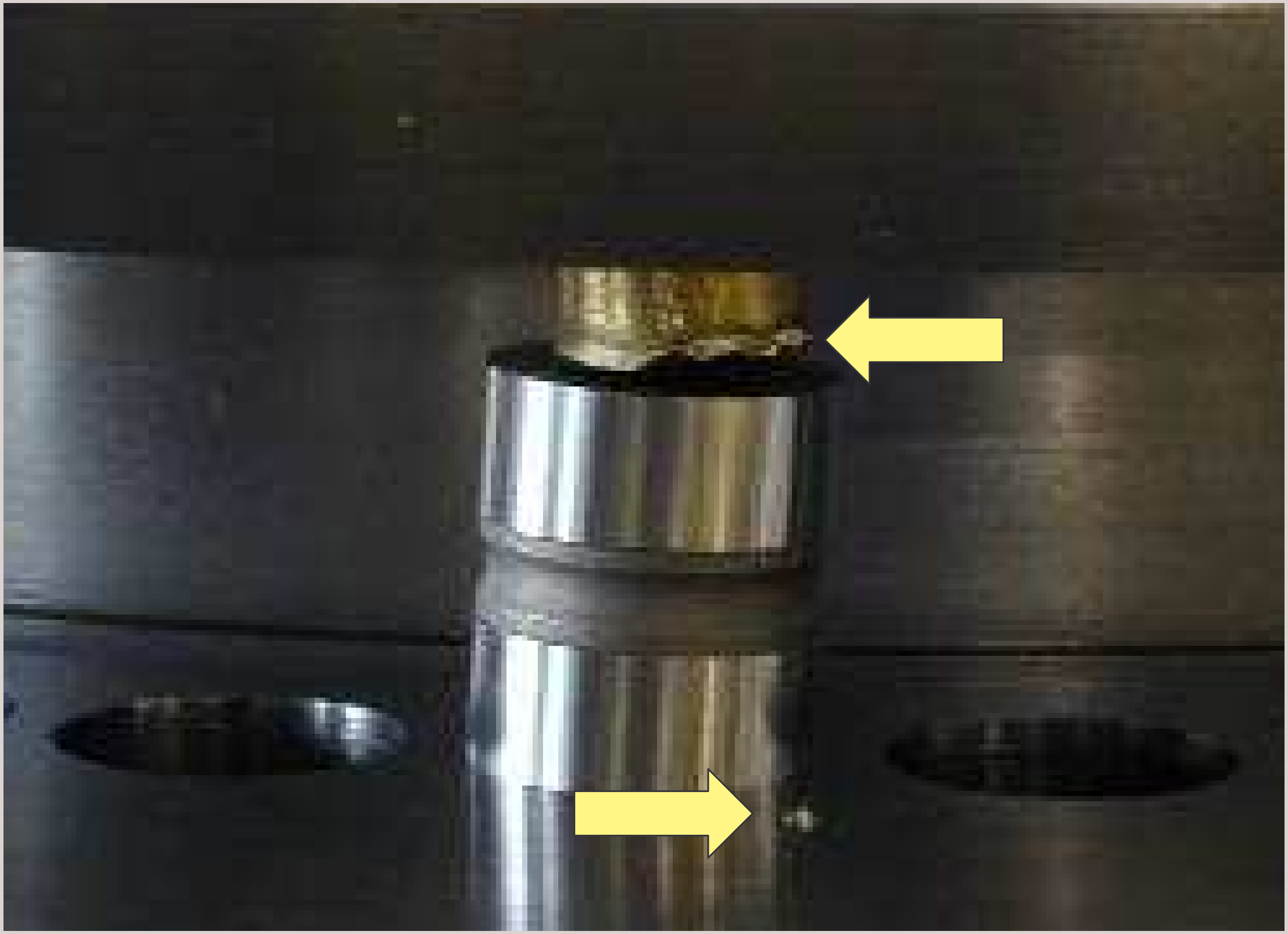
INSTALLING PUNCHES AND DIES



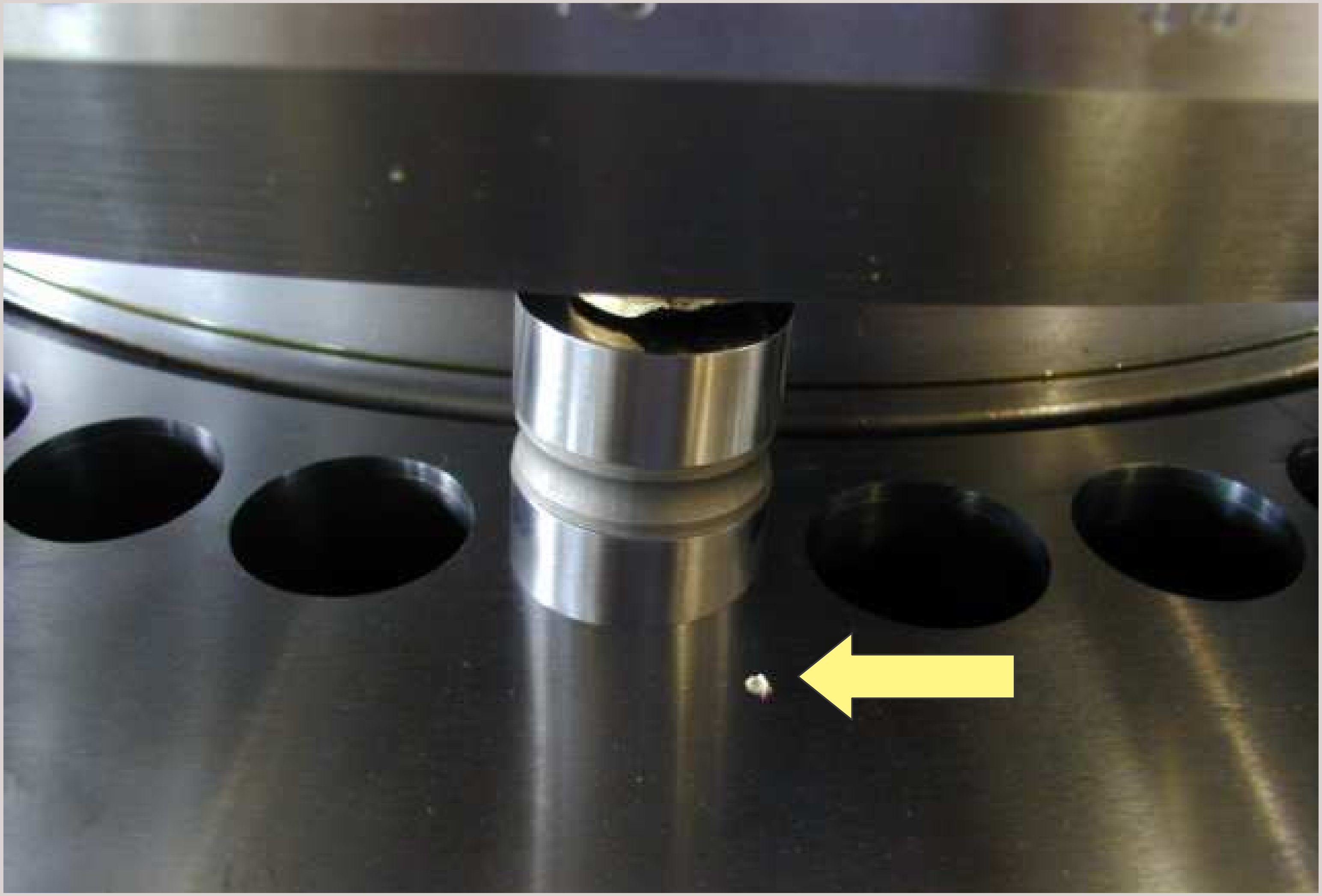
- THE CORRECT DIE DRIVING ROD MUST BE USED FOR EACH PRESS TO INSTALL DIES STRAIGHT DOWN.

A COMMON MISTAKE IS USING UNDERSIZED BRASS RODS TO INSTALL DIES

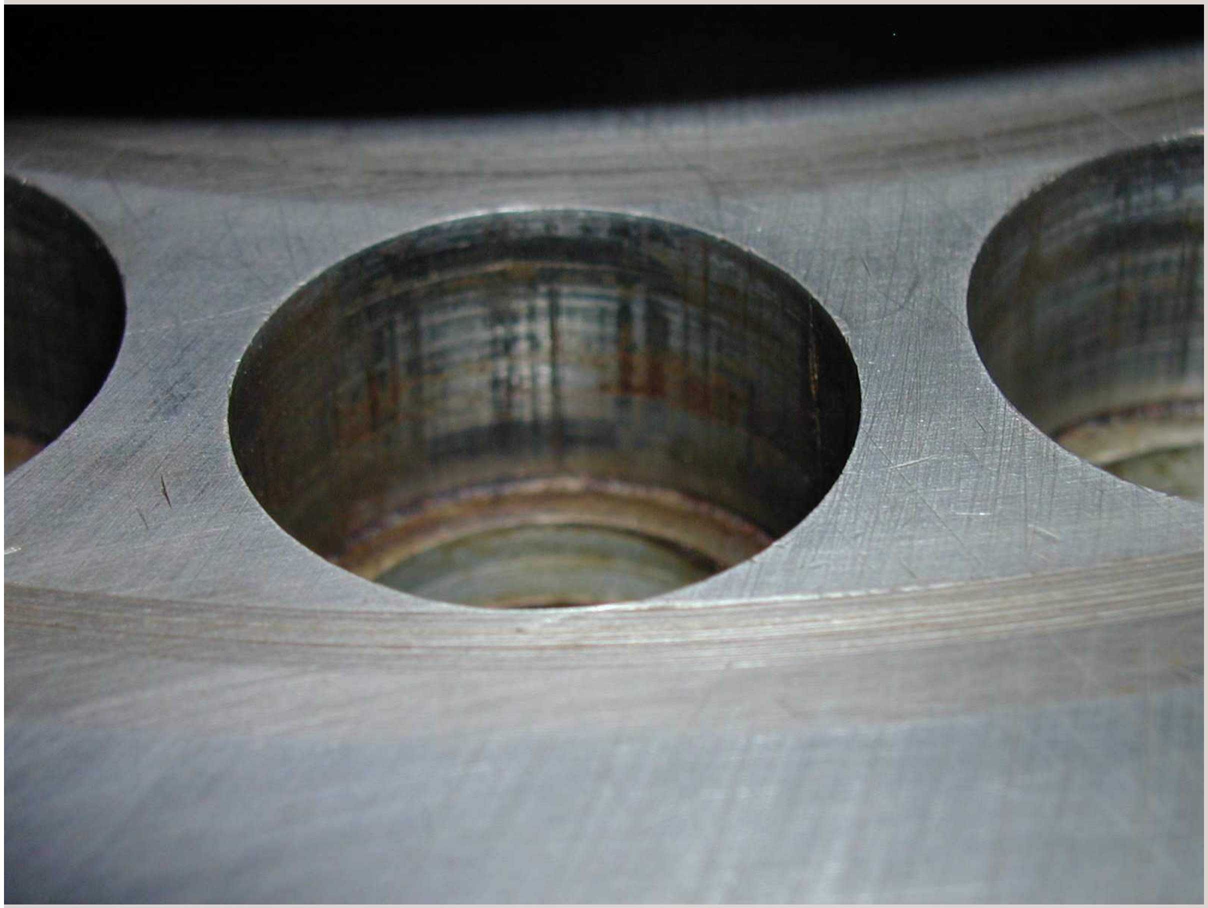
BRASS RODS SWELL OR "MUSHROOM" AND FLAKE



WHERE WILL THIS METAL GO ?
IN YOUR TABLETS ?
IN YOUR PRESS CAUSING DAMAGE ?



RADIAL LINES INDICATE DIES WERE “ROCKED IN”
VETICAL LINES ARE CAUSED BY DAMAGED DIE
DIAMETERS, GROOVES OR EDGES



- DAMAGED DIE POCKET DUE TO IMPROPER SET UP AND INSTALLATION OF NICKED OR DAMAGED DIES CAUSED BY IMPROPER HANDLING OR EXCESSIVE TORQUE

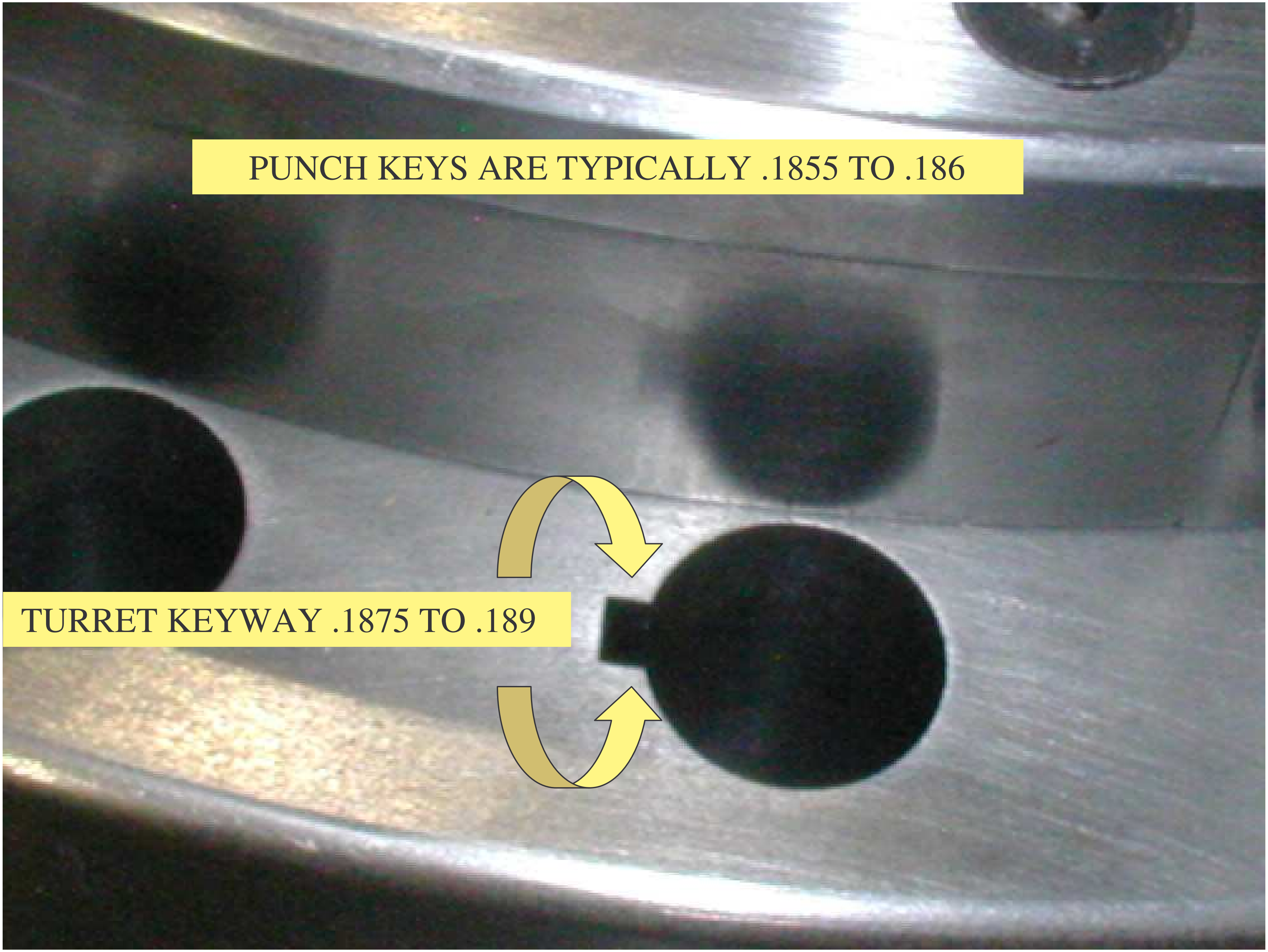
FRETTING

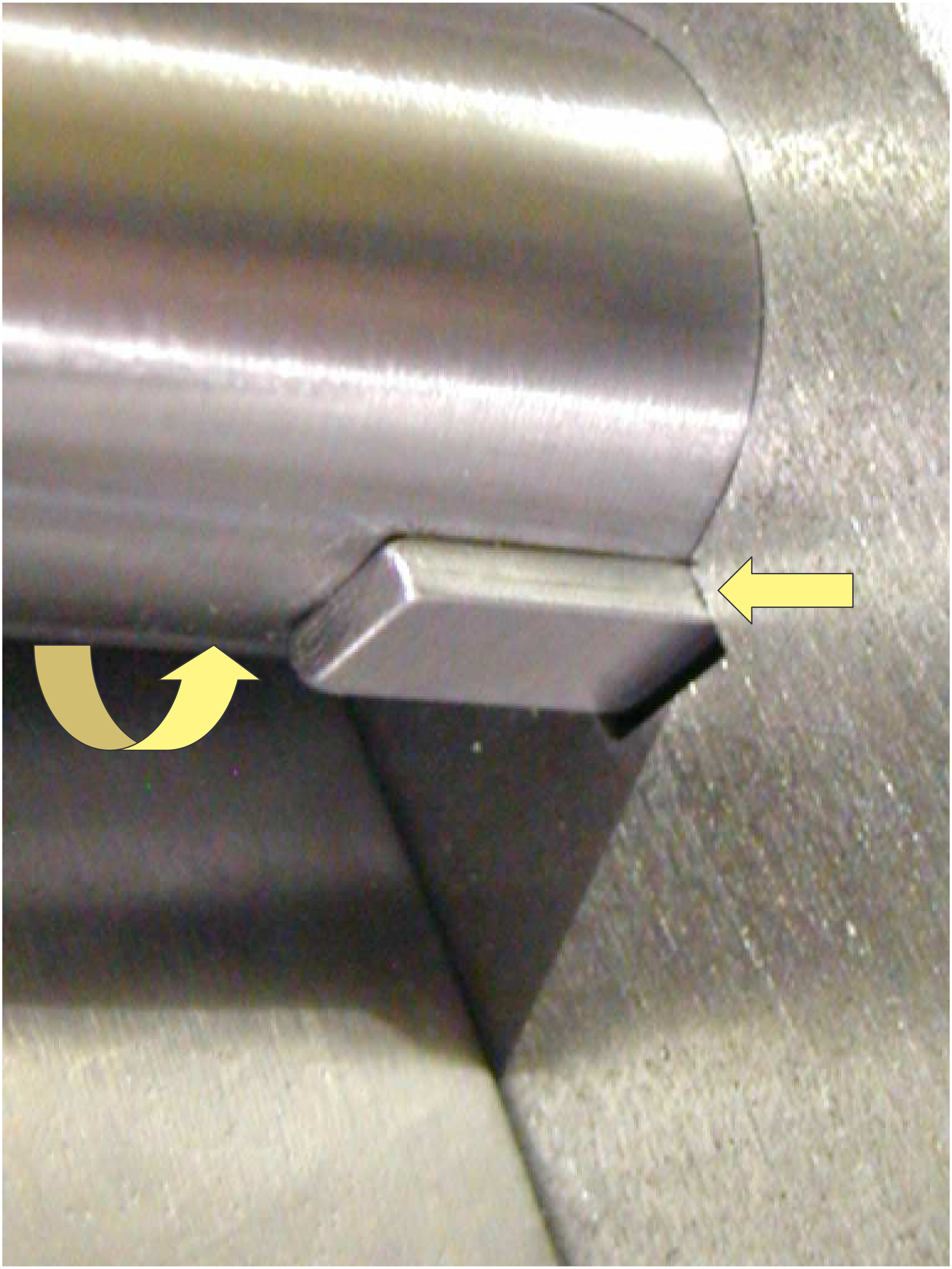
- FRETTING WEAR OCCURS BETWEEN PARTS THAT ARE ESSENTIALLY STATIONARY. IT IS A FORM OF MICROWELDING CAUSED BY SLIGHT CYCLIC MOTION THAT CAN BE OF EXTREMELY SMALL AMPLITUDE. IT IS ALSO CALLED FRETTING CORROSION BECAUSE THE DEBRIS FORMED CONTAINS OXIDES OF FERROUS METALS. THE DEBRIS IS REDDISH, BROWN OR BLACK MAKING IT LOOK LIKE RUST. FRETTING IS COMMON ON PRESS PARTS THAT ARE WORN OR OUT OF SPEC.

