8TH ANNUAL PTI TRAINING PROGRAM

FORMULATION AND PROCESS DEVELOPMENT FOR ORAL DOSAGE FORMS

A 5-Day Modular and Case Study Oriented Training Program

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

Historical Location, Reputable Speakers & Innovative Program

Module 7: FILM COATING

PHARMACEUTICAL COATING TECHNOLOGY

Overview of Pharmaceutical Coating

Linda Felton, Ph.D.

Chair, Pharmaceutical Sciences Department

Associate Professor of Pharmaceutics

University of New Mexico

College of Pharmacy

Outline

- **Introduction**
- **Overview of the film coating process**
- **Critical properties in film coating processes**
  - Aqueous solubility, permeability, mechanical strength, adhesion, stability
- **Factors influencing coating performance**
  - Coating formulation
  - Substrate characteristics
  - Processing parameters

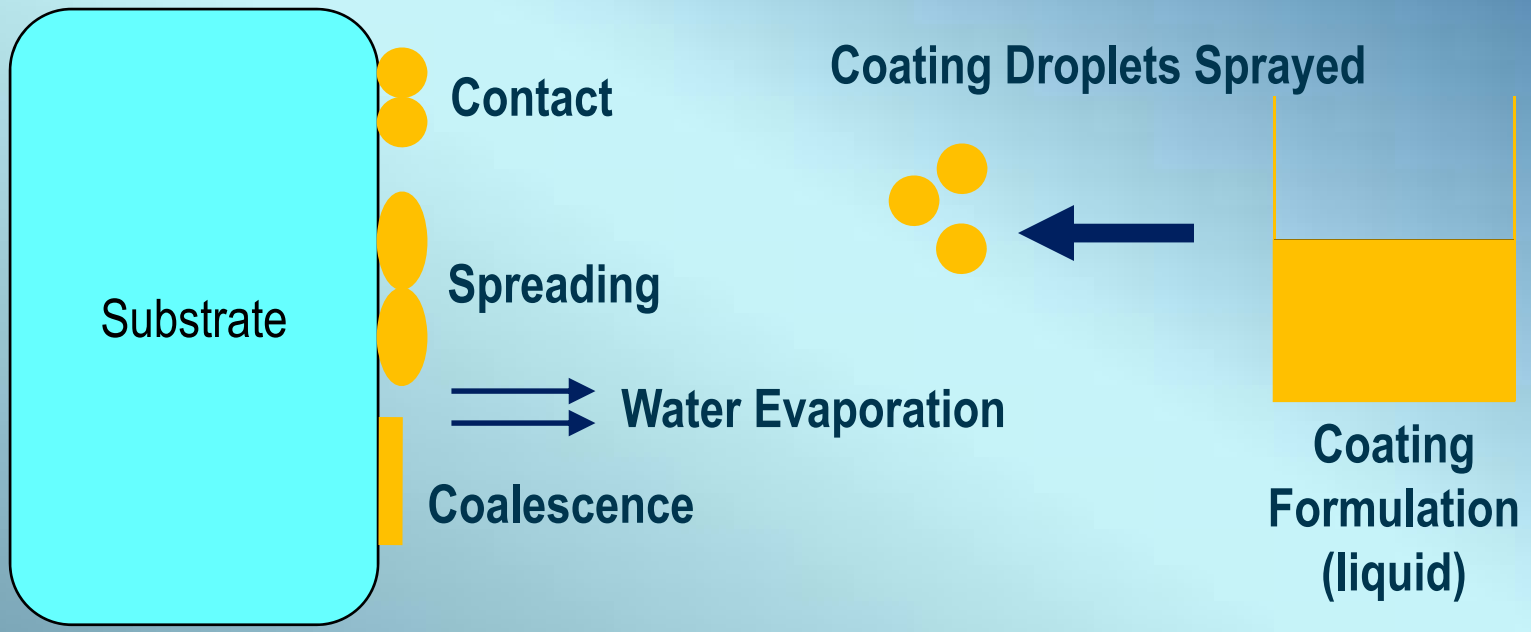
Reasons for Film Coating

- Improve appearance
- Enhance mechanical strength
- Protect from environmental factors
- Mask taste or odor
- Prevent inadvertent contact with active
- Facilitate swallowing
- Alter release characteristics

Disadvantages of Film Coating

- **Additional manufacturing step**
  - Increased costs in raw materials, time, QA
- **Substrate must be mechanically strong to withstand processing**
- **Possible damage to the substrate**
  - Abrasion
  - Surface erosion
- **Potential interactions between the coating and the substrate**

Overview of Film Coating



Substrate Variables

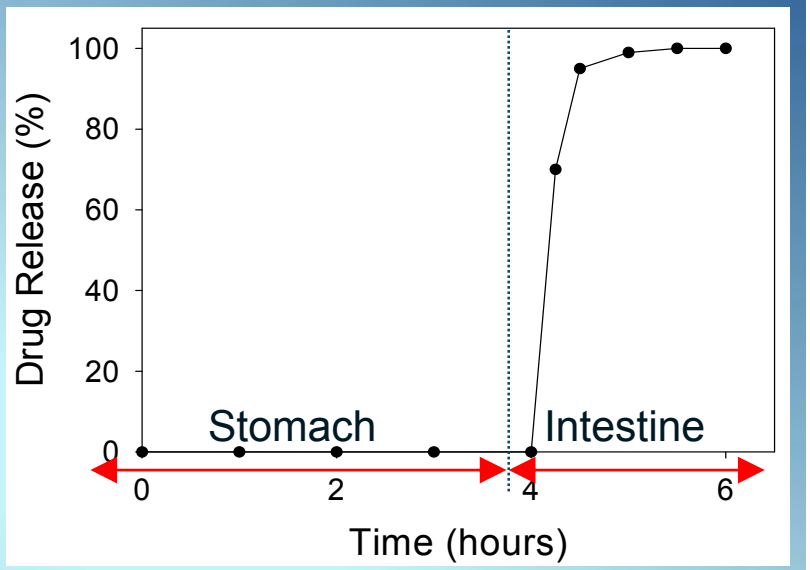
Processing Variables

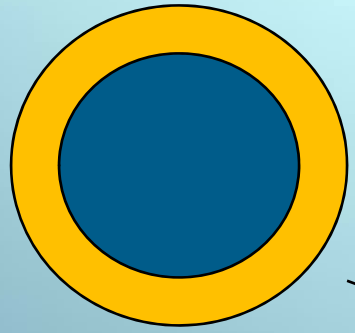
Coating Variables

Water Soluble Polymers

- Improve appearance
- Enhance mechanical strength
- Protect from environmental factors
- Mask taste or odor
- Prevent inadvertent contact with active
- Facilitate swallowing
- Not used to alter release kinetics
- Examples
  - HPMC, HPC, Polyvinyl alcohol

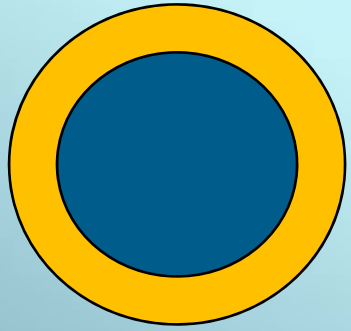
pH Dependent Solubility (Enteric/Colonic)