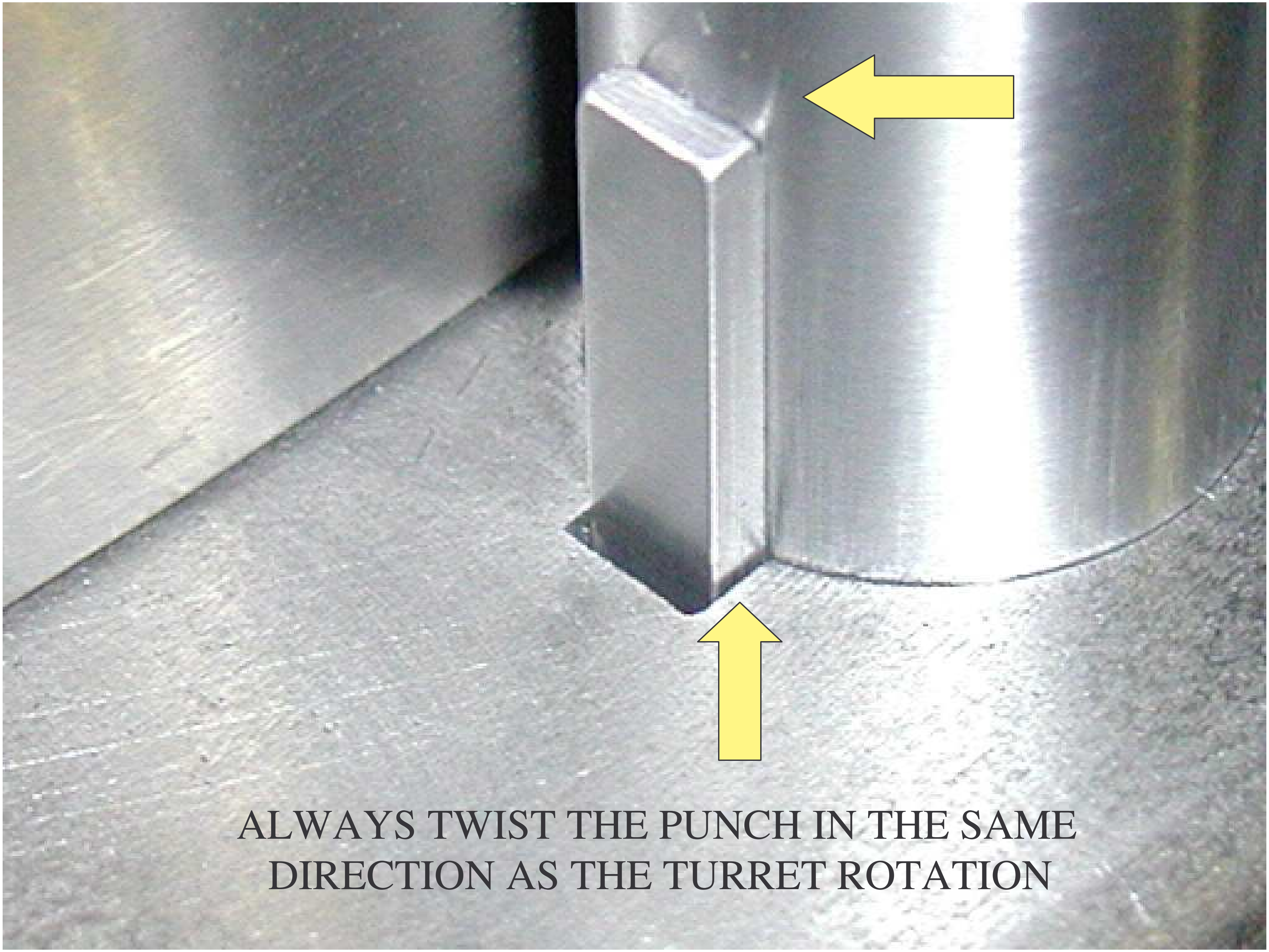
- CRACKED DIES DUE TO OVERSIZE DIE POCKETS. FRETTING ON THE OUTSIDE DIAMETER IS CONFIRMATION THIS CONDITION EXISTS.

PRELOADING PUNCHES

CERTAIN CLEARANCES ARE NORMAL IN PRESSES.
THIS ONE CAN CAUSE PREMATURE TOOL WEAR
AND BREAKAGE UNLESS TOOLS ARE SET UP
WITH THIS PROCEEDURE

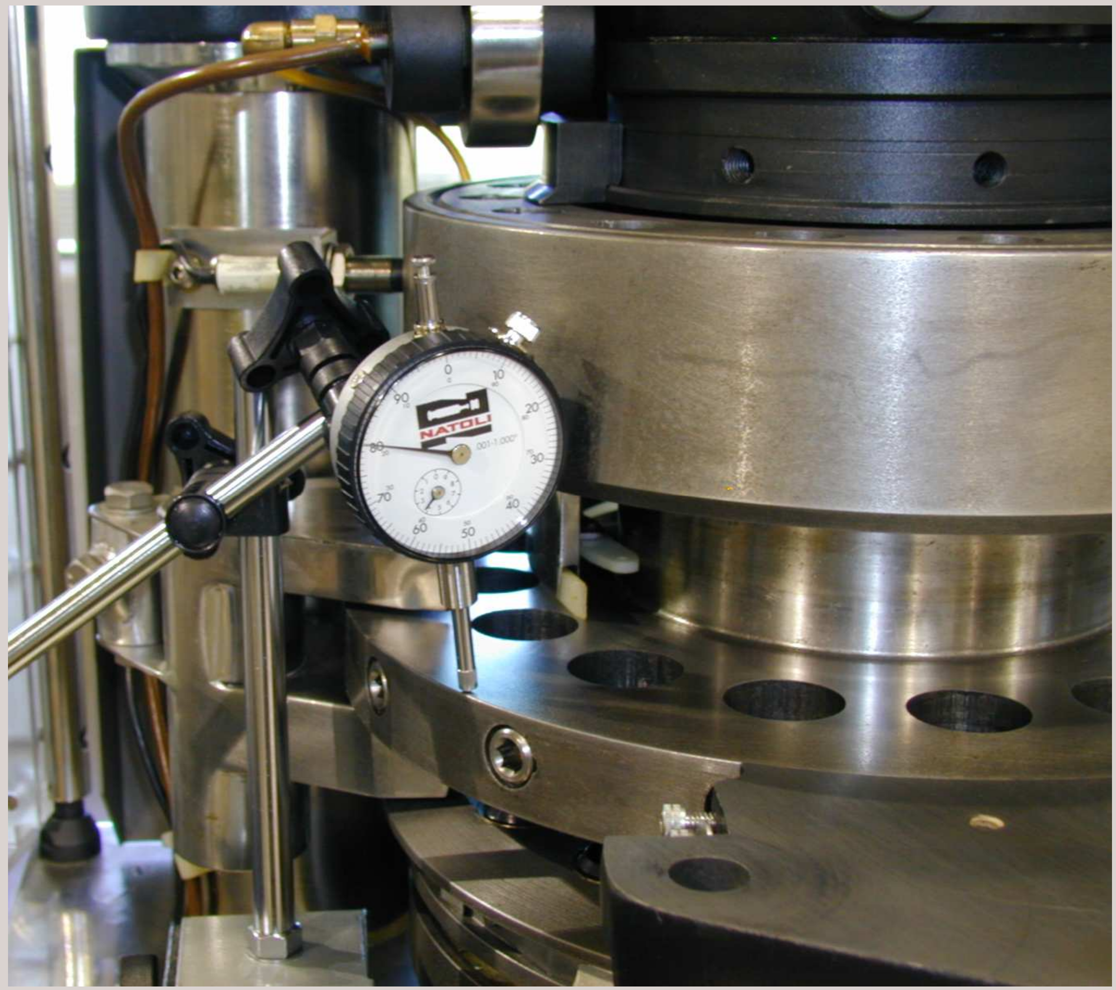

PUNCH KEYS ARE TYPICALLY .1855 TO .186
TURRET KEYWAY .1875 TO .189



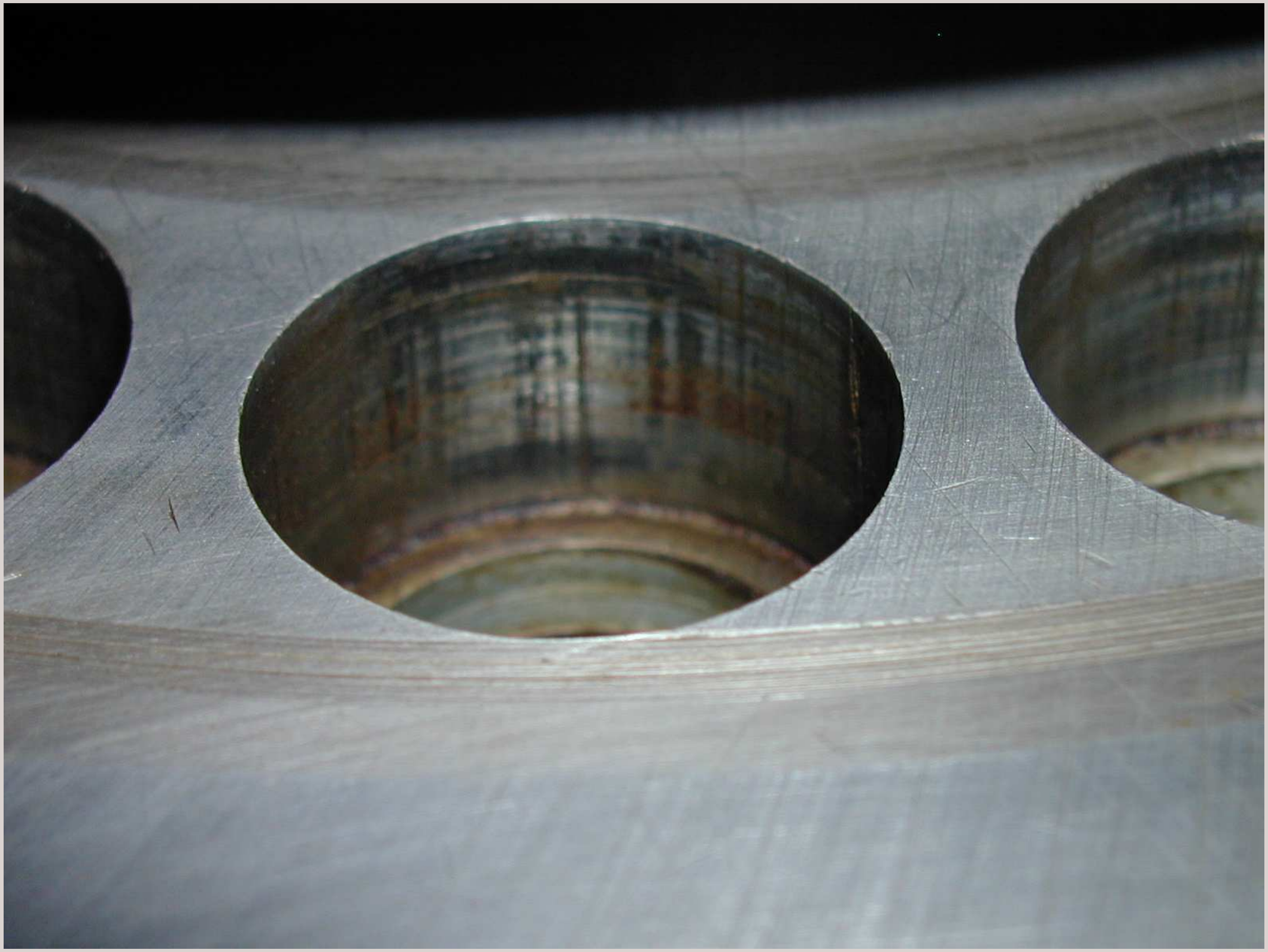

ALWAYS TWIST THE PUNCH IN THE SAME
DIRECTION AS THE TURRET ROTATION

- TYPICAL DAMAGE CAUSED BY NOT PRE-LOADING KEYED PUNCH

- A DIAL INDICATOR IS USED TO FIND THE HIGH POINT OF THE DIE TABLE. THE FEEDER CLEARANCE IS ALWAYS SET AT THE HIGH POINT OTHERWISE THE FEEDER AND DIE TABLE WILL BE DAMAGED.

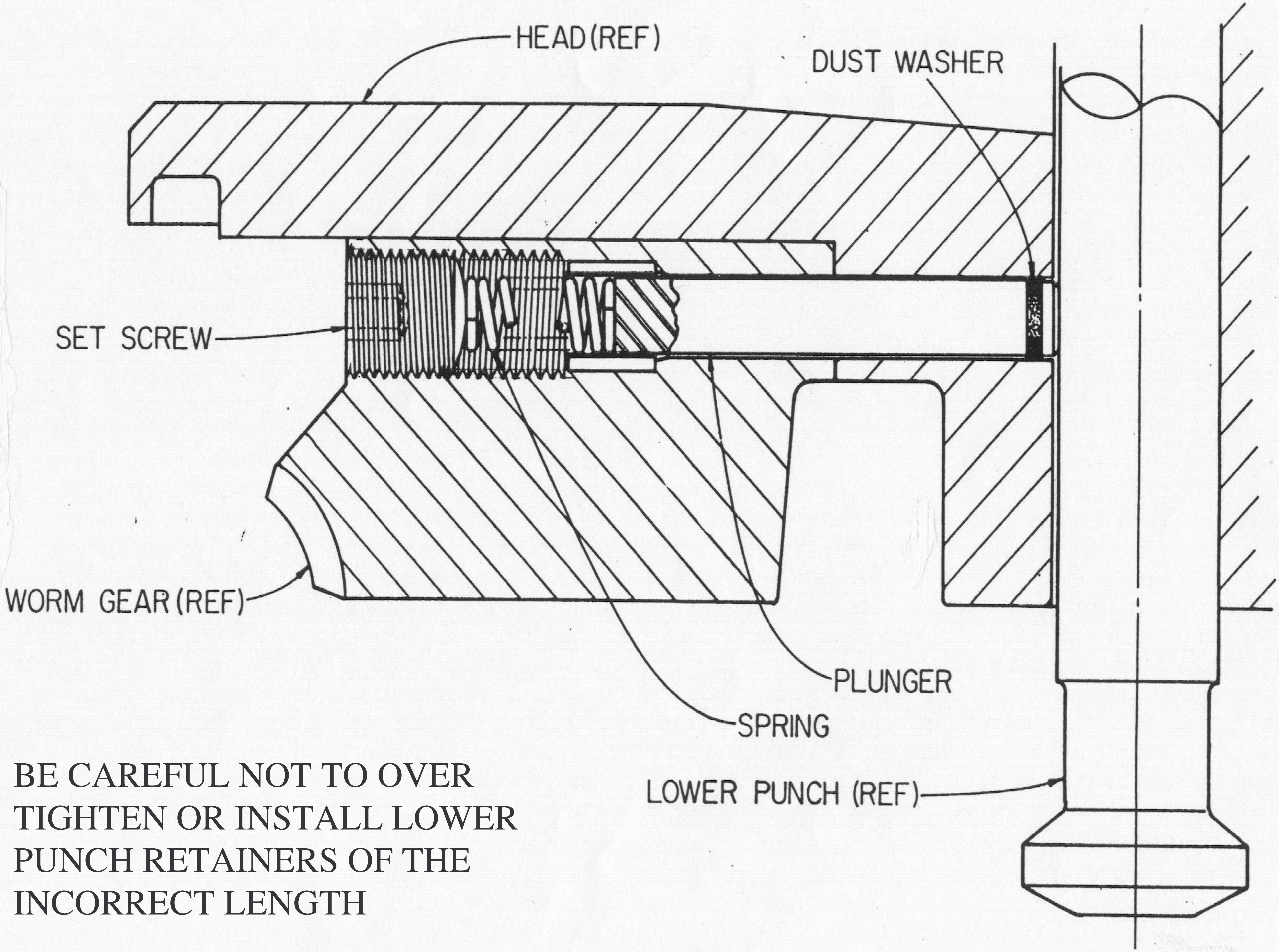


SCORED DIE TABLE CAUSED BY IMPROPER FEEDER SET UP



FEEDER DAMAGE CAUSED BY IMPROPER CLEARANCE AND/ OR SETTING THE FEEDER AT THE LOW POINT OF DIE TABLE RUN OUT. THIS WILL RESULT IN METAL PARTICLES IN THE PRODUCT AND CAUSE EXCESSIVE GRANULATION LOSS.

- BINDING BETWEEN PUNCH BARREL AND GUIDE OR PUNCH TIP AND DIE BORE WILL CAUSE THIS TYPE OF WEAR. IT CAN ALSO BE CAUSED BY IMPROPERLY SET OR INCORRECT LENGTH LOWER PUNCH RETAINERS.