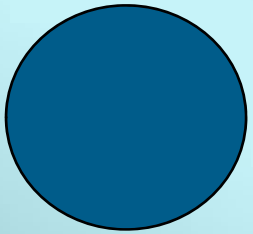
Coated tablet

Acidic pH



Coating intact

More basic pH



Coating dissolves; Core exposed

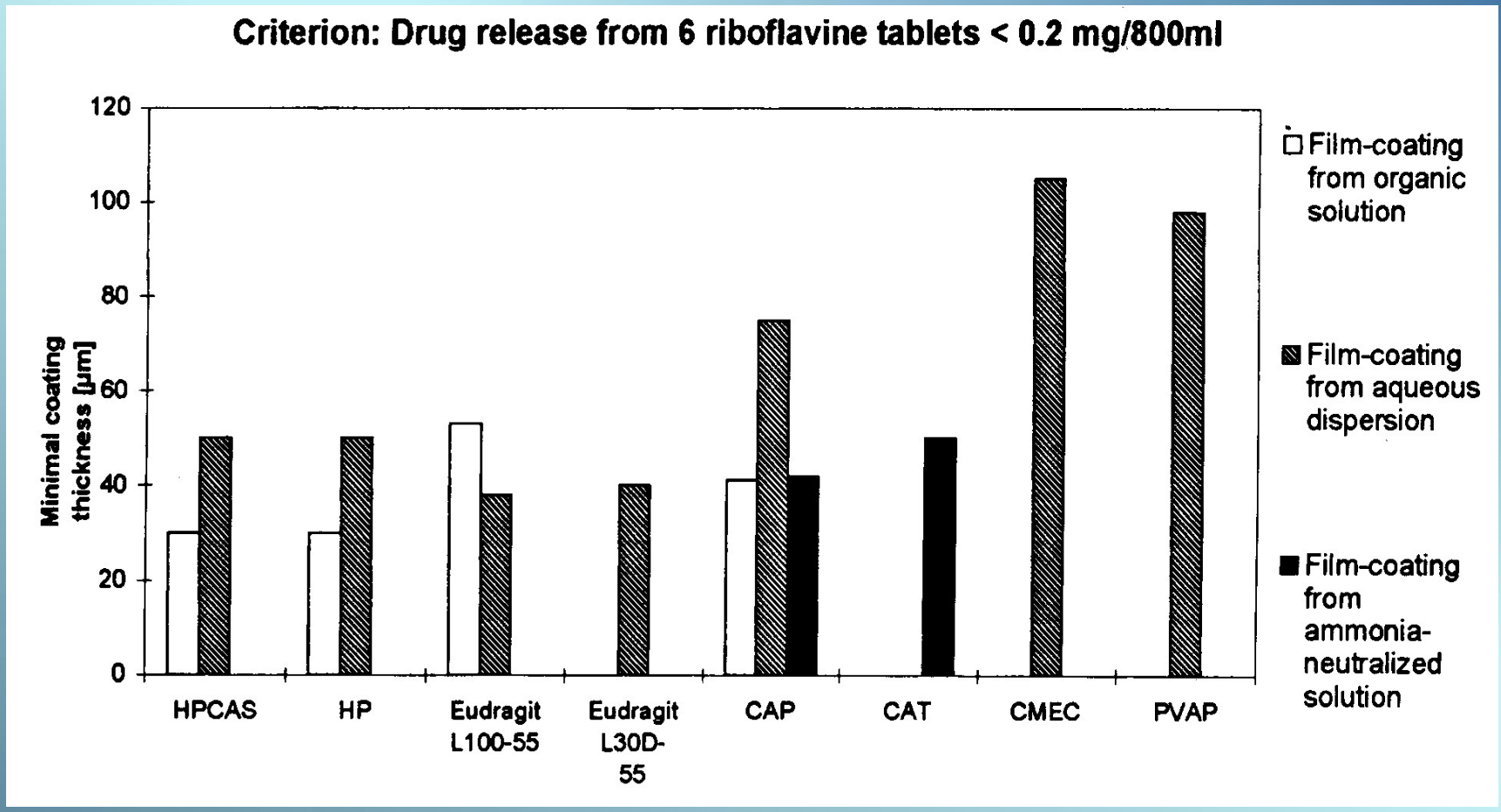
Examples:

-Phthalate derivatives [Aquacoat (CAP), Sureteric (PVAP)]

-Hydroxypropyl methylcellulose acetate succinate (AQOAT, HPMCAS)

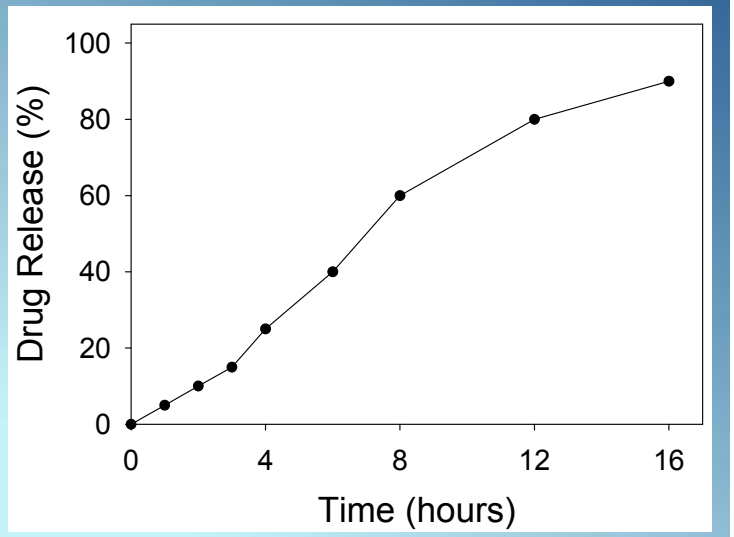
-Methacrylic acid-ethyl acrylate copolymers (Eudragit L30D55)

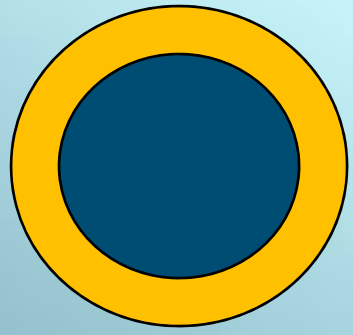
Minimum Coating Thickness for Various Enteric Polymers



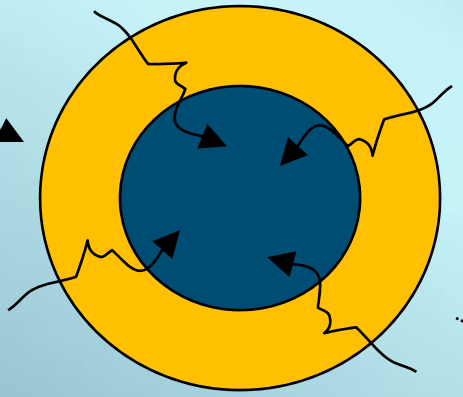
Thoma and Bechtold, Eur J Pharm Biopharm, 1999

Water-Insoluble Polymers (Sustained Release)