BE CAREFUL NOT TO OVER TIGHTEN OR INSTALL LOWER PUNCH RETAINERS OF THE INCORRECT LENGTH

CLEANLINESS

KEEP IT CLEAN AND PROPERLY LUBRICATED AND IT WILL RUN LONGER AND EFFICIENTLY

- SCRAPER SEALS ARE ESSENTIAL TO A CLEAN RUNNING PRESS. SEALS MUST BE REPLACED PERIODICALLY. IF THIS IS NOT DONE, WEAR ON TOOLING, CAM TRACKS AND TURRET WILL BE GREATLY ACCELERATED.

- WORN SCRAPER SEALS WILL ALLOW GRANULATION TO SIFT BETWEEN THE PUNCH BARREL AND TURRET. WORN LOWER SEALS WILL ALLOW GRANULATION TO WORK INTO CAM TRACKS.

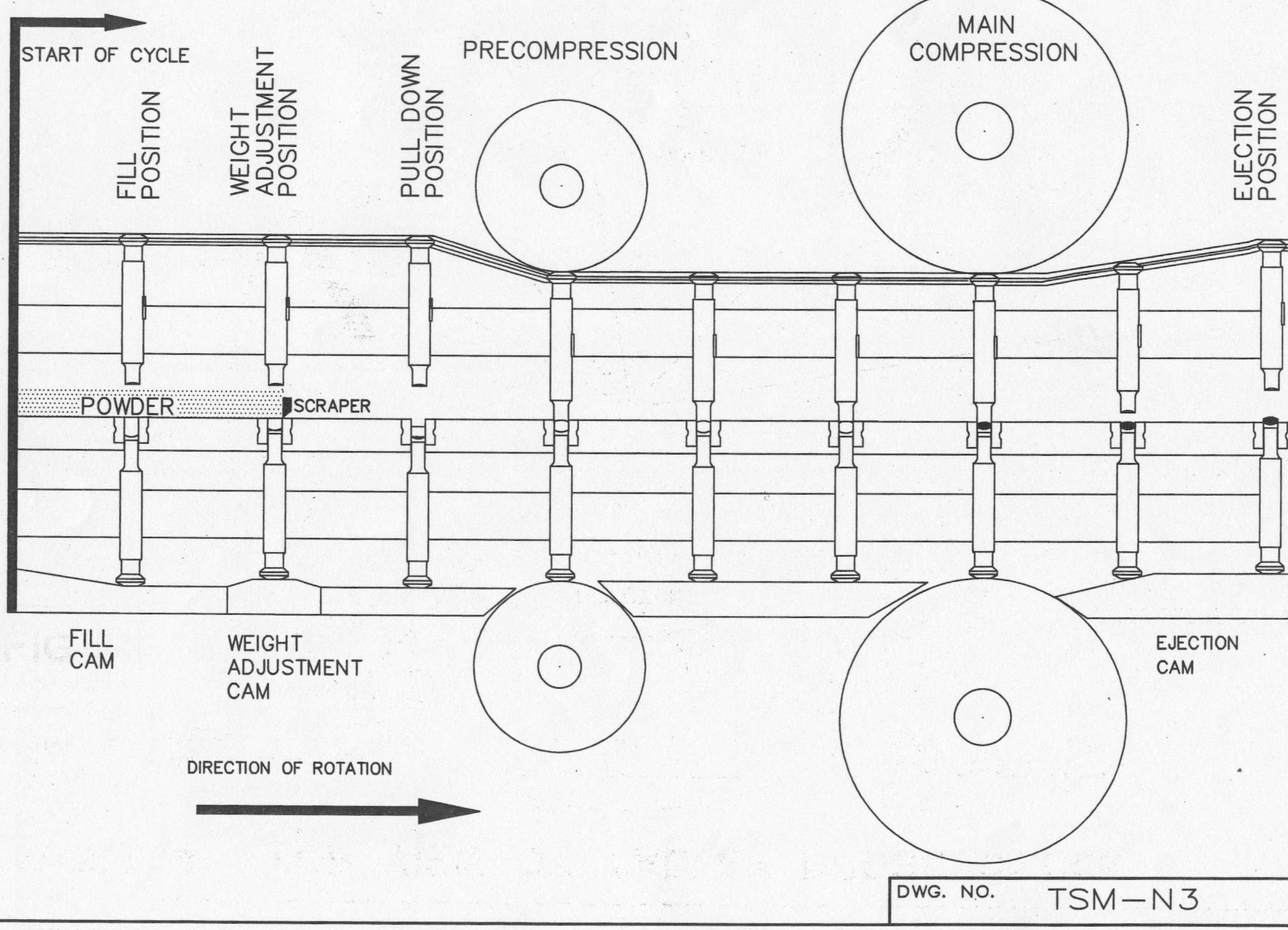
FILL CAMS

CHOOSE THE PROPER FILL CAM

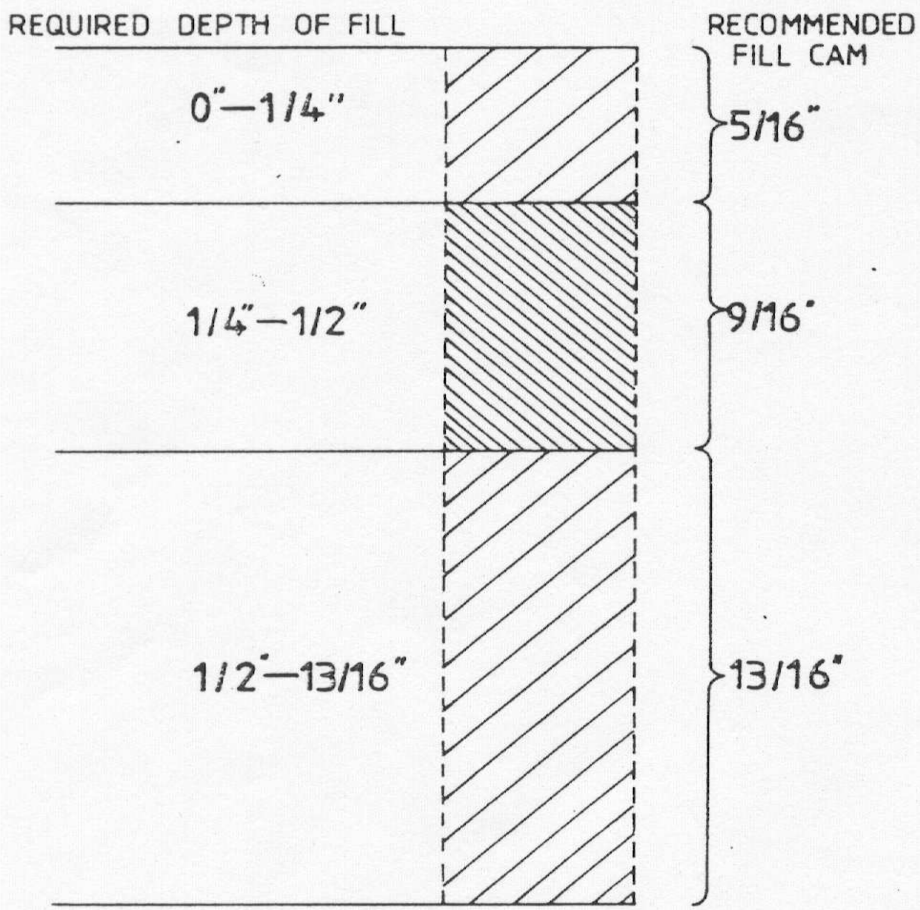
PRESSES RUN ON THE OVERFILL PRINCIPLE.

USE THE LEAST AMOUNT OF FILL AS POSSIBLE AND THE PRESS WILL RUN CLEANER

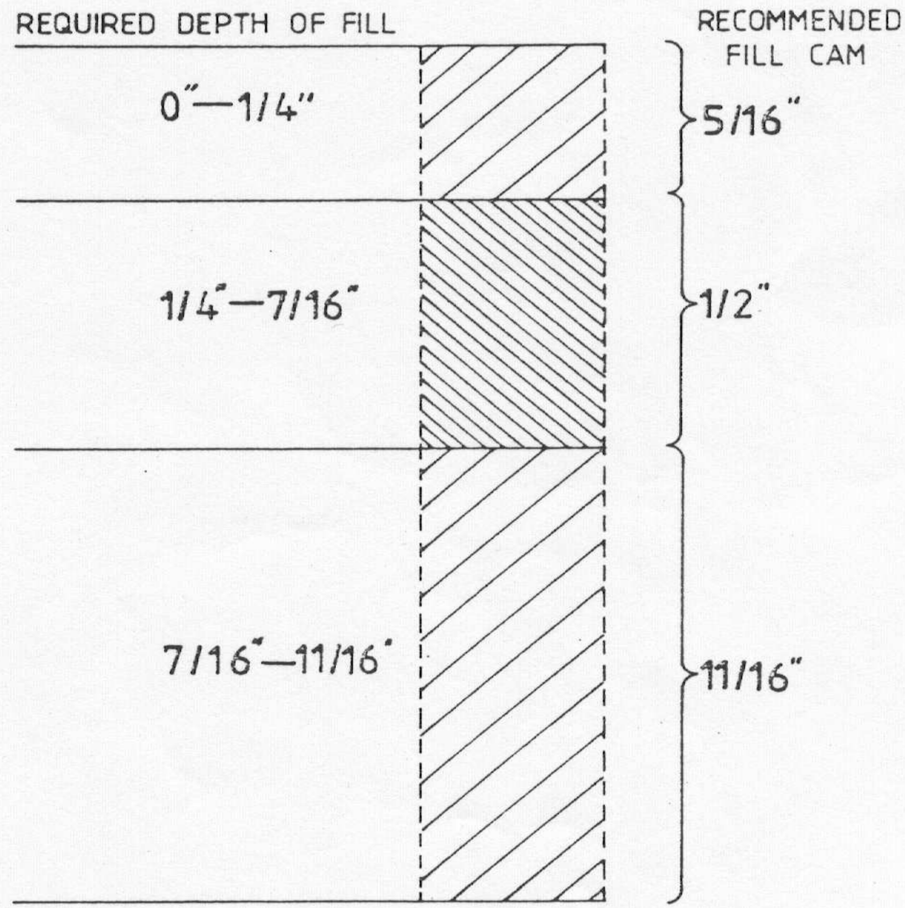
FIGURE 3. ROTARY TABLET PRESS CYCLE



RECOMMENDED USE OF FILL CAMS



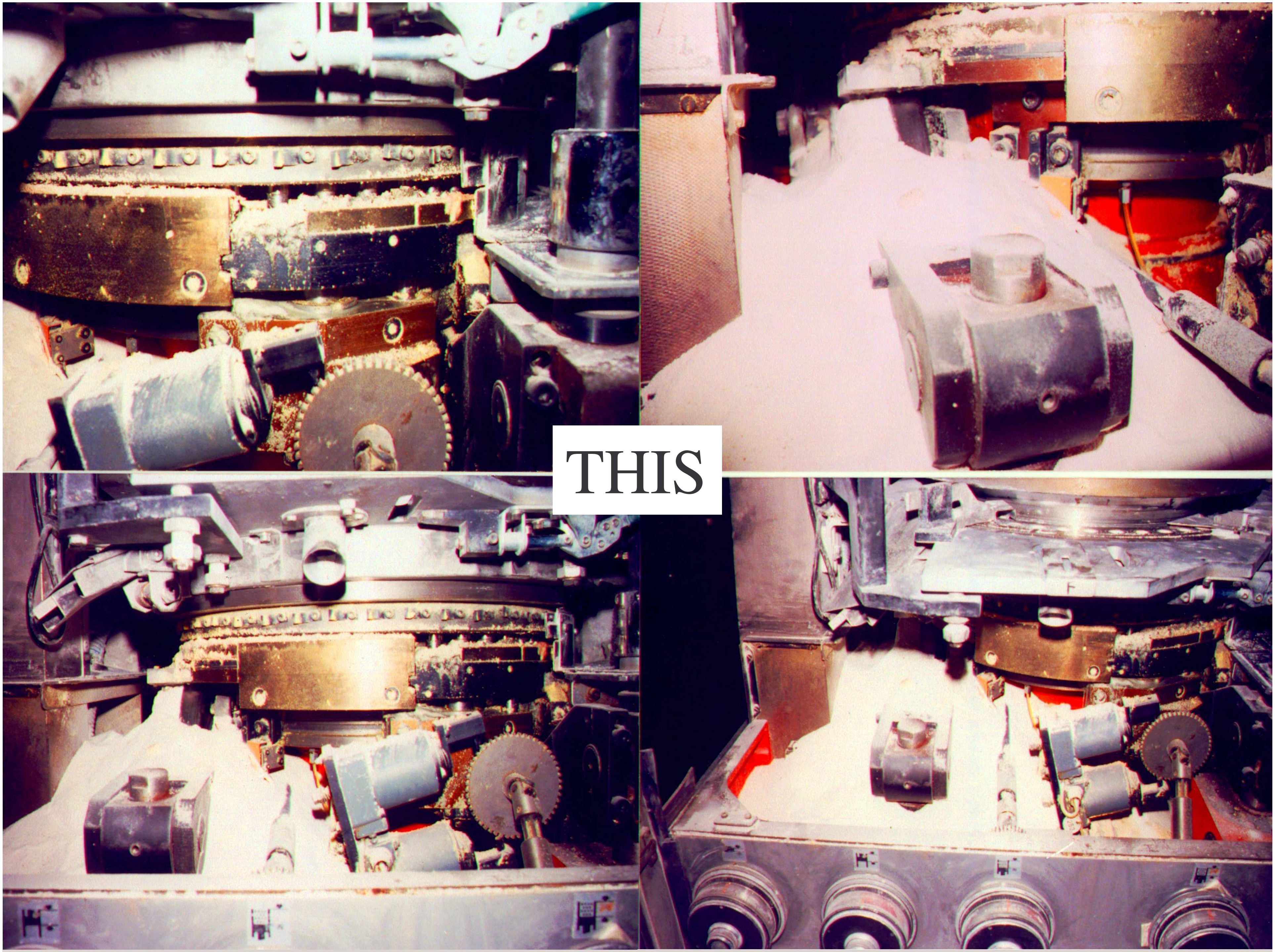
"D" TOOLING



"B" TOOLING

CLEANLINESS IS IMPORTANT THROUGHOUT THE PRESS INCLUDING ELECTRICAL COMPONENTS

A PROPERLY CLEANED AND MAINTAINED PRESS DOES NOT LOOK LIKE THIS OR…


THIS

OR THIS !

ACHIEVING OPTIMUM PERFOMANCE

- PRESSES AND TOOLING MUST BE WELL MAINTAINED
- GRANULATION MUST BE PROPERLY BLENDED
- OPERATORS REQUIRE THOROUGH TRAINING
- INTERDEPARTMENTAL COMUNICATION
- UTILIZE ALL INFORMATION AVAILABLE
- KNOW AND UNDERSTAND ALL OF YOUR OPTIONS

Thank You !

NATOLI

BROCK solutions

Process Control with PAT & Plant Floor Automation

Paul Lomelo

Brock Solutions

Date: June *23, 2005*

Agenda

- PAT Manufacturing Basics
- Factory Floor Architecture
- Using Information to Control the Manufacturing Process
- HMI for Blender Control Based on Effusivity Control Points

PAT Manufacturing Basics

- Industrialization Goal
  - Understand & Control Manufacturing Process
    - **Improve productivity**
    - **Increase efficiency**
    - **Improve quality & product consistency**
    -

PAT Manufacturing Basics

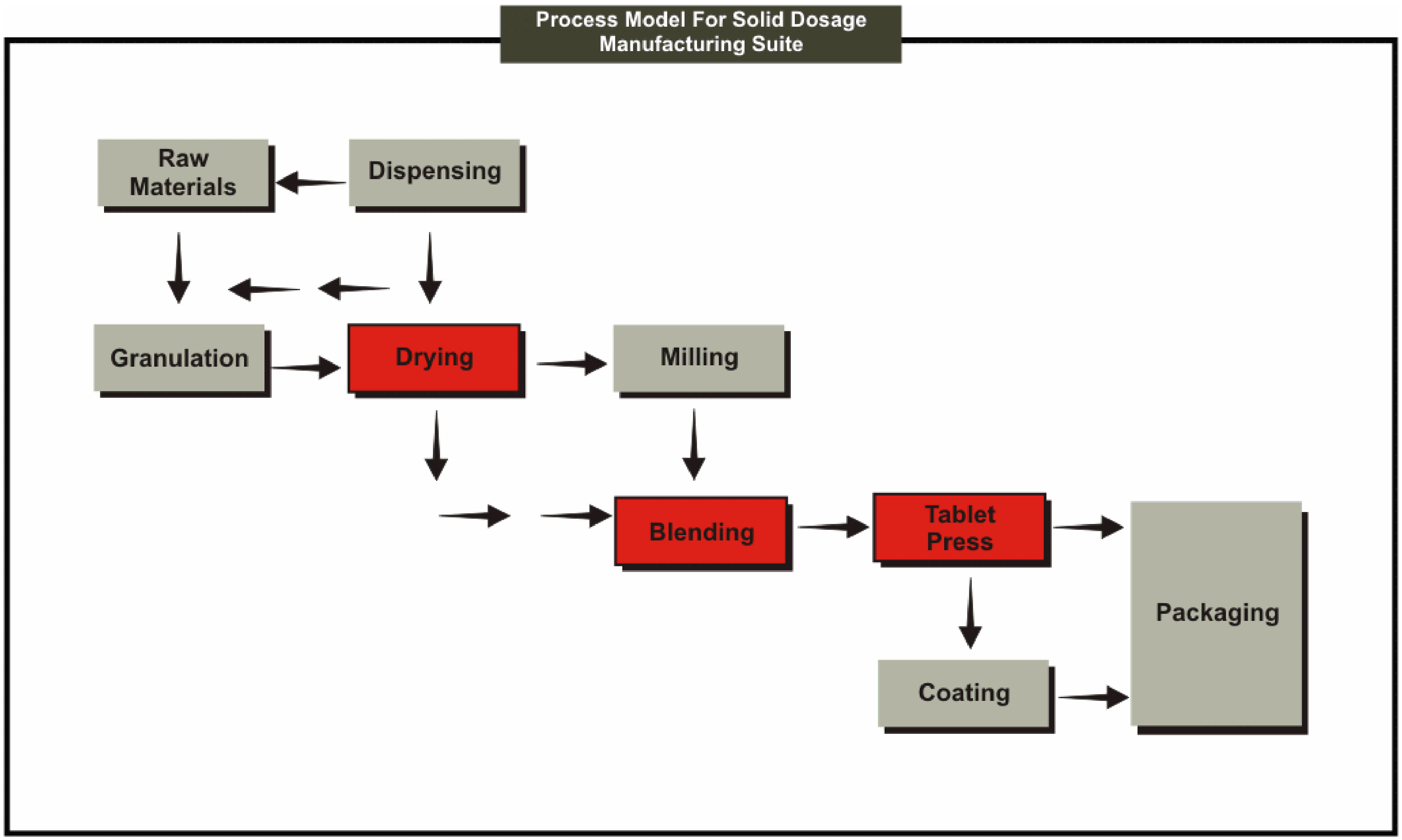
Product Drivers

- Patient's Needs Products
  - Right level of active ingredients & dissolution
- Product Standards
  - Products currently can be +/- 15% of labeled dosage
- Product Specifications
  - Samples & Statistical Process Control
- Measuring & Control
  - Process Parameters are controlled
  - Product Attributes are measured

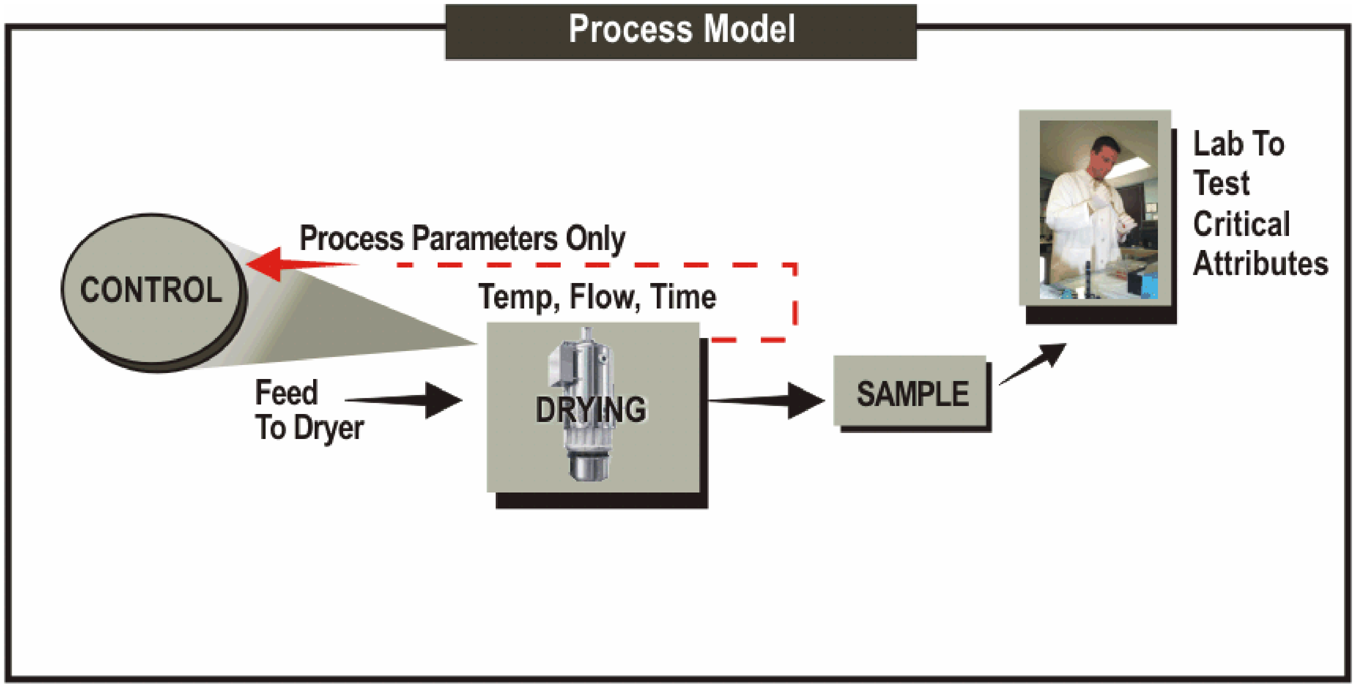
PAT Manufacturing Basics

- Opportunity Cost / ROI
  - Go from Batch to Real Time Releases
  - Reduce or eliminate
    - Incident reports
    - Deviations
    - Out of Spec Product
    - Batch Failures
    - Recalls

PAT Manufacturing Basics

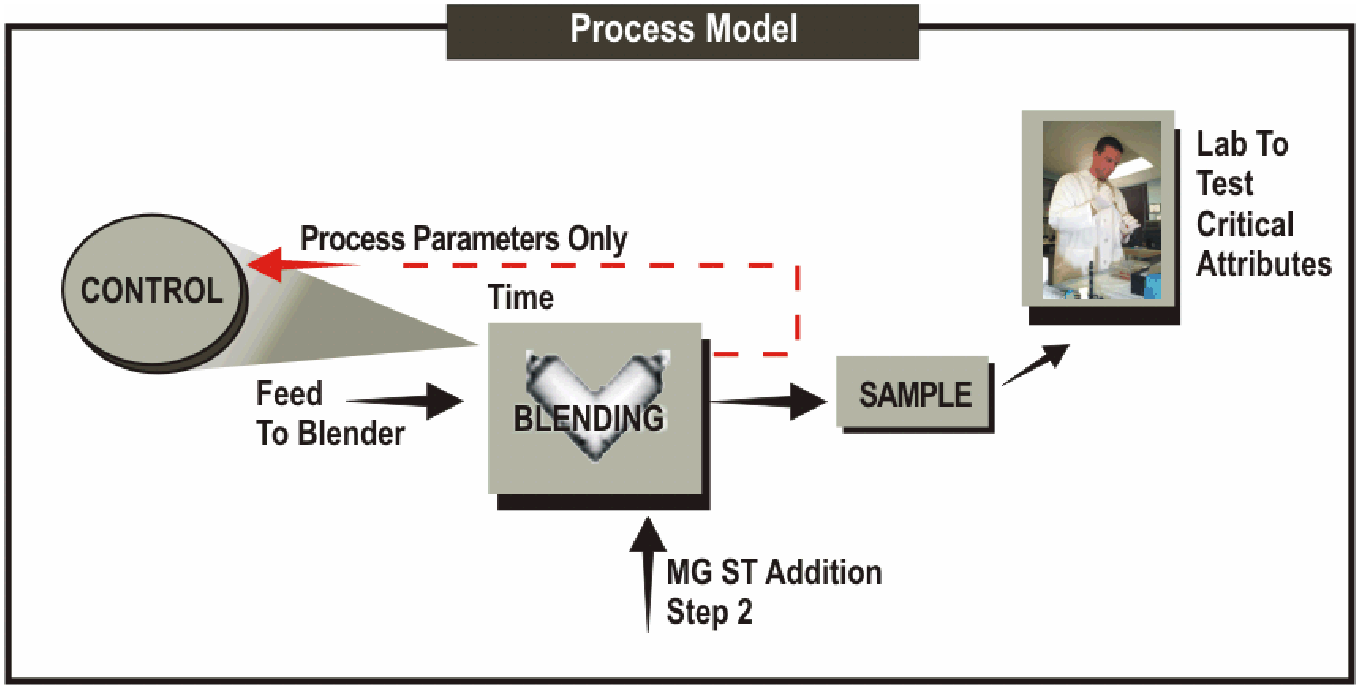


PAT Manufacturing Basics



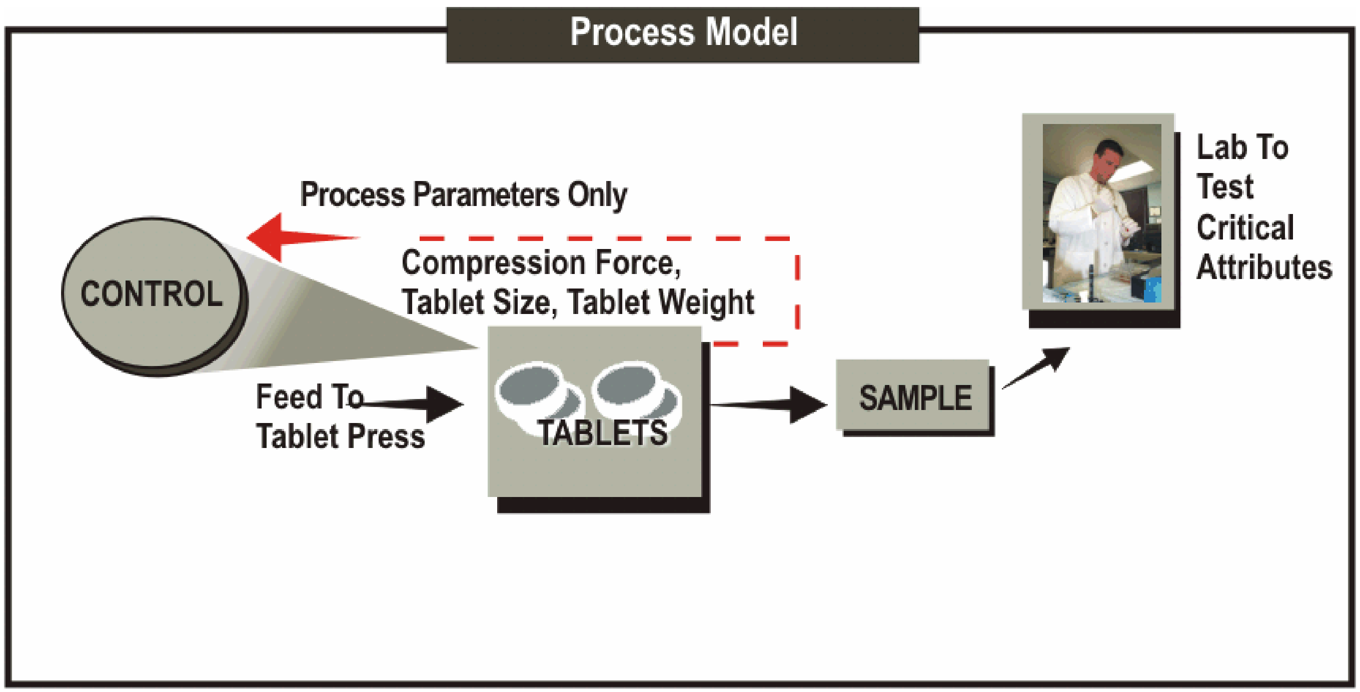
Dryer still running while lab does testing

PAT Manufacturing Basics



Batch is held while lab does testing

PAT Manufacturing Basics



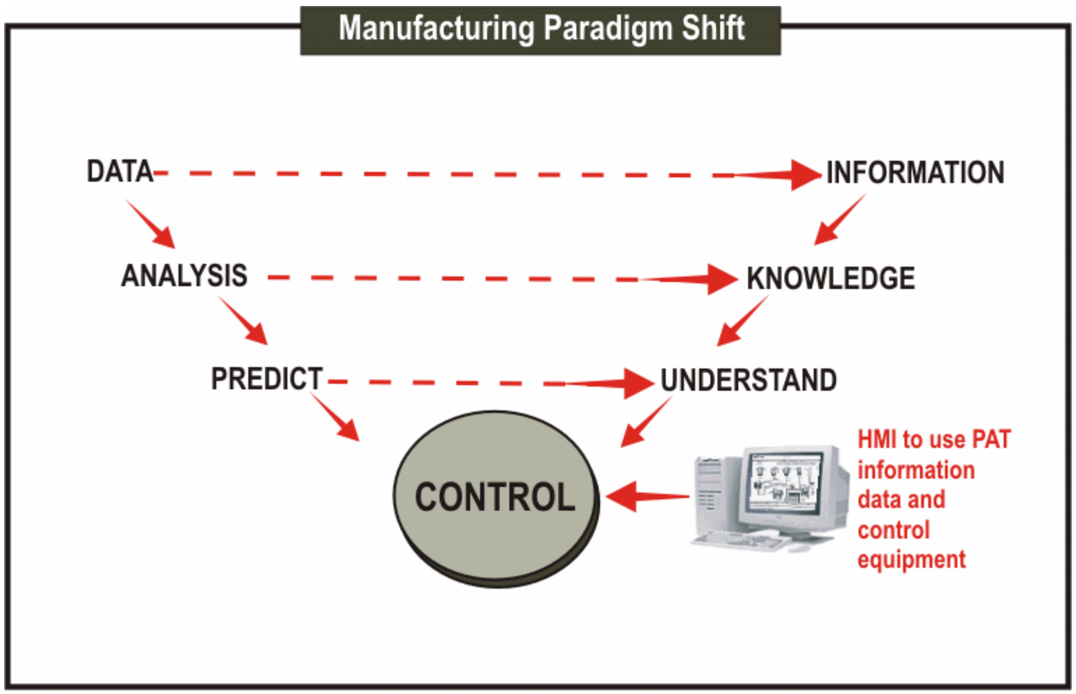
Batch is held while lab does testing

PAT Manufacturing Basics

- Use PAT tools to:
  - Monitor multiple parameters to enhance process
  - Determine critical to quality attributes of materials
  - Determine critical control points of process
  - Develop feedback / feedforward controls to reduce variables in the process
  - Use product attributes as control parameters

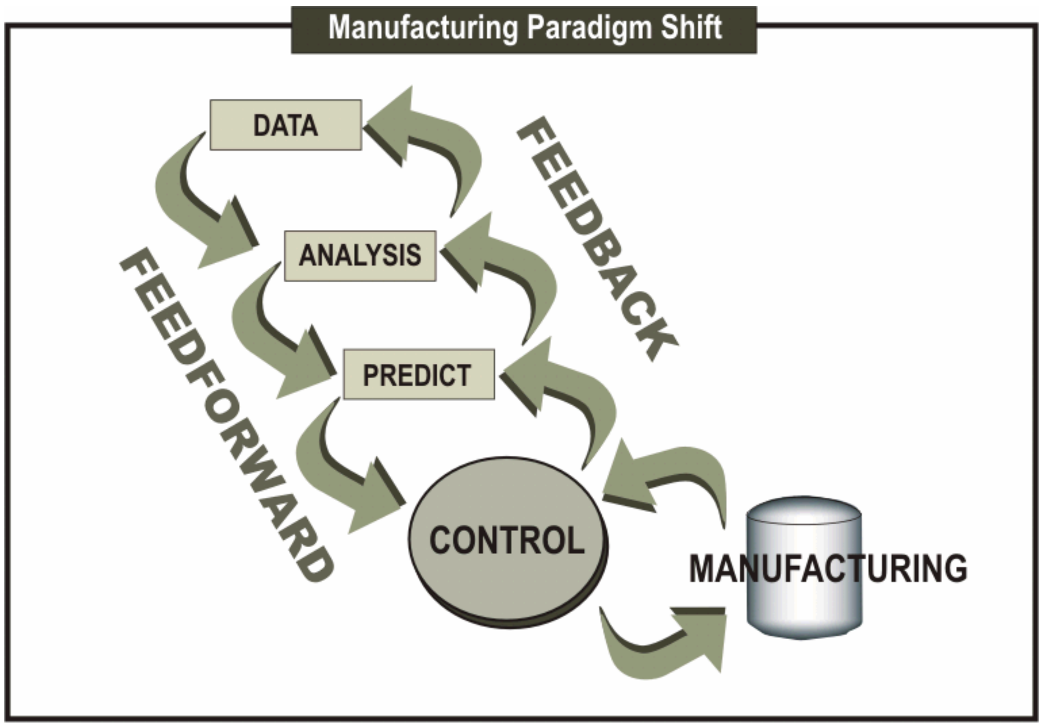
PAT Manufacturing Basics

- Design Model, Analysis of Data, Control Process

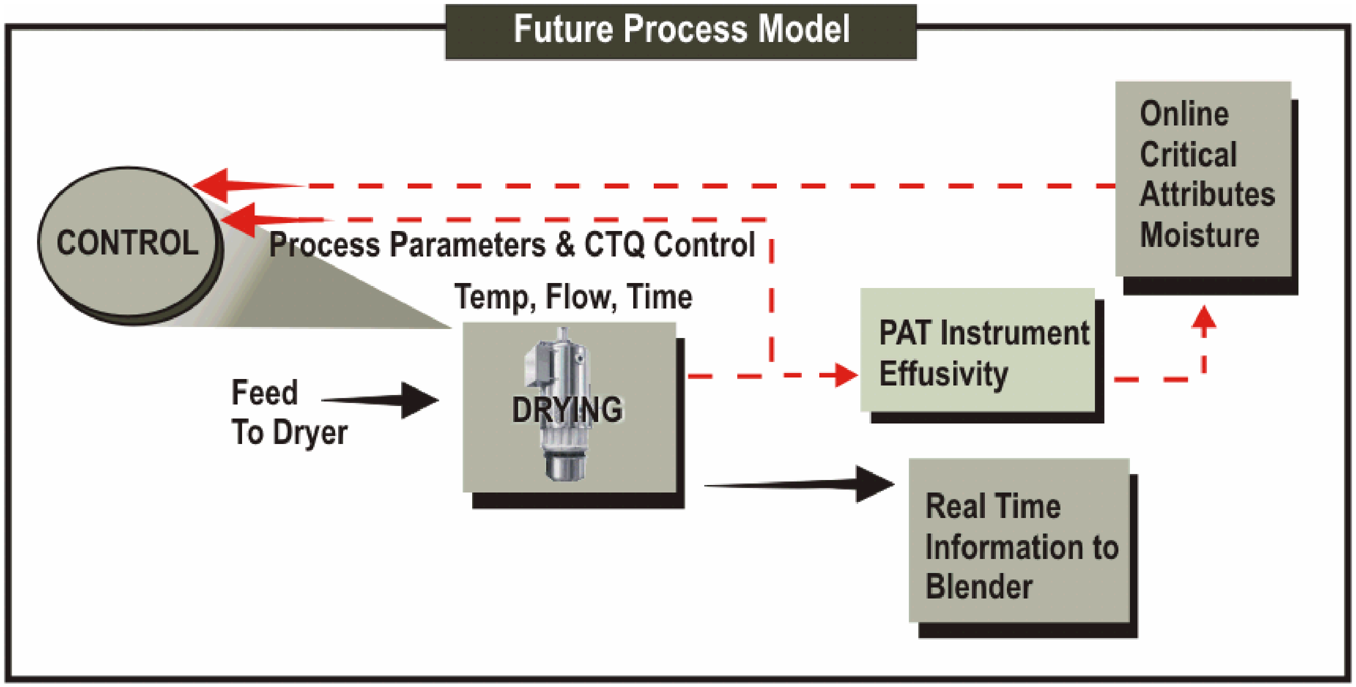


PAT Manufacturing Basics

- Manufacturing Paradigm Shift
  - Design Model, Analysis of Data, Control Process