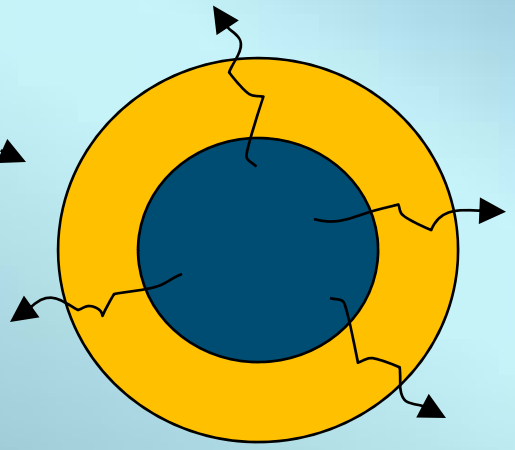




Coated tablet



Water diffuses in and drug dissolves



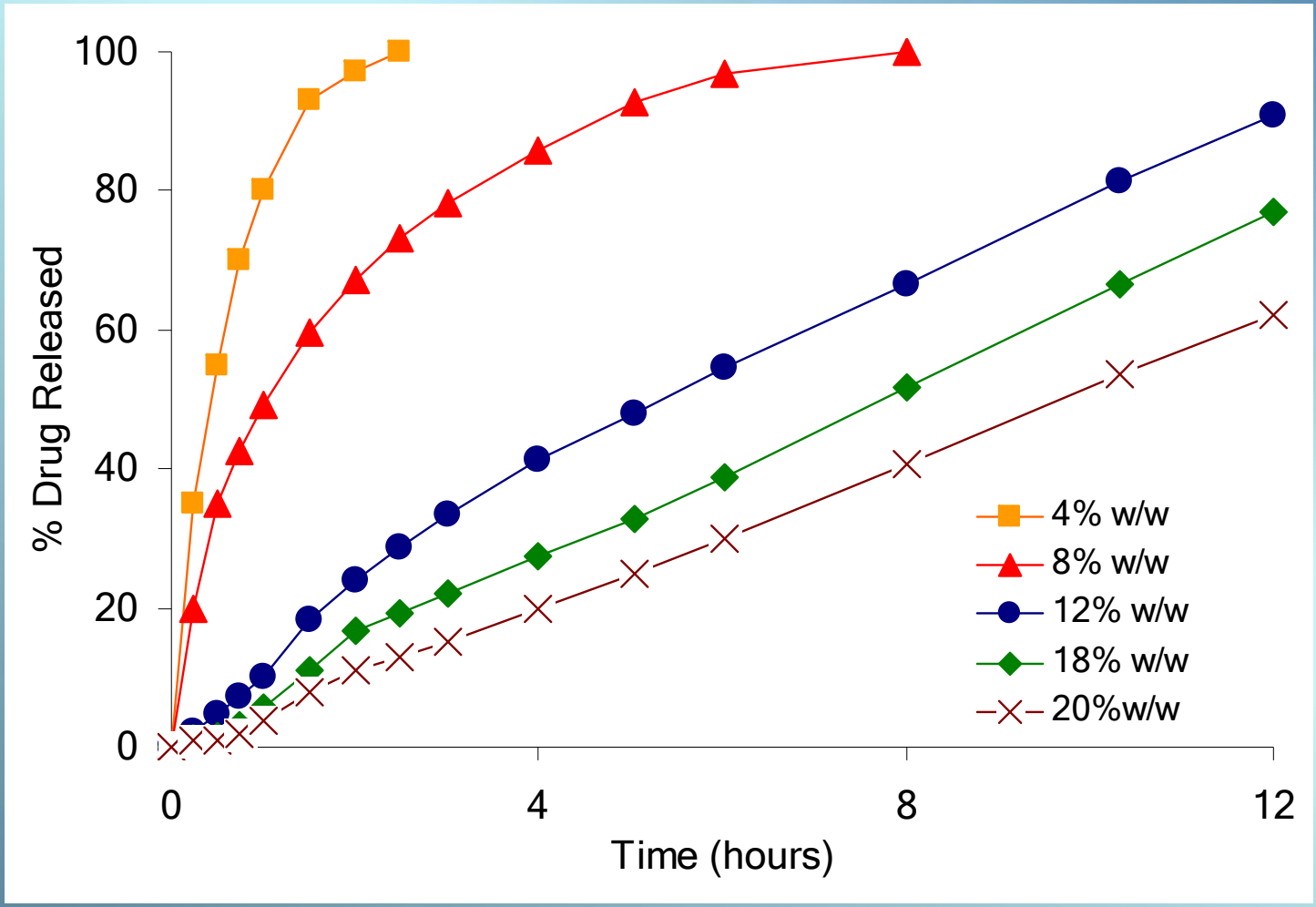
Drug diffuses out

Examples:

- -Ethyl Cellulose
- -Polymethacrylates with quaternary ammonia groups
- -Polyvinyl acetate

Polymer Thickness Influences Release

Chlorpheniramine maleate beads coated with Surelease®



Rajabi-Siahboomi and Farrell, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

Amount of Coating to be Applied

- Theoretical weight gain

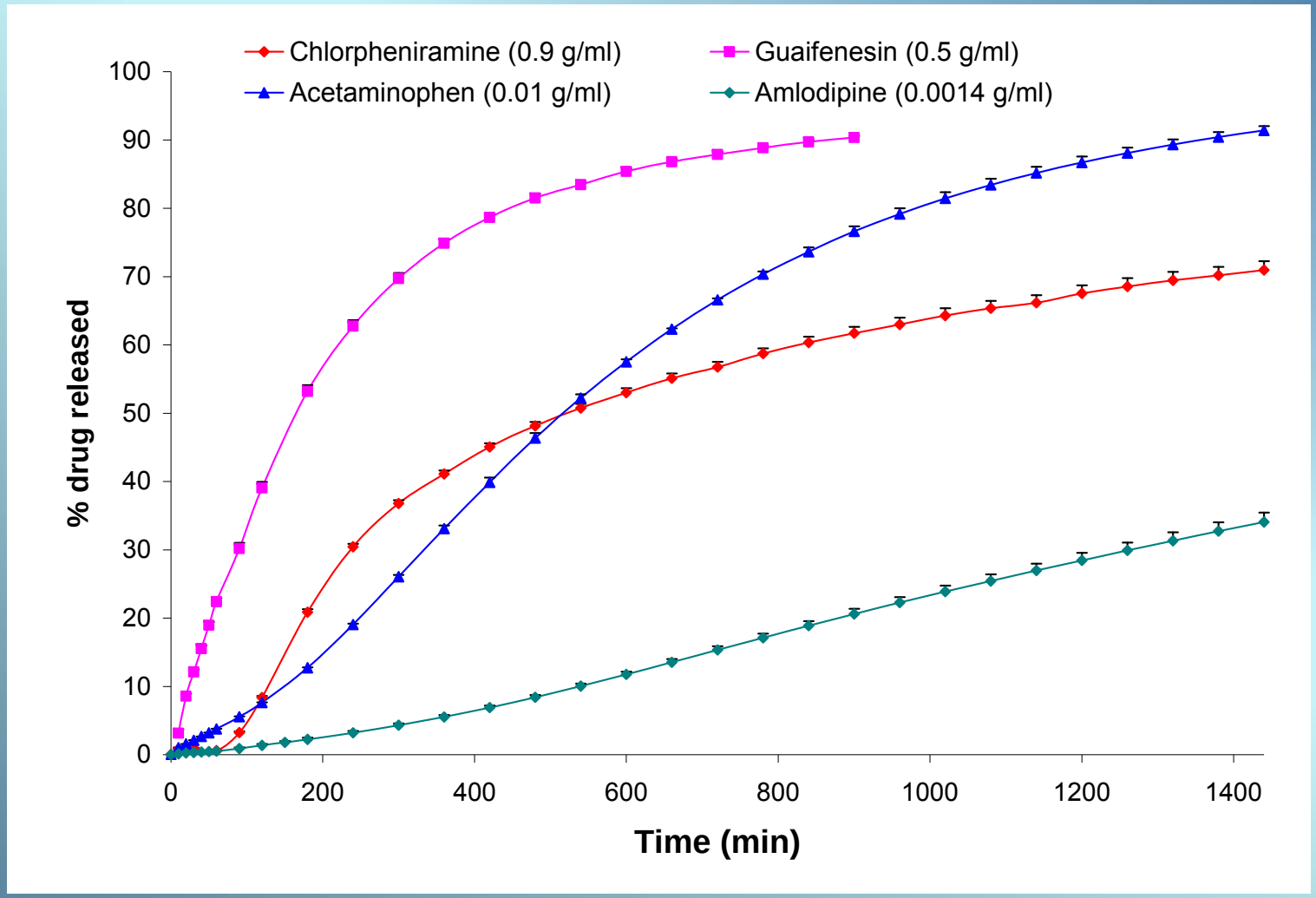
$$g\ (\text{dry polymer}) = \text{Batch Size (g)}\ x\ \text{Desired Weight Gain (\%)}$$