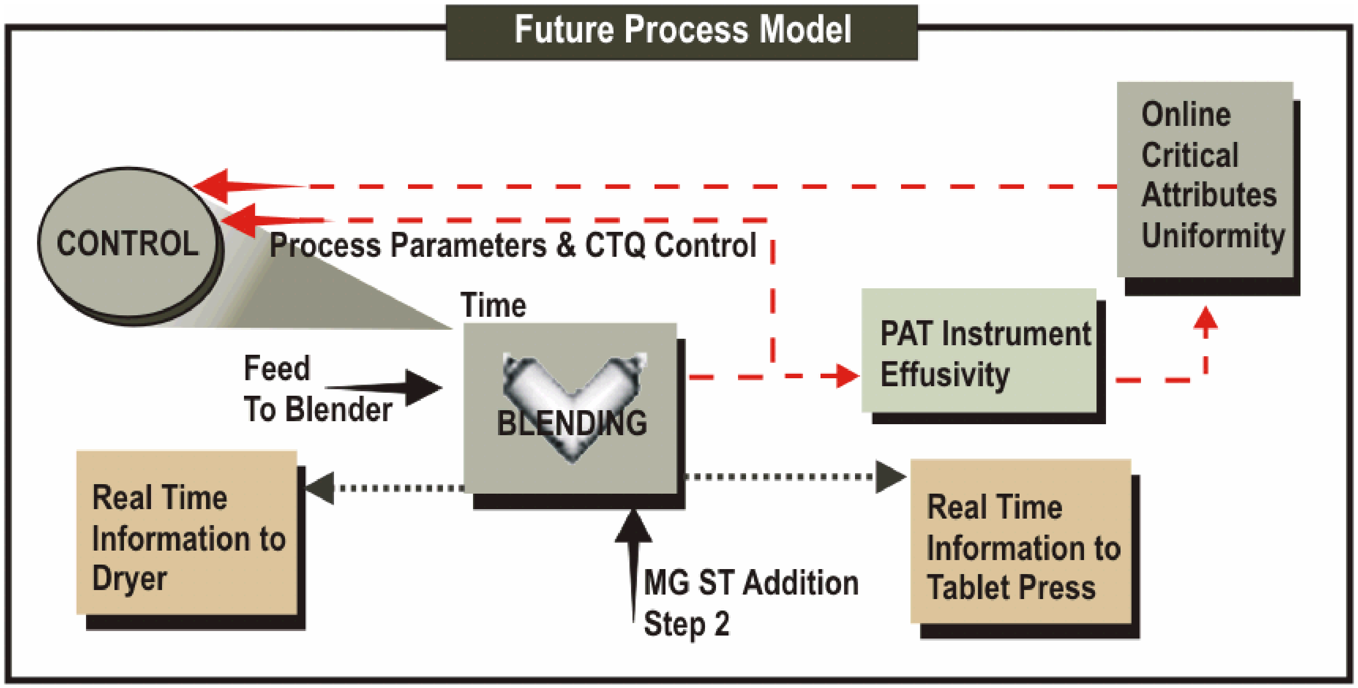


PAT Manufacturing Basics



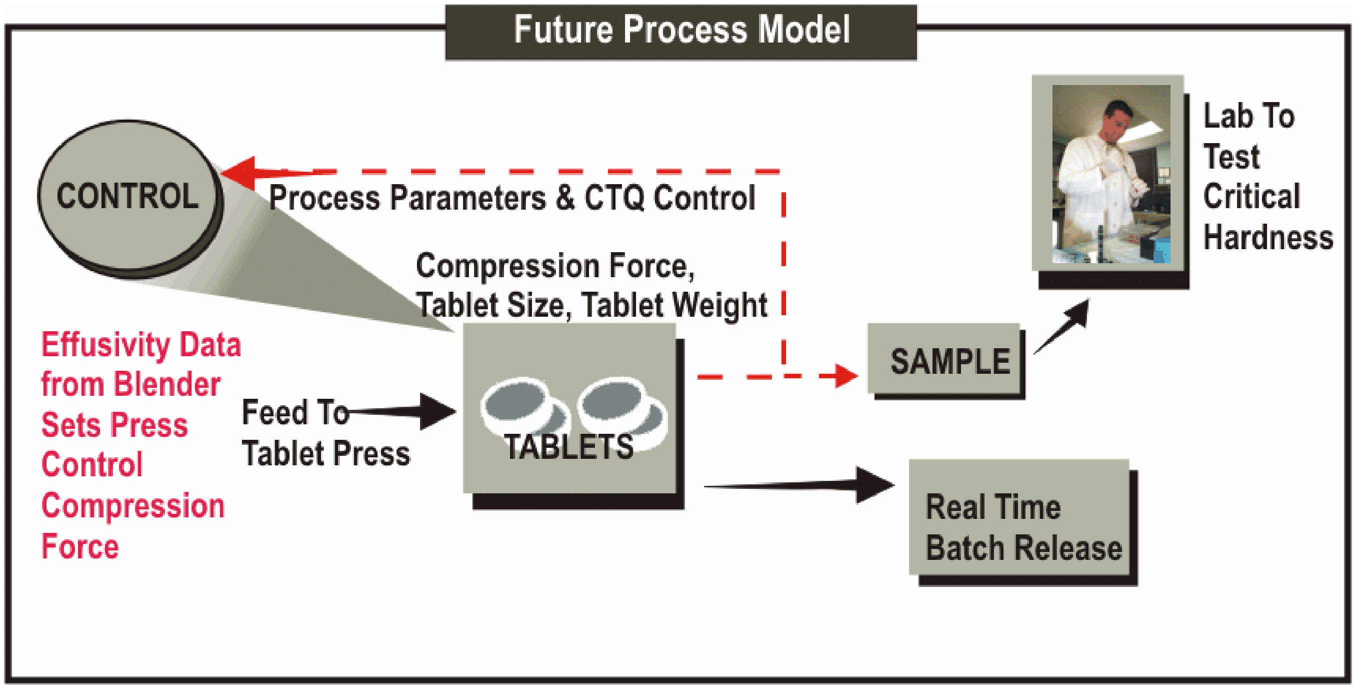
Feed forward control setting to blender

PAT Manufacturing Basics



Feedforward control setting to tablet press
Feedback to the dryer on output material CTQ attributes

PAT Manufacturing Basics



Batch can be released while lab does testing, because CTQ Attributes can be predicted from blender effusivity data

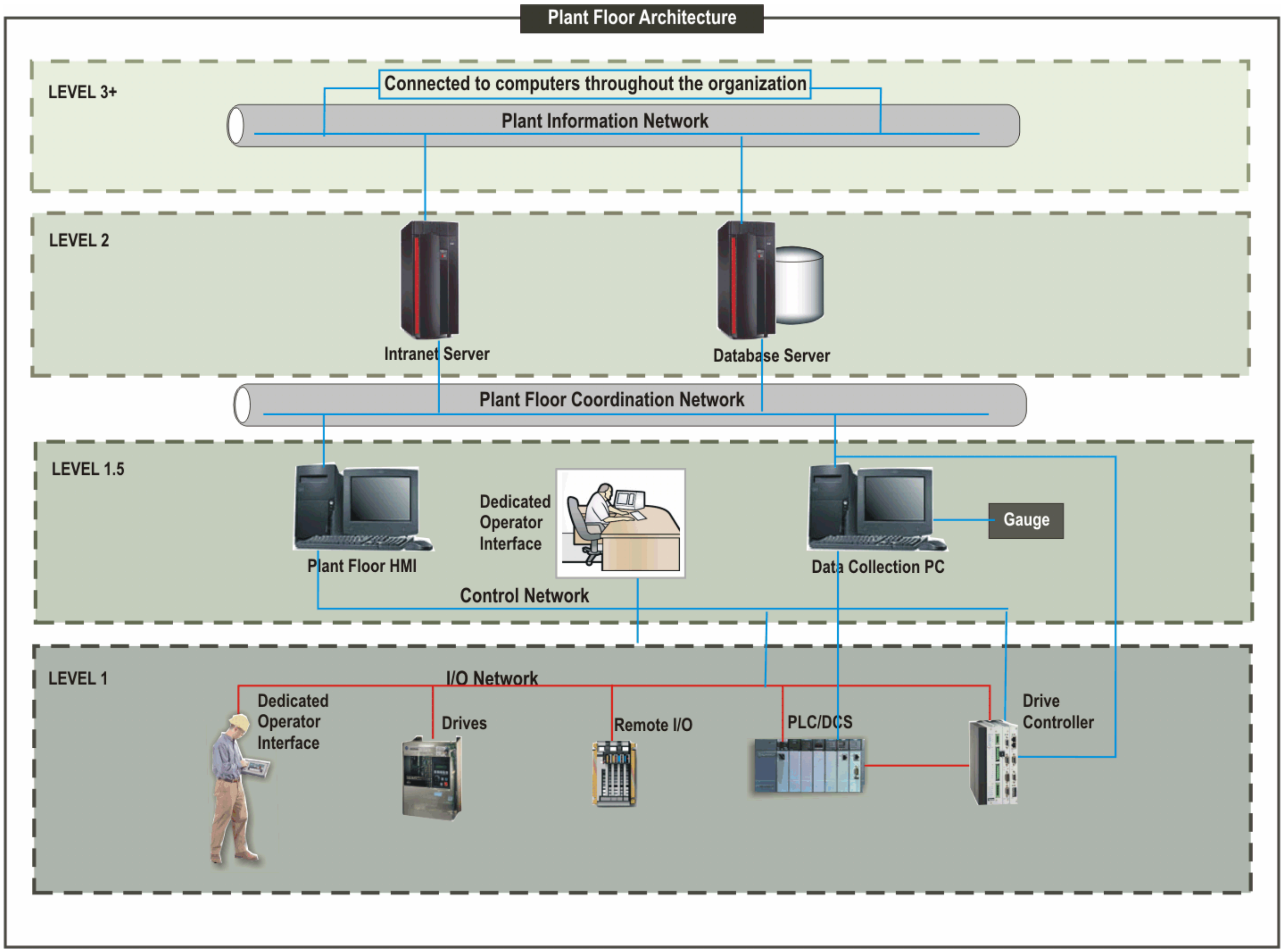
Agenda

- PAT Manufacturing Basics
- Factory Floor Architecture
- Using Information to Control the Manufacturing Process
- HMI for Blender Control Based on Effusivity Control Points

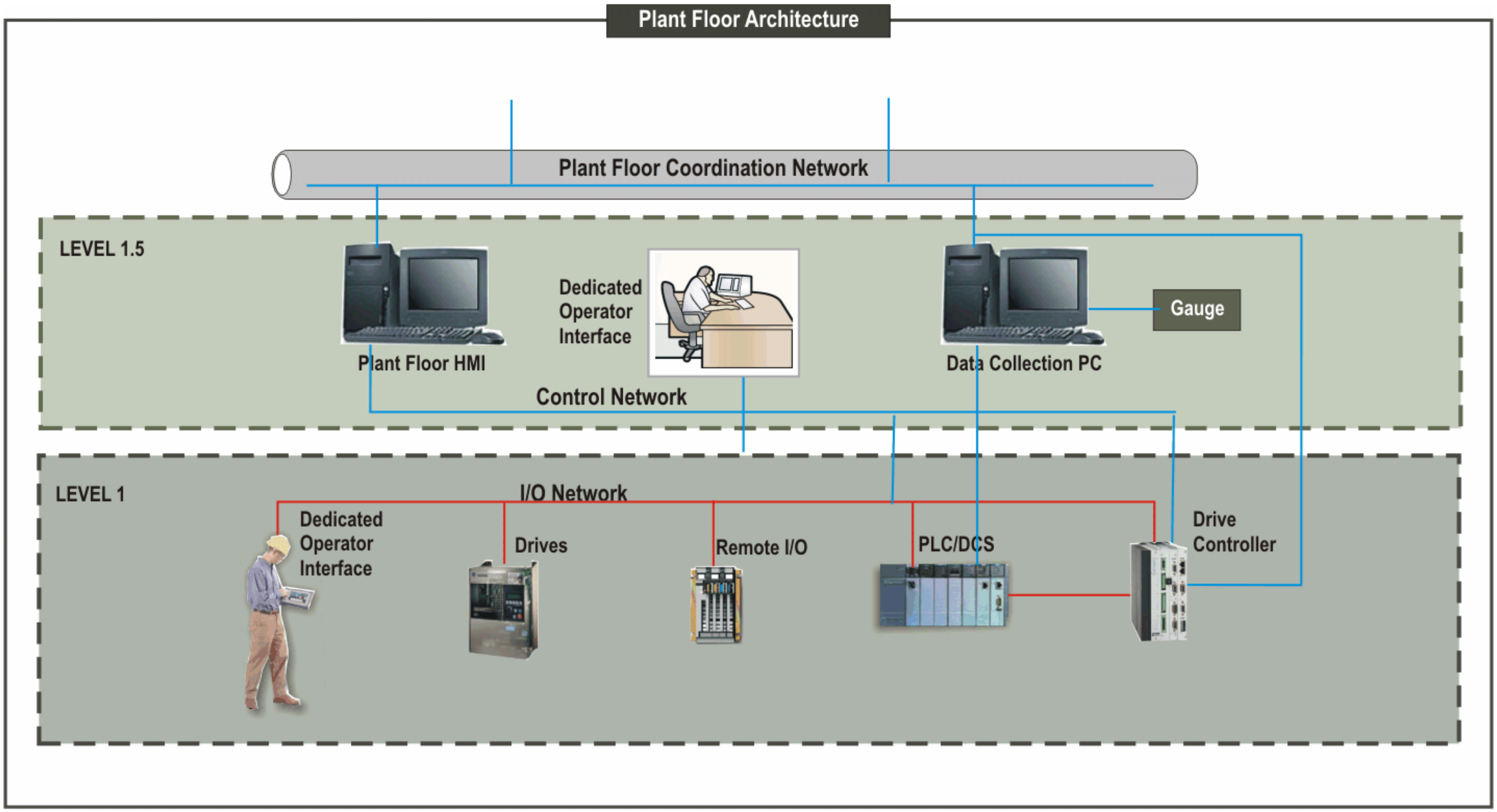
Plant Floor Architecture

- Level 1 - PLCs, drives, instrumentation, DCSs, field devices
- Level 1.5 - plant floor PCs for HMIs, data collection
- Level 2 - Database/application servers, Intranet servers
- Level 3+ - MIS, front office applications, ERP/MRP

Sample Plant Floor Architecture

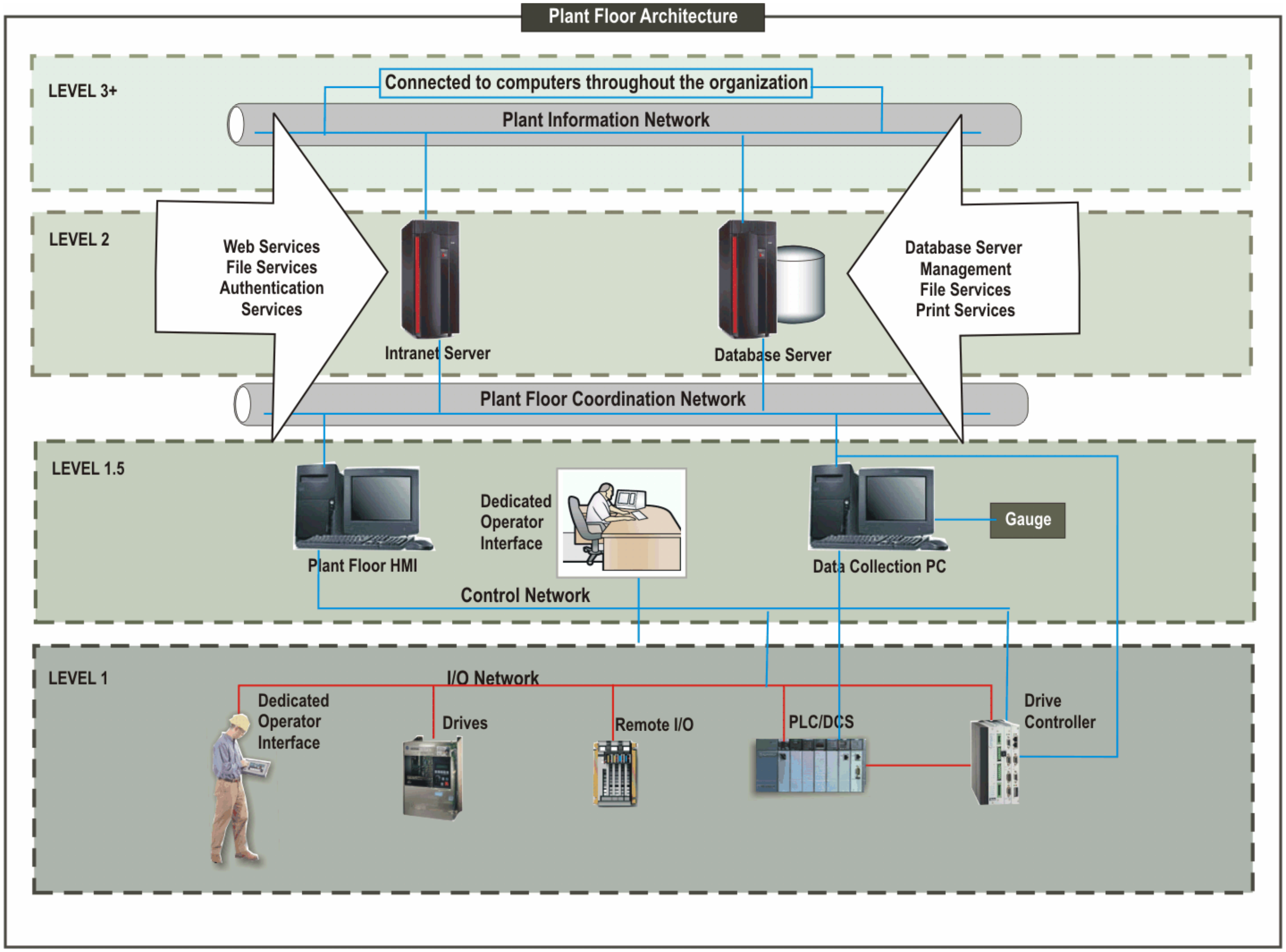


Level 1.5



Plant Floor Architecture
Plant Floor Coordination Network
LEVEL 1.5
Dedicated
Operator
Interface
Gauge
Plant Floor HMI
Data Collection PC
Control Network
LEVEL 1
I/O Network
Dedicated
Operator
Interface
Drives
Remote I/O
PLC/DCS
Drive
Controller