- Desired film thickness

$$g\ (\text{dry polymer}) = \frac{\text{Film thickness (mg/cm}^2)\ x\ \text{Batch (g)}\ x\ \text{Surface Area (mm}^2)}{100{,}000\ x\ \text{Tablet Weight (g)}}$$

Drug Release Influenced by API Solubility

Drug release from beads coated with 16% (w/w) Surelease®

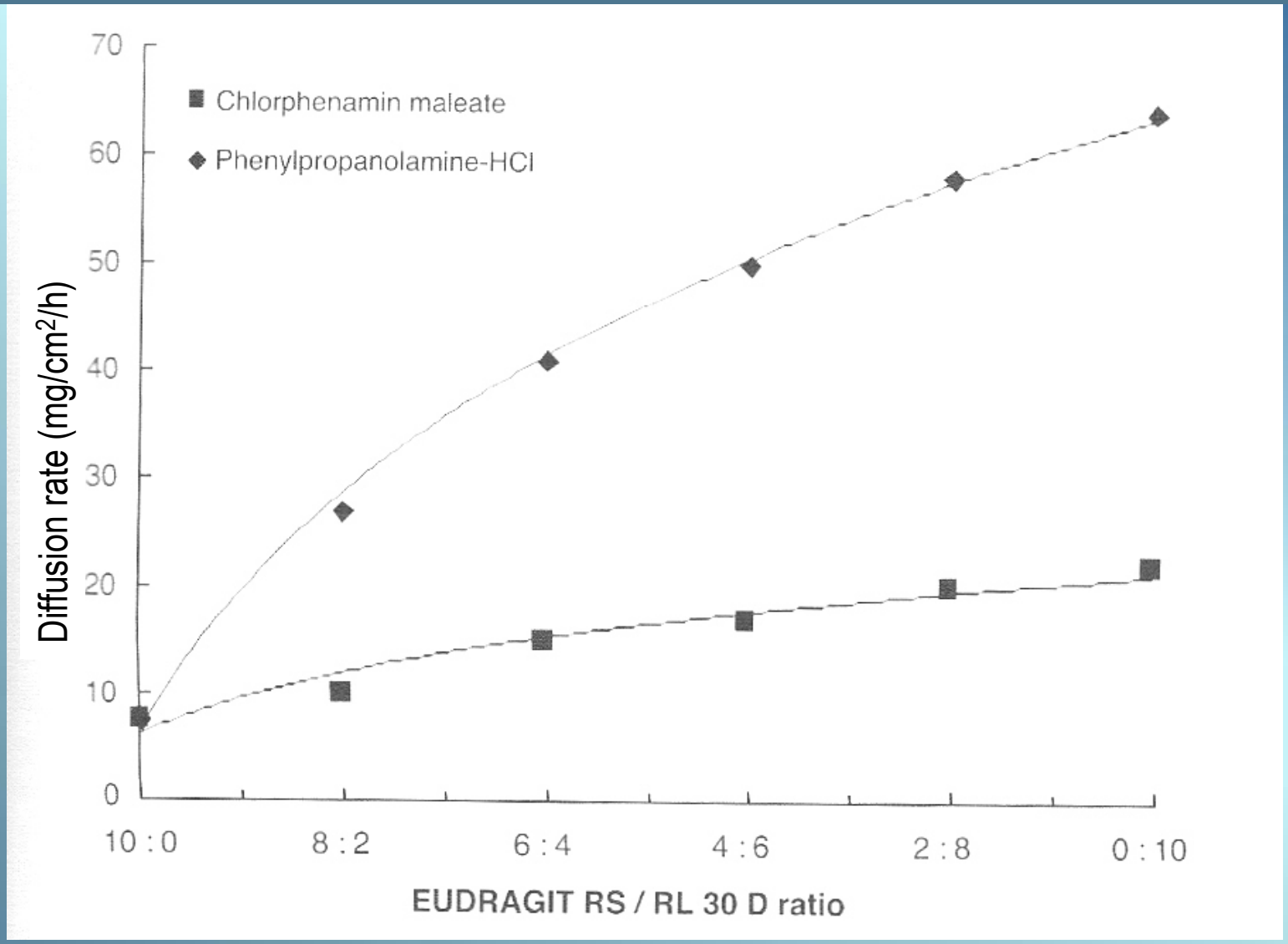


Rajabi-Siahboomi and Farrell, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

Polymer Blends to Achieve Desired Release

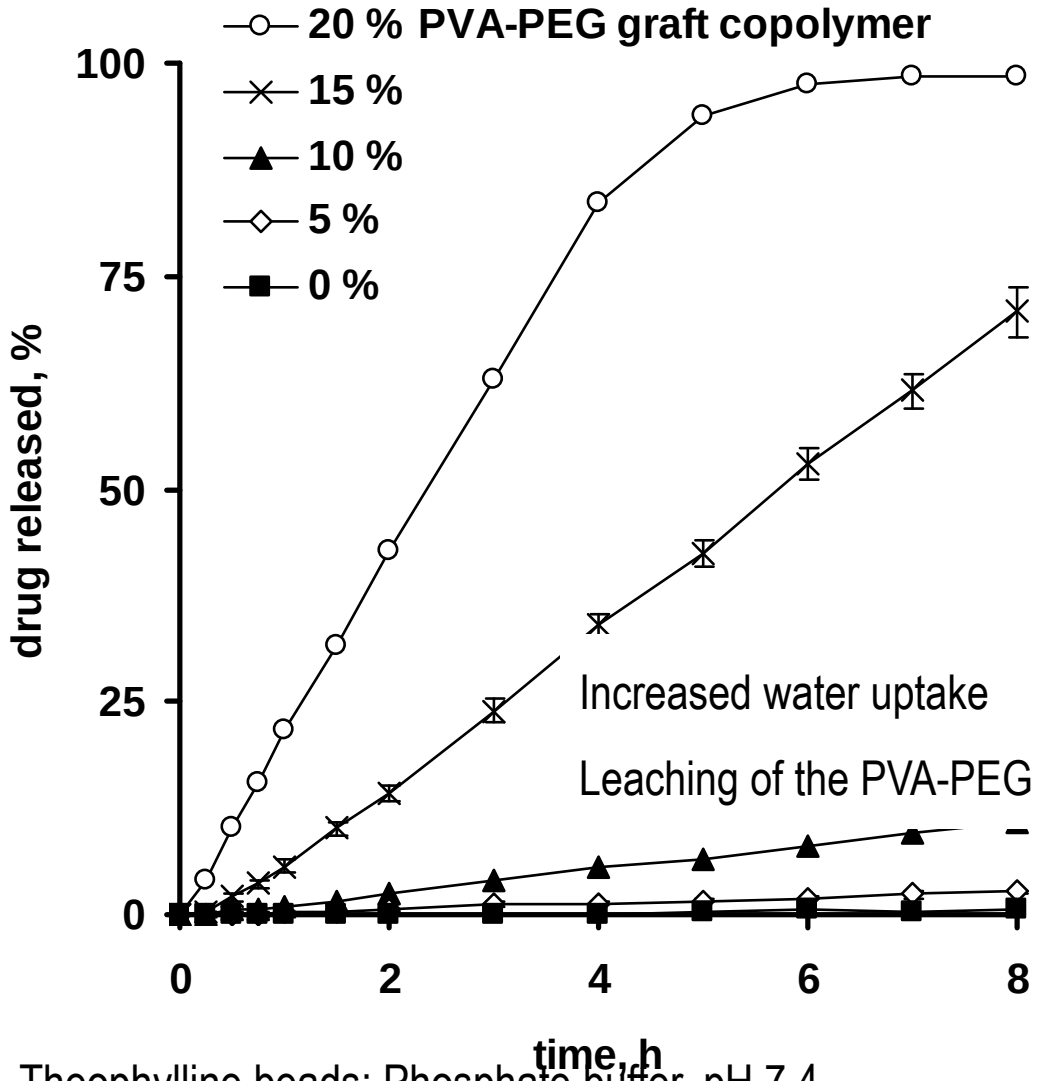
- **Combinations of polymers to modify film permeability**
- **Add water soluble polymers to form pores**
- **SR and enteric polymer**
  - Enteric polymer dissolves at high to pH create pores
  - pH-independent release of weak bases
    - Increased permeability compensates for lower solubility at higher pH

Blend of Eudragit RS and RL Polymers to Alter Permeability



Skalsky and Petereit, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Informa, 2008

PVA-PEG as a Pore Former in Aquacoat Films



Theophylline beads; Phosphate buffer, pH 7.4

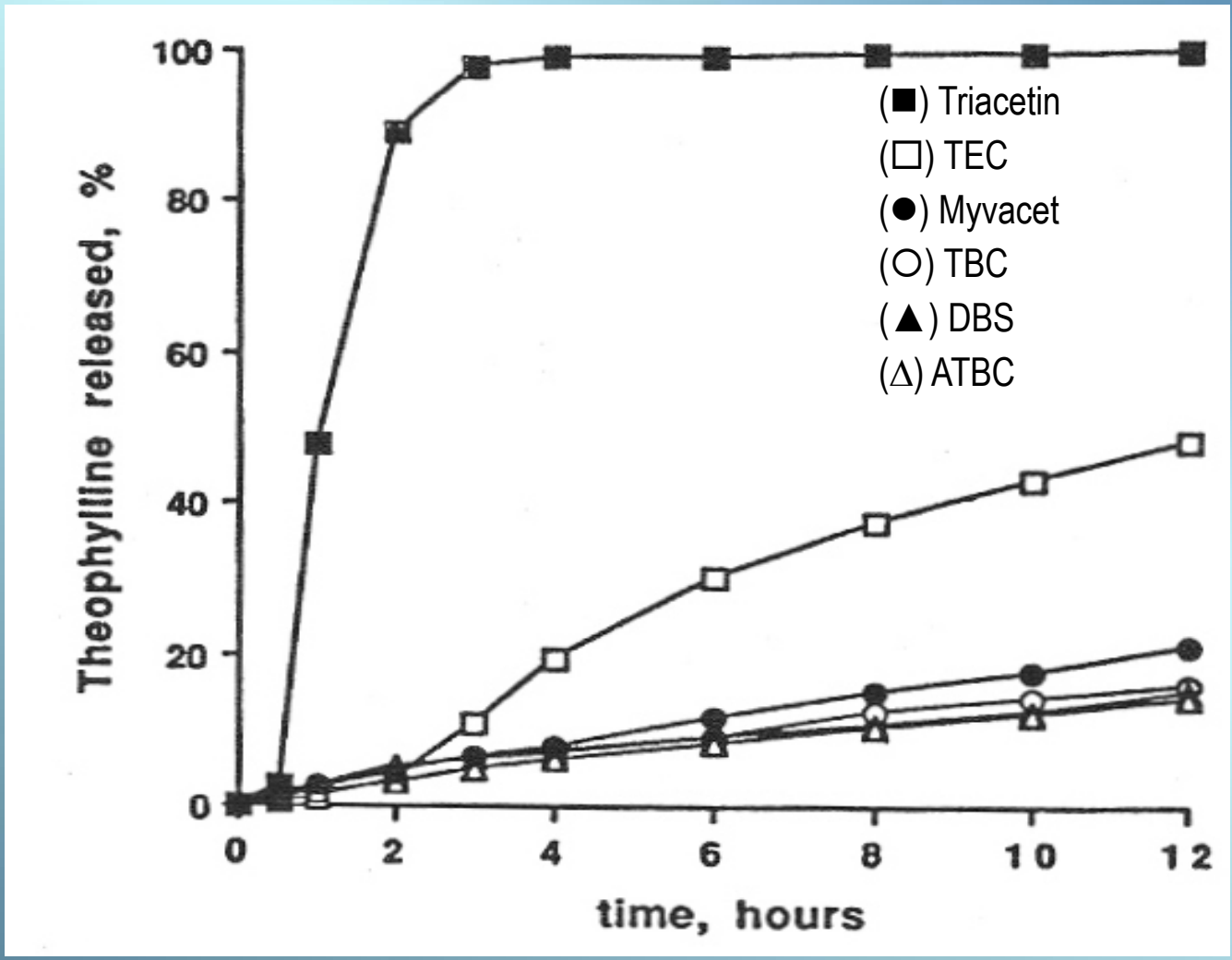
Siepmann et al, J. Control. Rel,. 2007

Plasticizers

- Reduce intermolecular attractions between polymer chains
- Reduce brittleness
- Impart flexibility
- Decrease tensile strength
- Lower glass transition temperature
- Influence drug release

Plasticizer Type Influences Drug Release

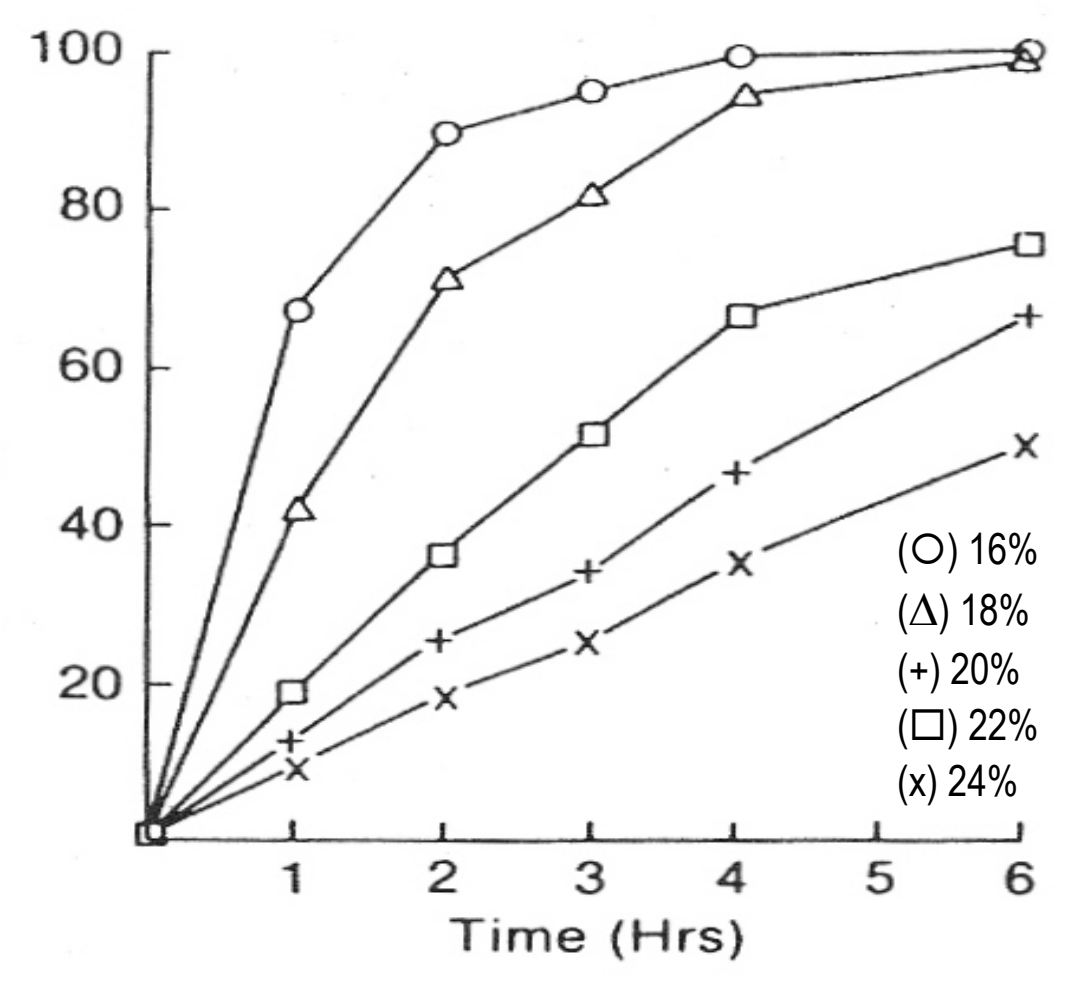
Aquacoat ECD coated on theophylline beads