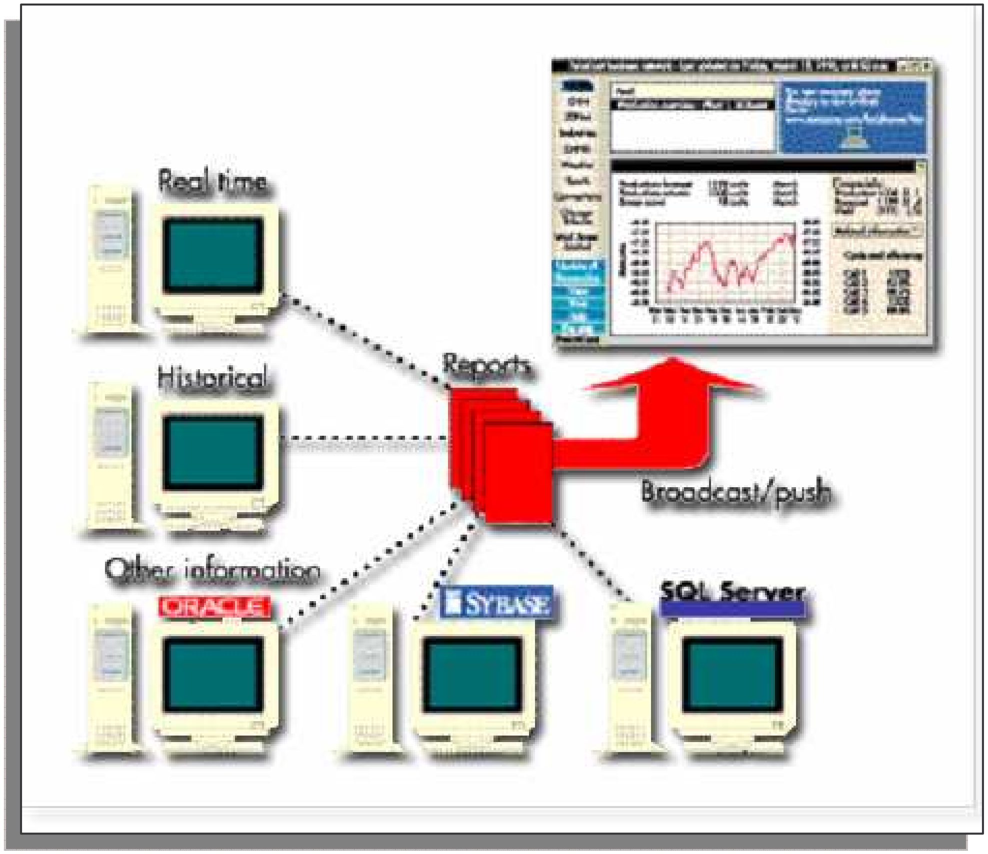
Servers



Plant Floor Architecture
LEVEL 3+
Connected to computers throughout the organization
Plant Information Network
LEVEL 2
Web Services
File Services
Authentication Services
Intranet Server
Database Server
Database Server
Management
File Services
Print Services
Plant Floor Coordination Network
LEVEL 1.5
Plant Floor HMI
Dedicated Operator Interface
Data Collection PC
Gauge
Control Network
LEVEL 1
I/O Network
Dedicated Operator Interface
Drives
Remote I/O
PLC/DCS
Drive Controller

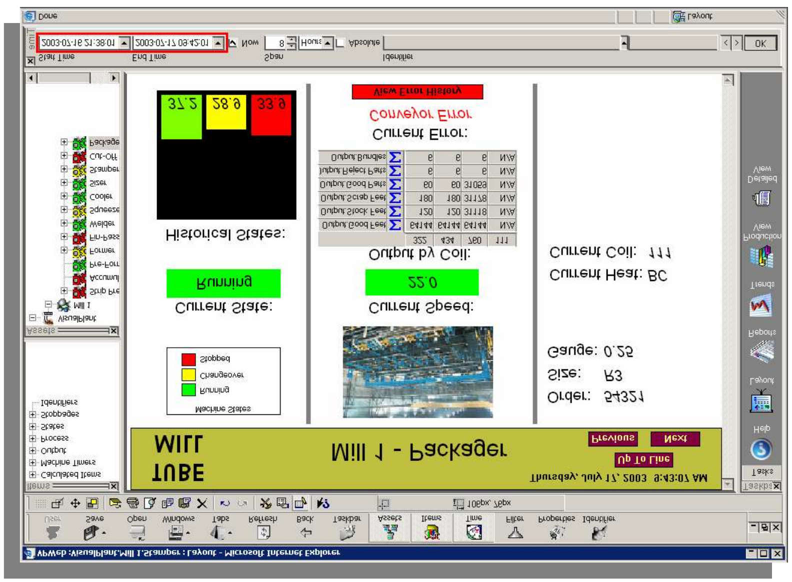
Intranet Technology

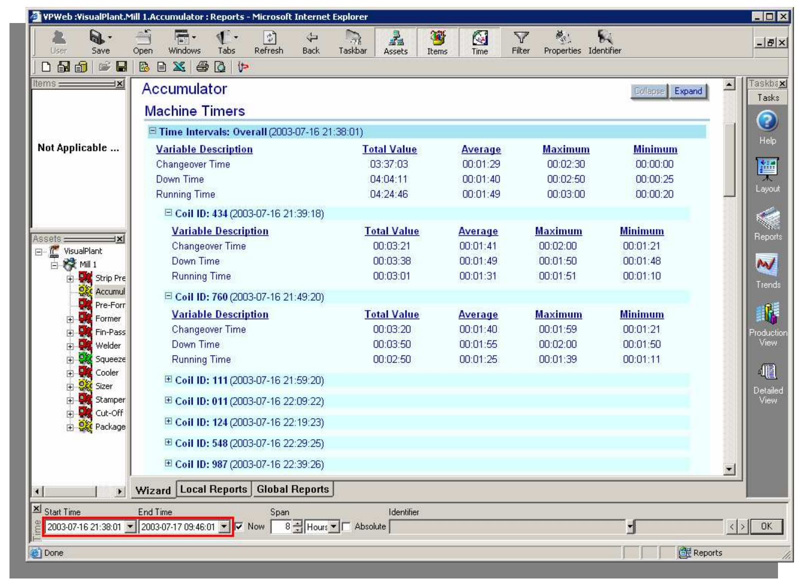
- Pull vs push technology
- Push automatically delivers reports to desktops without having to search for them
- Can be automatically updated
- Reduces (even eliminates) paper reports



Web Monitoring

- Intranet (internal) and Internet (external)
- HMI packages offering web client view-only
- Custom pages and reports with database backend
- Manufacturing Intelligence Tools for data collection repository



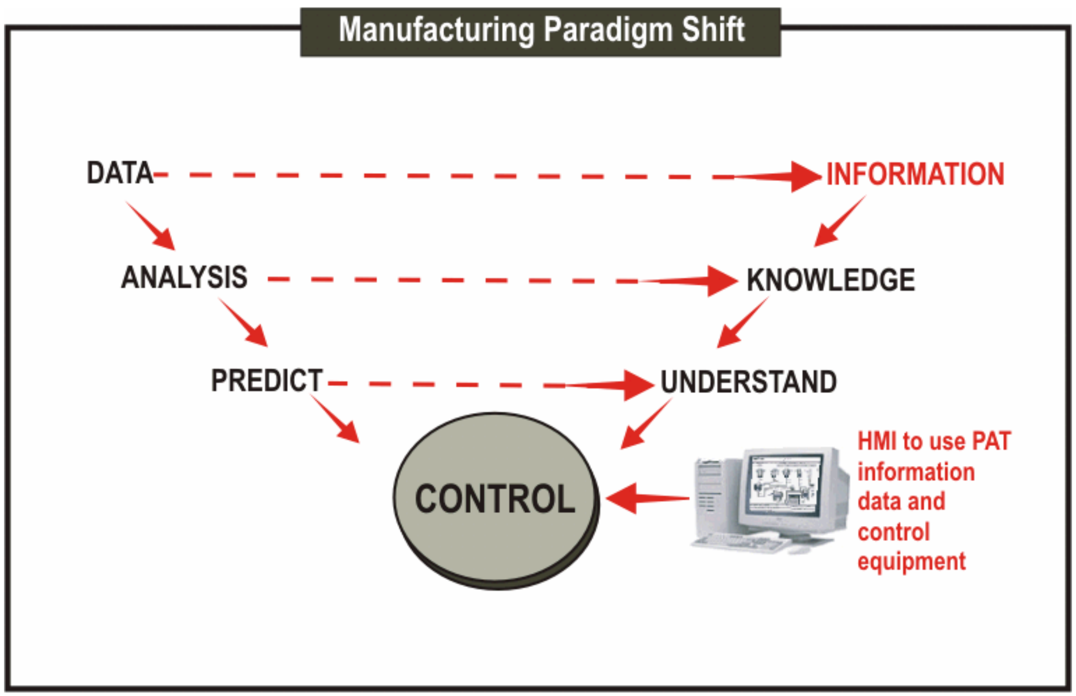


Agenda

- PAT Manufacturing Basics
- Factory Floor Architecture
- Using Information to Control the Manufacturing Process
- HMI for Blender Control Based on Effusivity Control Points

Using Information to Control the Process

- Design Model, Analysis of Data, Control Process



What is Information?

- Is there a Difference Between Data & Information?
  - There is a big difference between "Data" and "Information"
  - Data is points collected from any measuring source
  - Intelligence applied to data becomes Information
  - Information (timely and accurate) is the backbone of every Decision
  - Delaying a Decision is as costly as making the wrong one

What is Information?

- What is Information?
  - To the Operator: process variation or alarm
  - To the Production Supervisor: shift production level
  - To the Department Manager: asset utilization
  - To the Plant Manager: per unit total costs
  - To the CEO: Enterprise competitiveness

- Some of these are are plant floor level controls, some are middle and top floor level Information management.
  - They all come from the same Data.

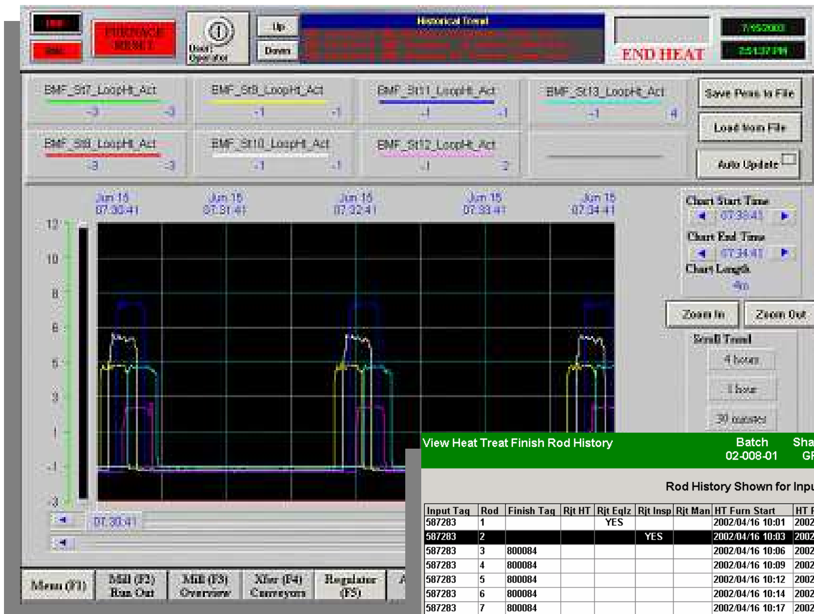
Data to Information

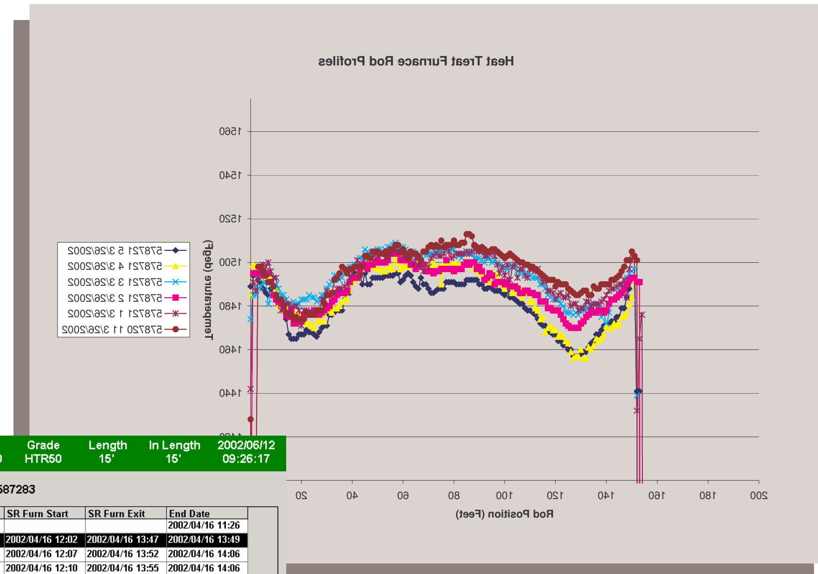
- Data Collection
- Viewing Data
- HMI for Data Viewing & Equipment Control
- Databases

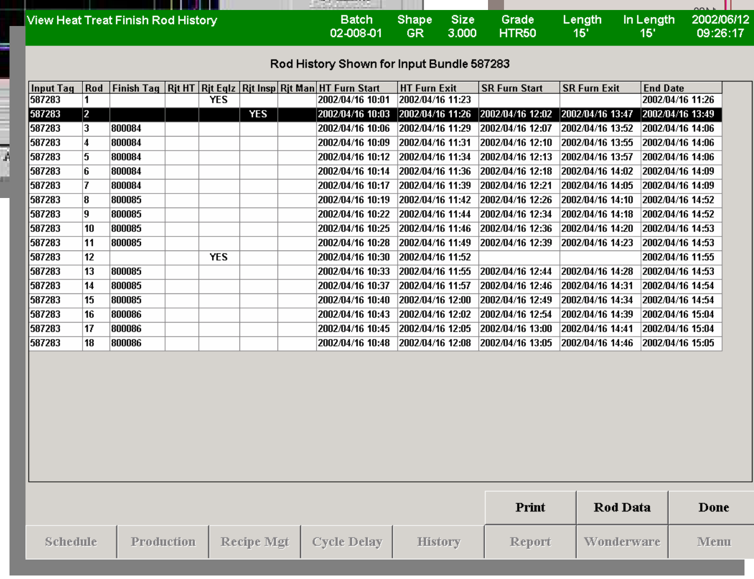
Data Collection

- Multiple Options/Features:
  - Real-time trending in HMI packages
  - Dedicated trending stations/applications
  - Database for long-term storage
  - Level II Information Systems (or MES) for production summary, equipment usage (number of batches)
  - Event (e.g. end-of-batch) vs. Time-Based data
- Speed of collection
- How to view data?
- Who is going to use data and for what? (electronic records)
- How long should data be kept? Archived?

Viewing Data







View Heat Treat Finish Rod History

Batch	Shape	Size	Grade	Length	In Length	2002/06/12
02-008-01	GR	3.000	HTR50	15'	15'	09:26:17

Rod History Shown for Input Bundle 587283

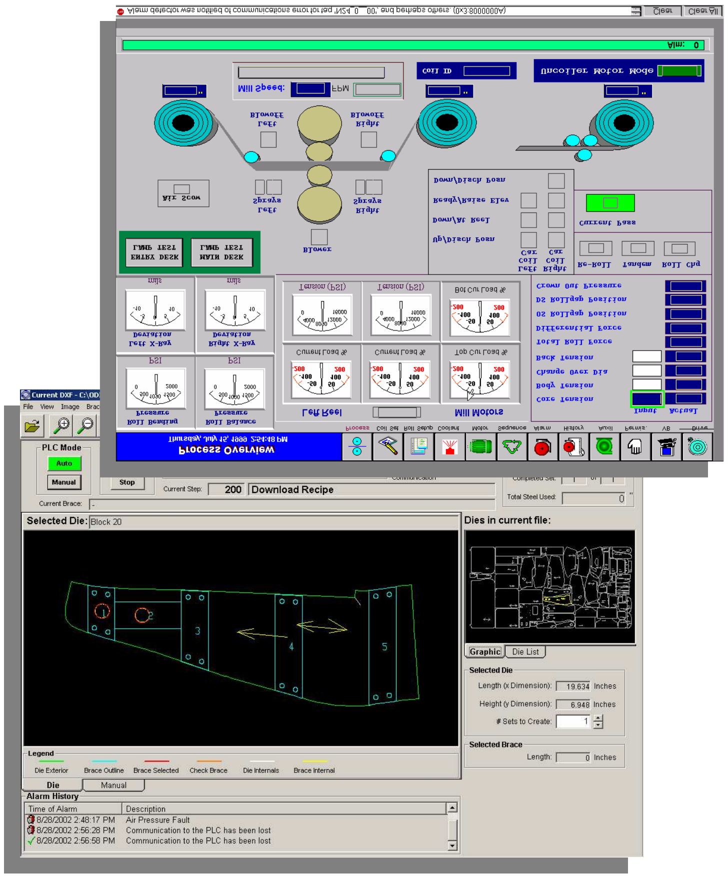
Input Tag	Rod	Finish Tag	Rjt HT	Rjt Eqlz	Rjt Insp	Rjt Man	HT Furn Start	HT Furn Exit	SR Furn Start	SR Furn Exit	End Date
587283	1			YES			2002/04/16 10:01	2002/04/16 11:23			2002/04/16 11:26
587283	2				YES		2002/04/16 10:03	2002/04/16 11:26	2002/04/16 12:02	2002/04/16 13:47	2002/04/16 13:49
587283	3	800084					2002/04/16 10:06	2002/04/16 11:29	2002/04/16 12:07	2002/04/16 13:52	2002/04/16 14:06
587283	4	800084					2002/04/16 10:09	2002/04/16 11:31	2002/04/16 12:10	2002/04/16 13:55	2002/04/16 14:06
587283	5	800084					2002/04/16 10:12	2002/04/16 11:34	2002/04/16 12:13	2002/04/16 13:57	2002/04/16 14:06
587283	6	800084					2002/04/16 10:14	2002/04/16 11:36	2002/04/16 12:18	2002/04/16 14:02	2002/04/16 14:09
587283	7	800084					2002/04/16 10:17	2002/04/16 11:39	2002/04/16 12:21	2002/04/16 14:05	2002/04/16 14:09
587283	8	800085					2002/04/16 10:19	2002/04/16 11:42	2002/04/16 12:26	2002/04/16 14:10	2002/04/16 14:52
587283	9	800085					2002/04/16 10:22	2002/04/16 11:44	2002/04/16 12:34	2002/04/16 14:18	2002/04/16 14:52
587283	10	800085					2002/04/16 10:25	2002/04/16 11:46	2002/04/16 12:36	2002/04/16 14:20	2002/04/16 14:53
587283	11	800085					2002/04/16 10:28	2002/04/16 11:49	2002/04/16 12:39	2002/04/16 14:23	2002/04/16 14:53
587283	12			YES			2002/04/16 10:30	2002/04/16 11:52			2002/04/16 11:55
587283	13	800085					2002/04/16 10:33	2002/04/16 11:55	2002/04/16 12:44	2002/04/16 14:28	2002/04/16 14:53
587283	14	800085					2002/04/16 10:37	2002/04/16 11:57	2002/04/16 12:46	2002/04/16 14:31	2002/04/16 14:54
587283	15	800085					2002/04/16 10:40	2002/04/16 12:00	2002/04/16 12:49	2002/04/16 14:34	2002/04/16 14:54
587283	16	800086					2002/04/16 10:43	2002/04/16 12:02	2002/04/16 12:54	2002/04/16 14:39	2002/04/16 15:04
587283	17	800086					2002/04/16 10:45	2002/04/16 12:05	2002/04/16 13:00	2002/04/16 14:41	2002/04/16 15:04
587283	18	800086					2002/04/16 10:48	2002/04/16 12:08	2002/04/16 13:05	2002/04/16 14:46	2002/04/16 15:05