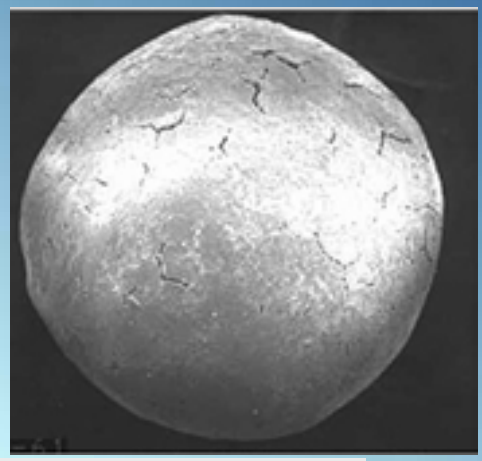


Siepmann et al., Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

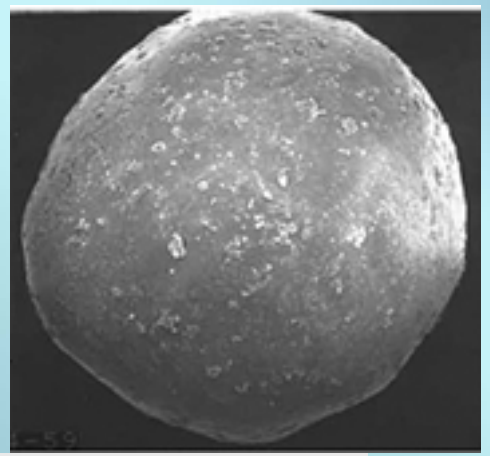
Plasticizer Concentration Influences Drug Release

6% Aquacoat ECD coated onto theophylline beads





16% DBS



24% DBS

Carlin, Li, and Felton, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

Theories on Plasticization

- **Lubrication theory**
  - Internal lubricant that facilitates chain movement
- **Gel theory**
  - Cleave intermolecular bonds within a 3-D gel (polymer)
- **Free volume theory**
  - Increase free space around polymer chains

Common Plasticizers

- **Citrate esters**
  - Triethyl citrate, acetyl triethyl citrate, tributyl citrate
- **Glycol derivatives**
  - Polyethylene glycols, propylene glycol
- **Phthalate esters**
  - Diethyl phthalate, dibutyl phthalate
- **Sebecate esters**
  - Dibutyl sebecate, dimethyl sebecate
- **Fatty acid esters**
  - Glycerol monostearate, stearyl alcohol

Criteria for Plasticizers

- **Permanence in film**
  - Exhibit little/no tendency for evaporation or volatilization
- **Partitioning of plasticizer into polymer**
  - Dependent on aqueous solubility and affinity to polymer
  - Allow sufficient time for uptake
- **Compatibility with polymer (Miscibility)**
  - Solubility parameters

Predict Polymer-Plasticizer Miscibility

- For miscibility, $\Delta\delta \leq 3$

	Solubility Parameter $(J/cm^3)^{1/2}$	Tg (°C)
Eudragit L100–55[1]	23.0	~100
Triethyl Citrate[1]	21.1	35.9 (2.5)
Triacetin[2]	21.0	37.9 (2.2)
Tributyl Citrate[1]	19.5	48.5 (3.5)

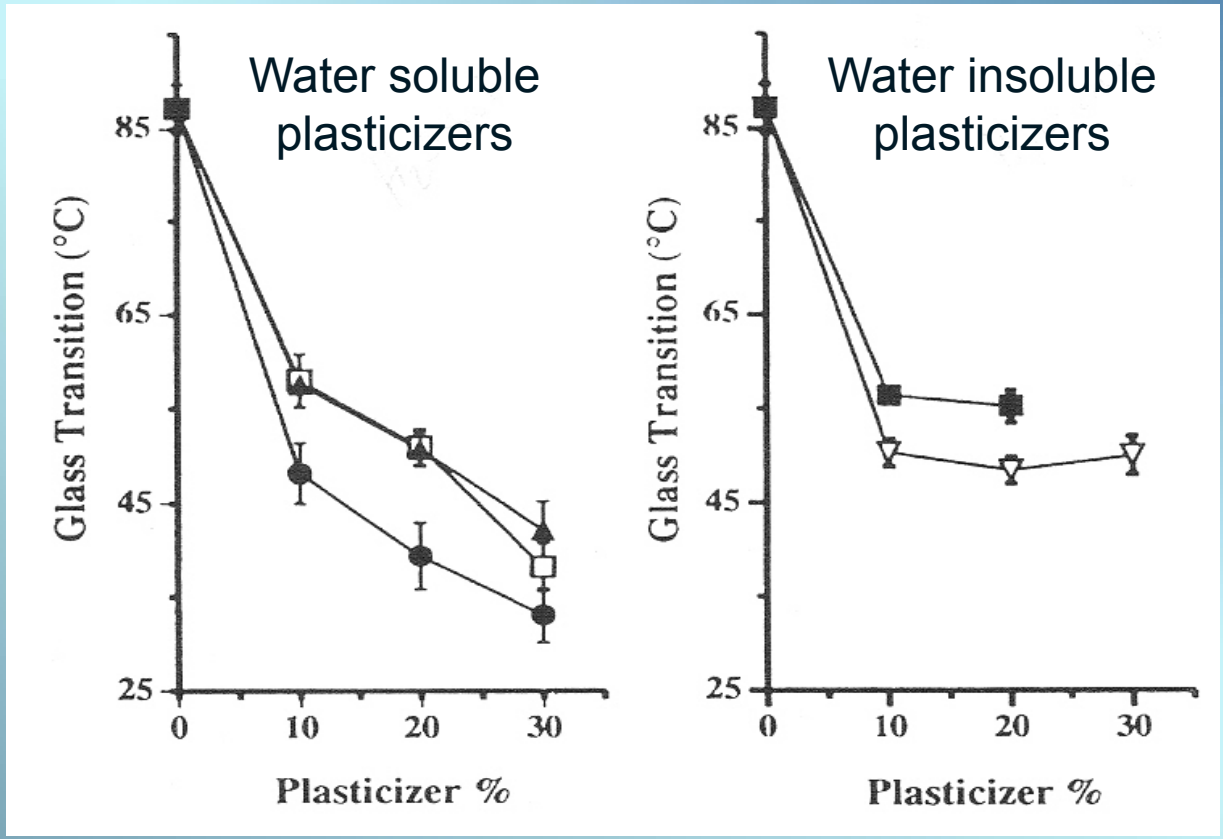
[1]Calculated by Van Krevelen method
[2]CRC Handbook of solubility parameters

Felton, et al., STP Pharma Sci., 1997

Glass Transition Temperature (Tg)

- **Temperature at which a polymer changes from brittle to rubber state**
  - T > Tg, polymer becomes soft and elastic
    - Related to an increase in free volume
    - More space available for molecular movement
- **Increase in Tg related to**
  - Restriction in mobility of the polymer chains
    - Tg used to quantify effectiveness of plasticizers
  - Increase in crystallinity of the polymer

Tg to Evaluate Polymer–Plasticizer Interactions



Effect of different levels of plasticizers on the Tg of Eudragit L100-55 films

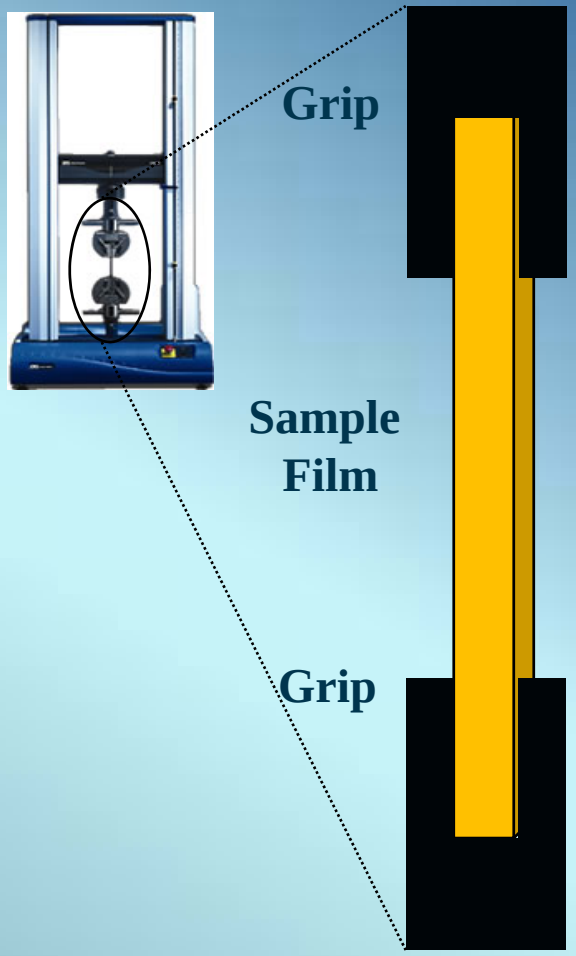
60 days at 23C/50%RH followed by 30 days at 23C/0%RH

(●) TRI; (□) TEC; (▲) ATEC; (▽) TBC; (■) ATBC

Gutierrez-Rocca and McGinity, Int. J. Pharm., 103, 1994

Tensile Testing

- Free films cut into strips
- Film placed in grips
- Stretched at specified rate
- Record force and displacement
- At least 5 replicates per sample
- Constant temperature and humidity
- Discard if film slips or fractures at grips



Stress–Strain Analysis

- Convert data to stress and strain

  Stress = Applied force ÷ initial cross-sectional area of the film (MPa)