Print | Rod Data | Done

Schedule | Production | Recipe Mgt | Cycle Delay | History | Report | Wonderware | Menu

HMI Design Options

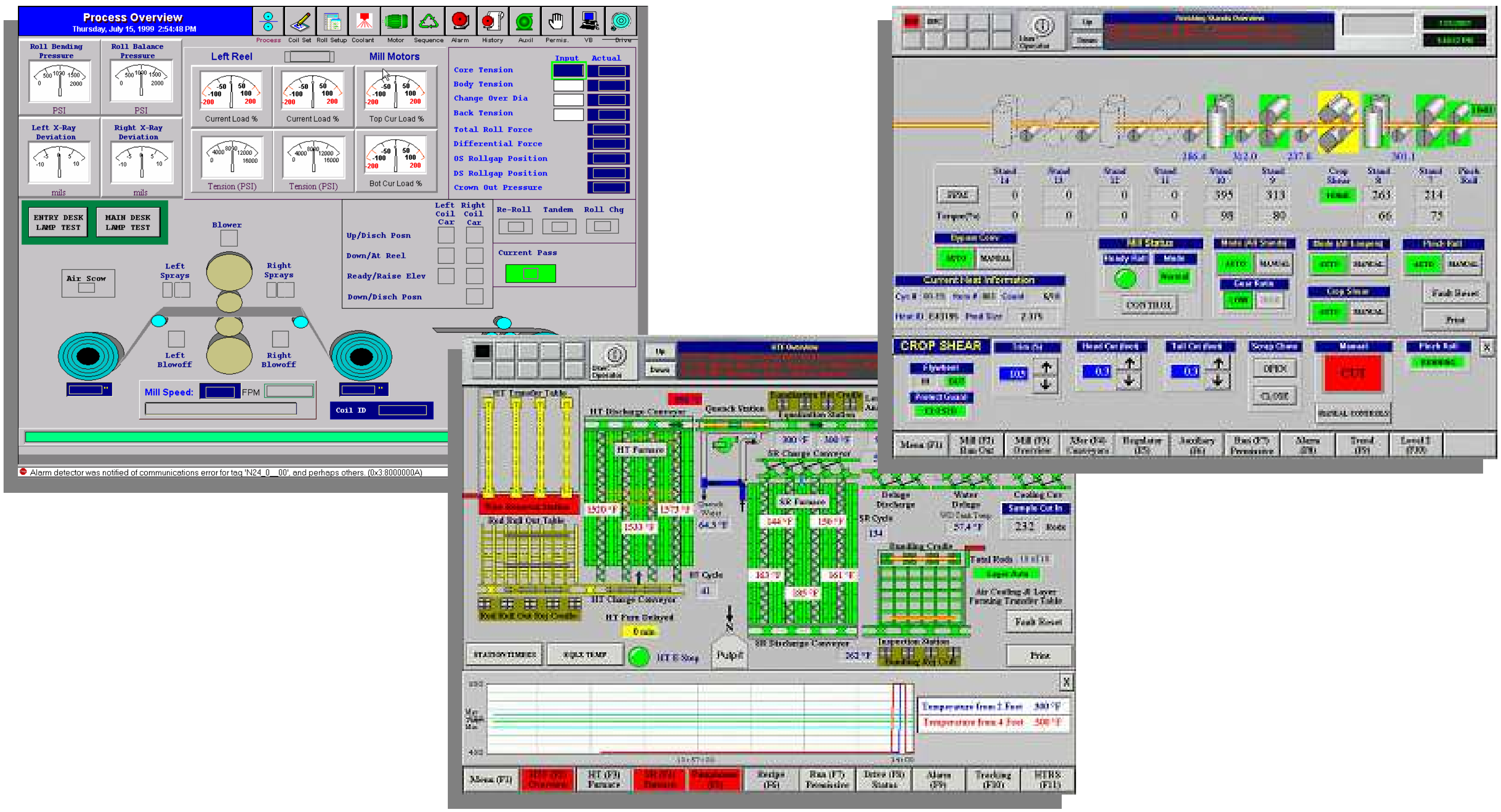
- “Off the shelf” 3rd Party Tools
  - Considered as the norm for HMI
- Custom HMI Programs
  - More exotic solutions
- Combination
  - Often solution implemented



HMI Features

- GUI (graphical user interface)
- Process Status
- Operator Control
- Logging/annunciating of alarms/events
- Trending capabilities
- Scripting
- Recipes
- Database interface
- Web enabling

HMI Screens


Process Overview
Left Reel
Mill Motors
Core Tension
Body Tension
Change Over Dia
Back Tension
Total Roll Force
Differential Force
OS Rollgap Position
DS Rollgap Position
Crown Out Pressure
Mill Speed:
CROP SHEAR

System Feedback - Alarms

- It is important to provide **COMPLETE** system feedback to operators and maintenance personnel.
- Feedback that should be provided includes:
  - **Fault Information** - Each device should have a fault alarm if is fails to operate when commanded or is unavailable.
  - **Interlock Information** - When an interlock is required relative to system operation or an operator command, an alarm should be generated so that the reason for system non-operation is known.
  - **Shutdown Events** - All events that causes a system shutdown must generate an alarm. This includes events that are tripped by inputs or initiated internally by logic such as conflicting modes of operation.
  - **Override Controls** - If system operational overrides have by-passes, there should be a warning alarm to indicate when they are set.

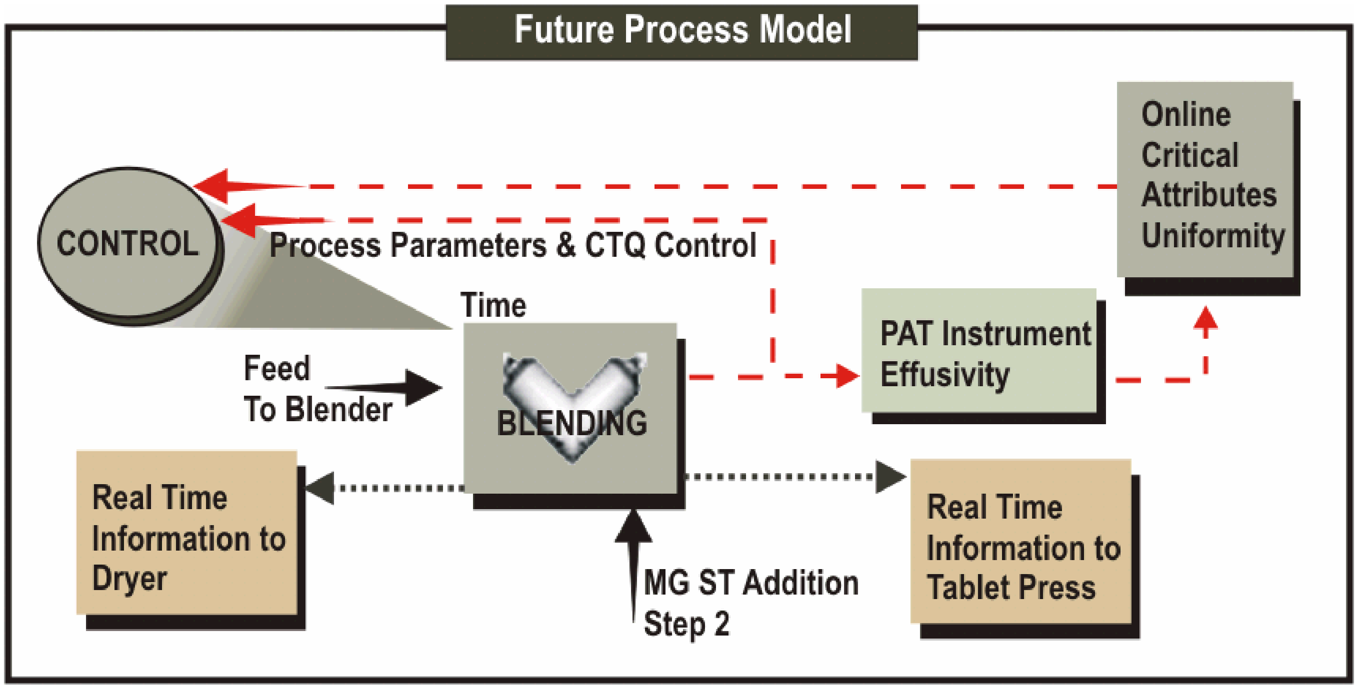
Database

- Large collection of data
  - Numerical, text, images, sound, video
- Efficient at storing numerical / text data
- Organize data in two-dimensional tables tied together using common attributes (known as keys) – Relational Database
- Design Considerations
  - Scalability – ability to manage further growth
  - Performance – triggers, stored procedures, condensing data
  - Interfaces – ODBC, OLE-DB, native drivers, SQL, XML
  - Availability – replication of data, backup and recovery

Agenda

- PAT Manufacturing Basics
- Factory Floor Architecture
- Using Information to Control the Manufacturing Process
- HMI for Blender Control Based on Effusivity Control Points

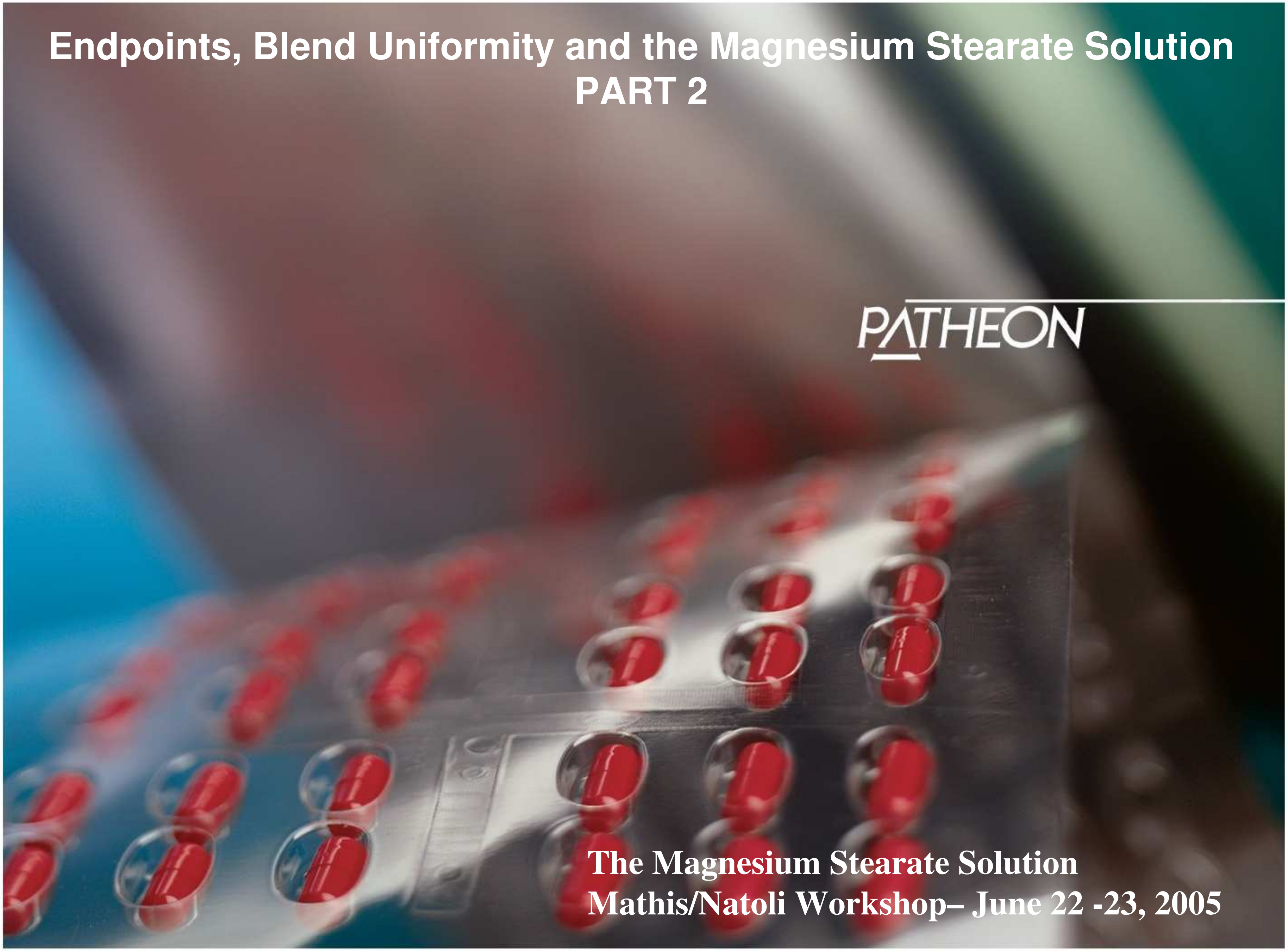
Effusivity Manufacturing Example



Feedforward control setting to tablet press
Feedback to the dryer on output material CTQ attributes

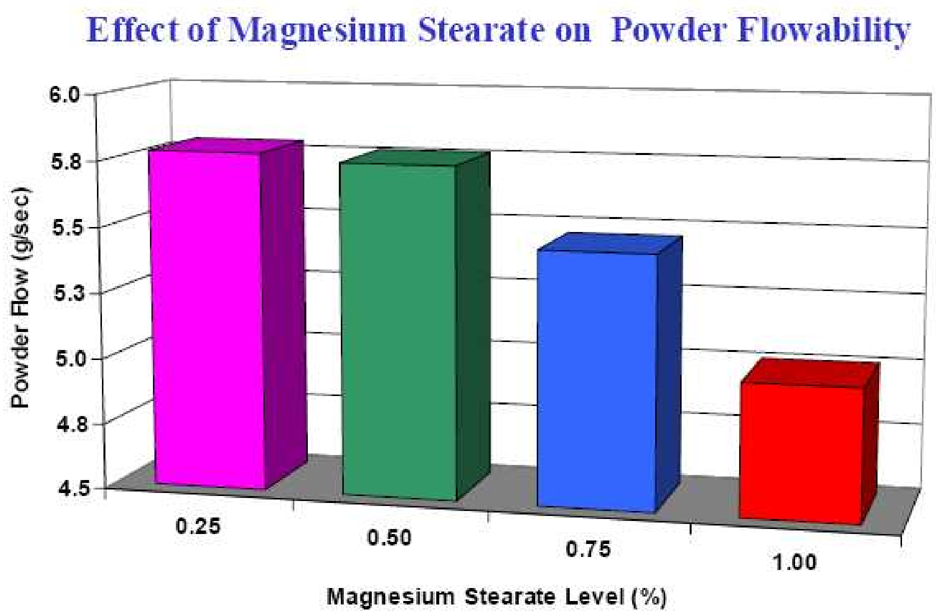
Effusivity HMI

- Screen shot of HMI or run a CD demo


Endpoints, Blend Uniformity and the Magnesium Stearate Solution
PART 2
PATHEON
The Magnesium Stearate Solution
Mathis/Natoli Workshop– June 22 -23, 2005

Mg Stearate and Powder Flow

- Magnesium Stearate has no effect on powder flow??
- FALSE… it negatively affects as % used increases



*Graphs in slide 2-6 courtesy of Colorcon "Optimizing Lubricant Usage in Direct Compression Hydrochlorothiazide Formulation containing a Plastically Deforming Excipients", Cunningham et al.

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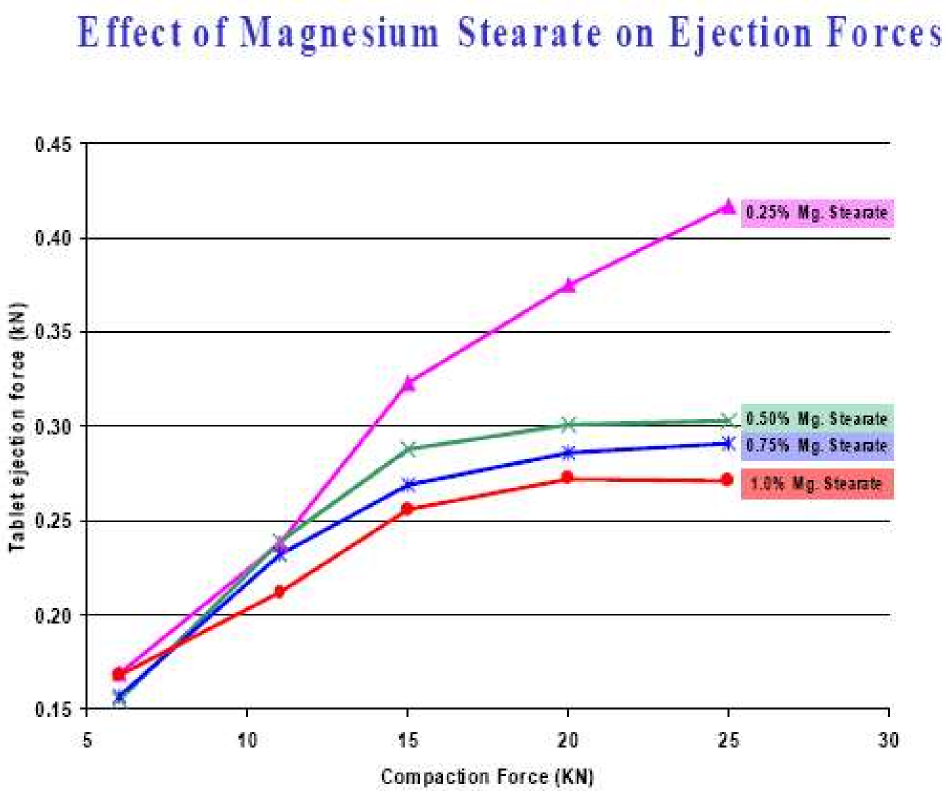
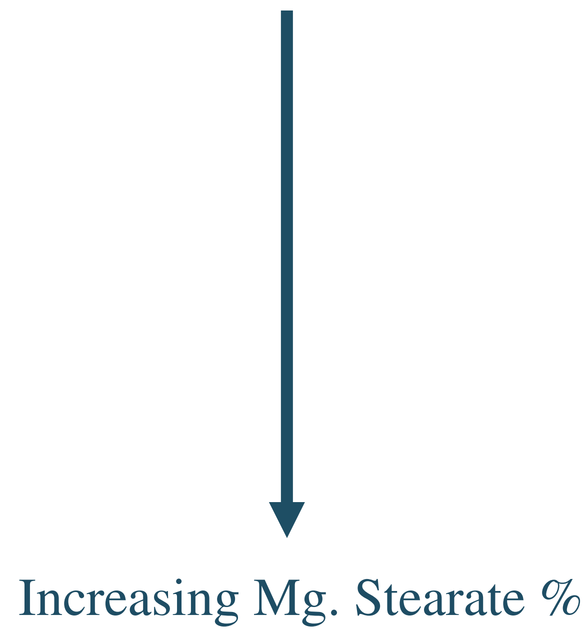
Mg Stearate and Ejection Force

- The more Magnesium Stearate the lower the ejection force??
- FALSE… beyond a certain quantity, increases in Magnesium Stearate have little effect on ejection force





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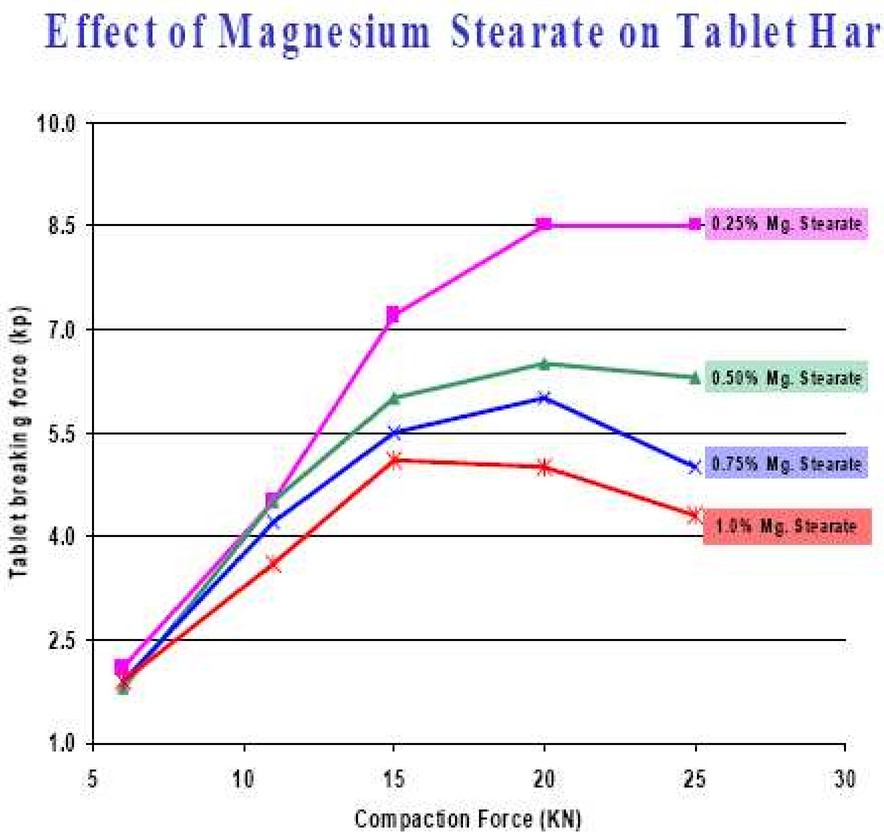
Mg Stearate and Tablet Hardness

- Magnesium Stearate affects Tablet Hardness??
- TRUE… increasing % leads to softening of tablets



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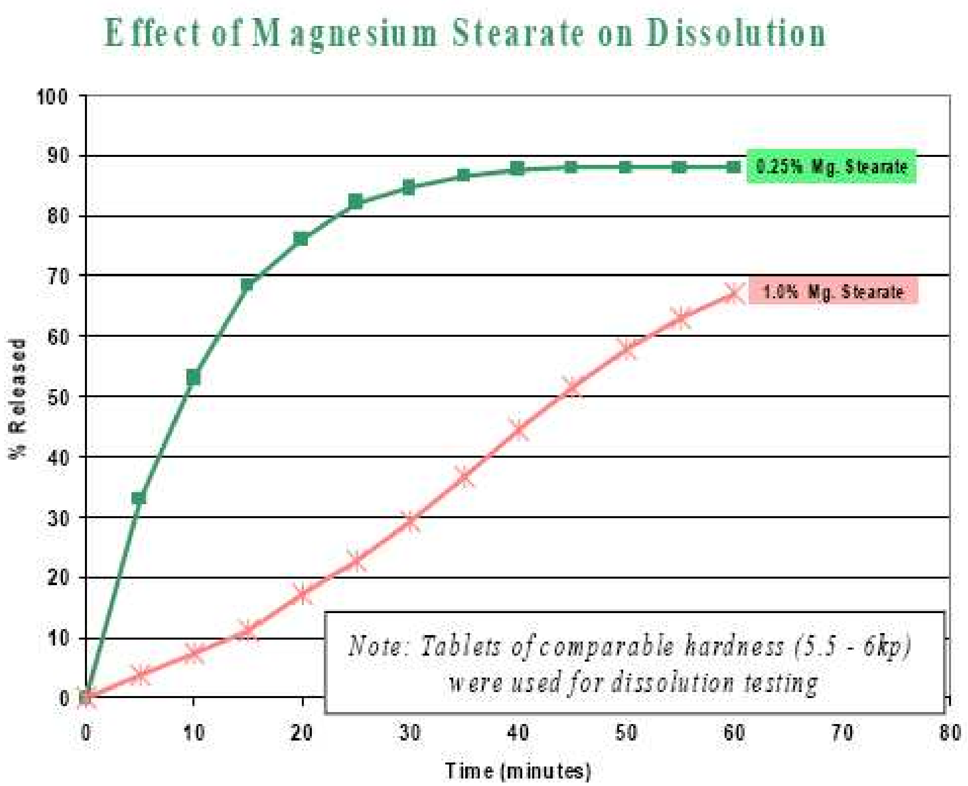
Mg Stearate and Dissolution

- Magnesium Stearate has an effect on dissolution??
- TRUE……..it can negatively affect our release profile
- A manufacturers biggest fear!!!



Increasing Mg. Stearate %

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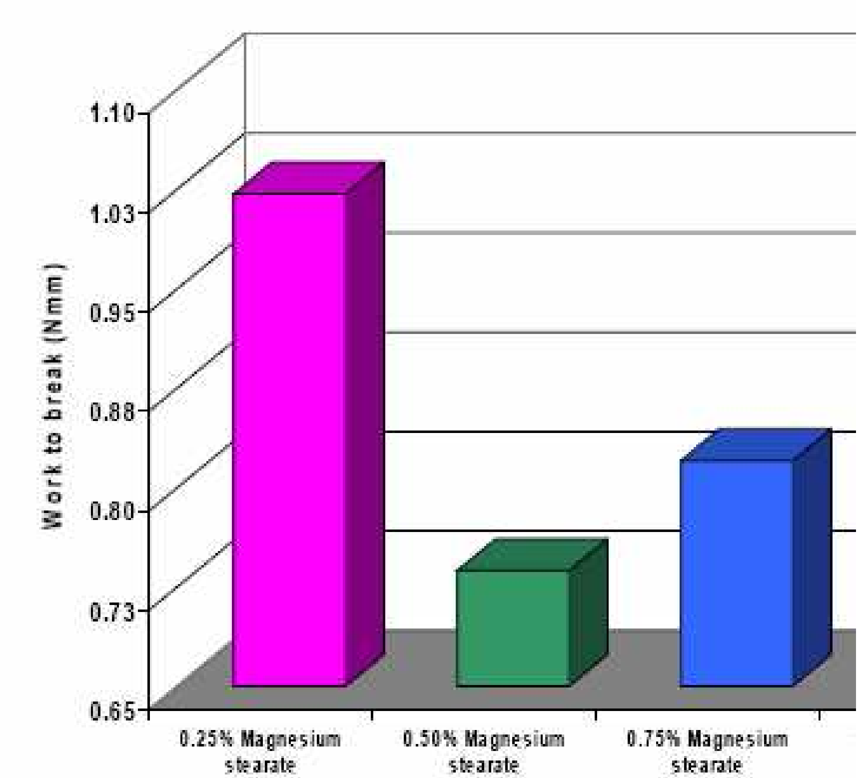
Mg Stearate and Film Adhesion

- Magnesium Stearate affects tablet film adhesion during coating??
- TRUE…increasing levels of Magnesium Stearate decrease film adhesion

Effect of Magnesium Stearate on Film Adhesion



Increasing Mg. Stearate %

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Optimal Region - Isolube

Mg%	Time	kp	Ejection (lbs/force)	Friability	Dis. (seconds)	Effusivity delta	Desirability
0.2	10.74	9.58	7.58667	0.106	75.0019	-1.95427	0.849
0.3	8.86	9.36	7.75148	0.139	74.9998	-1.83289	0.830
0.4	6.98	9.22	7.9163	0.155	74.9263	-1.71371	0.814
0.5	5.1	9.17	8.08111	0.154	75.0011	-1.58995	0.717
0.6	3.22	9.19	8.24593	0.138	75.0008	-1.46851	0.705
0.66	2.09	9.24	8.34481	0.120	75.0002	-1.39566	0.700

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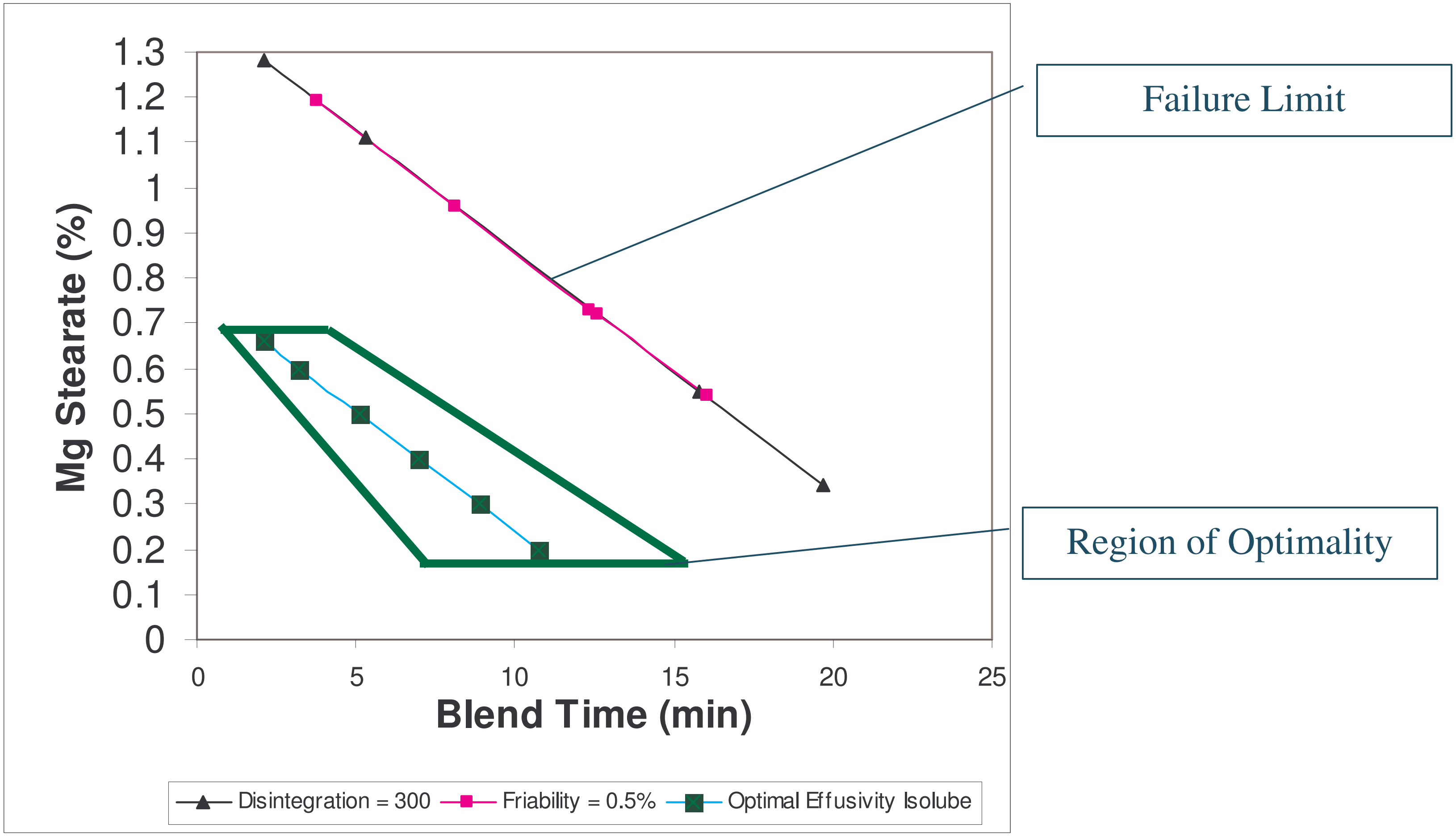
Process Window



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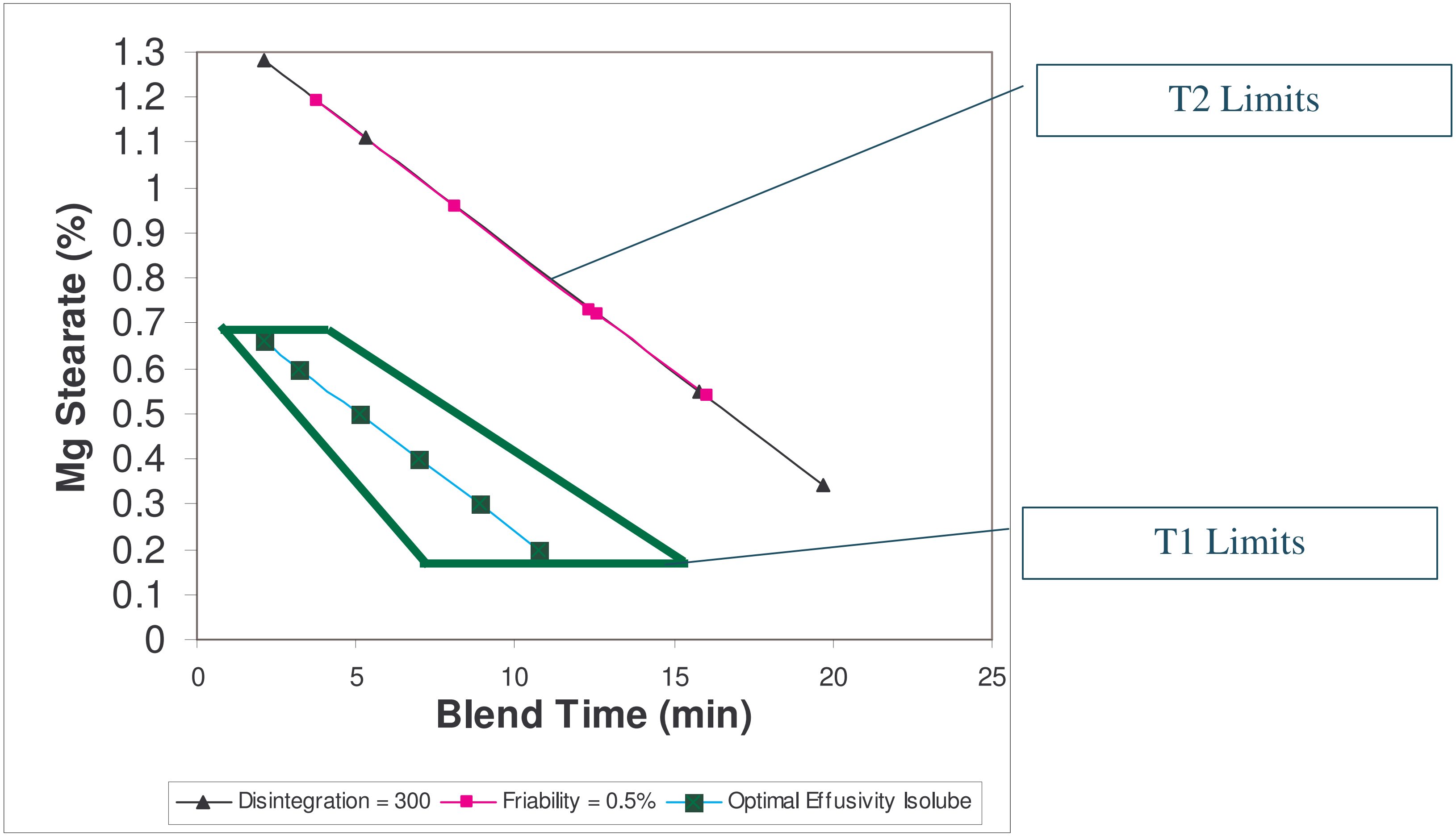
Continuous Processing Window



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