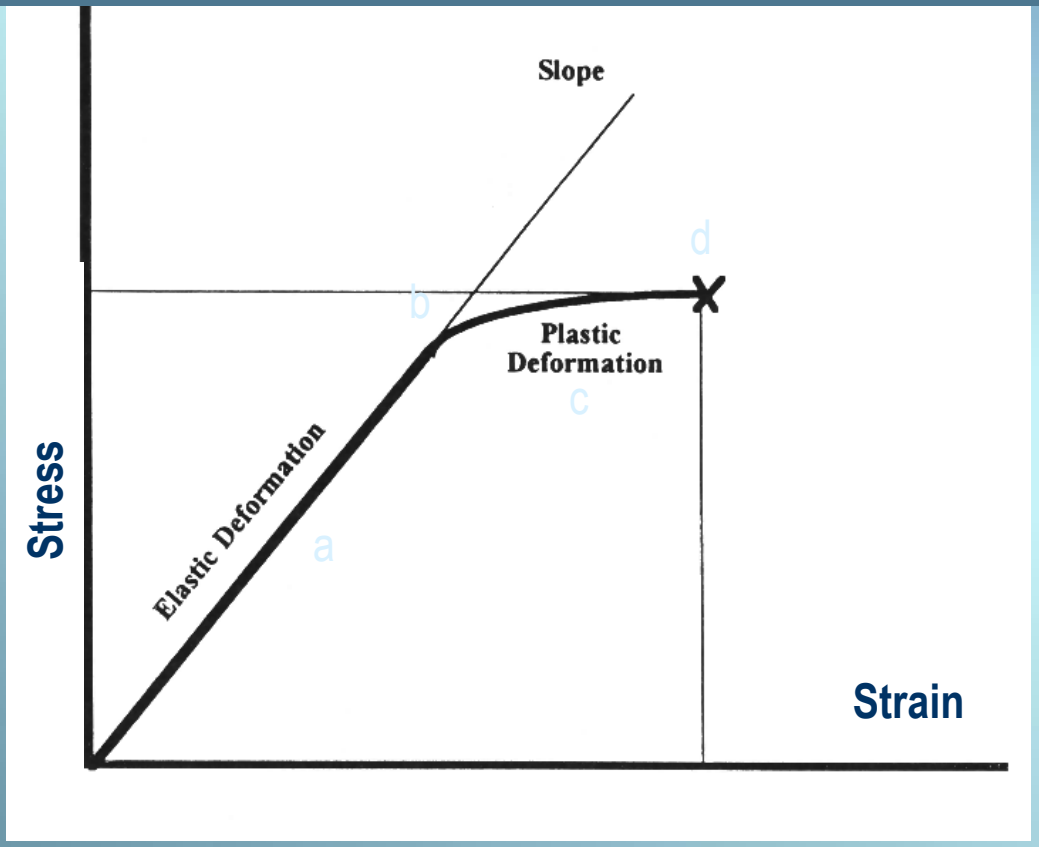
  - Measure of film strength

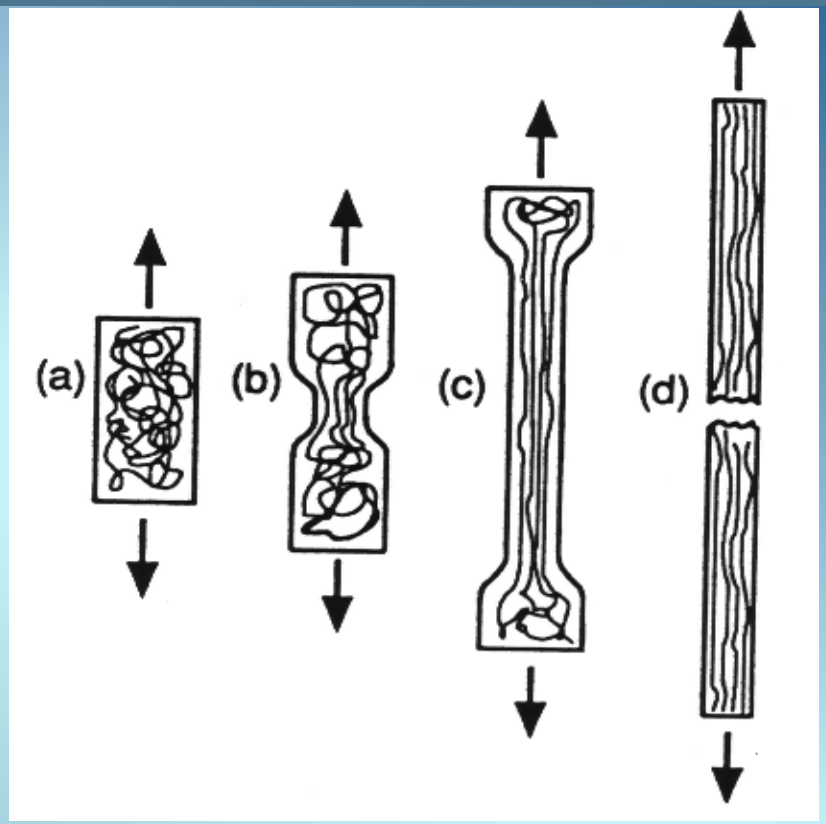
  Strain = Increase in length (elongation) of film during test ÷ initial length (between grips)

  - Generally expressed as a percentage
  - Measure of film ductility

- Plot stress vs strain

Example of a Stress-Strain Curve



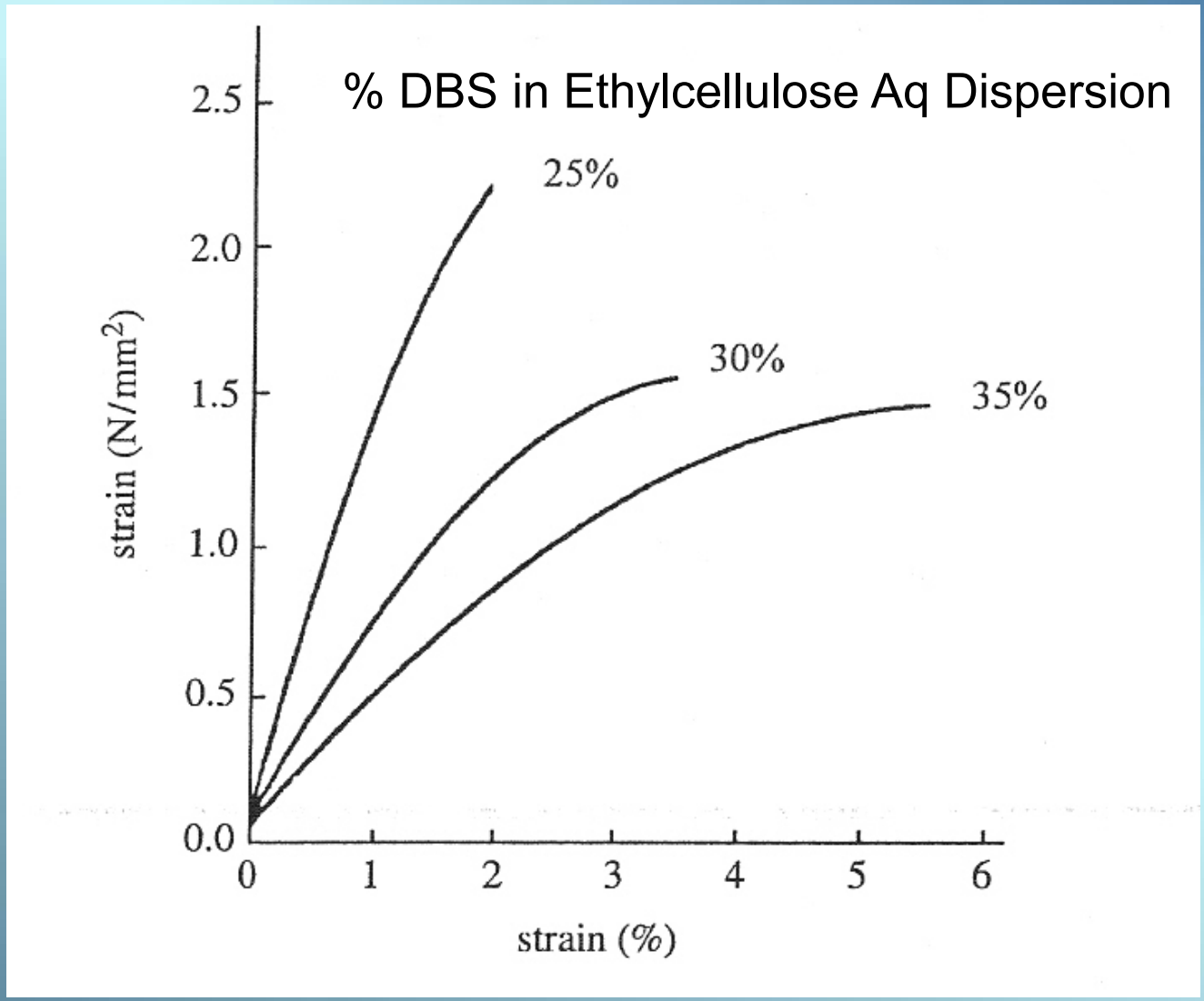


(a) Elastic deformation-stress directly proportional to strain
(b) Yield point
(c) Plastic deformation-polymer chains orient themselves
(d) Break

Other Mechanical Properties

- **Young's Modulus**
  - Slope of the linear region
  - Measure of the stiffness of the film
  - Higher modulus (greater slope) = greater stiffness
- **Area Under the Curve**
  - Work required to fracture the film
  - Measure of the toughness
- **Tensile strength/Young's modulus ratio**
  - Measure of crack resistance
    - Higher value, higher resistance to cracking

Plasticizer Concentration Influences Mechanical Properties of Free Films



Hutchings, Clarson, and Sakr, Int. J. Pharm., 104, 1994

Calculation of Plasticizer Quantity

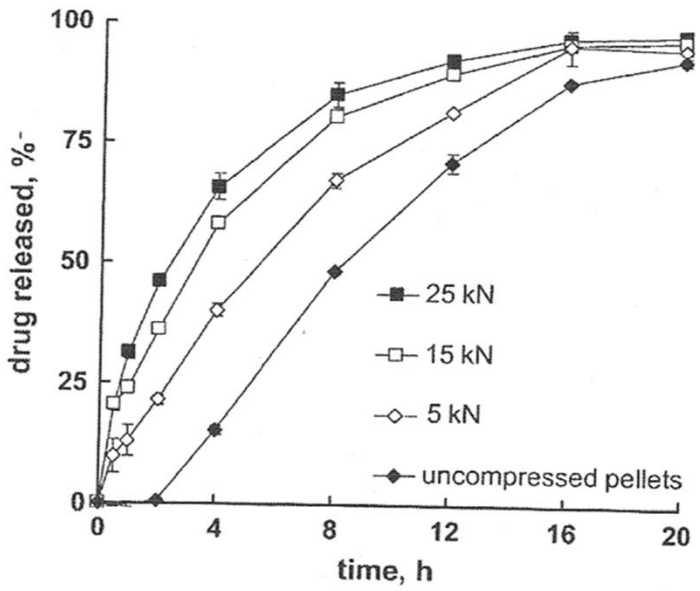
- **Typically 10–30% (w/w)**
- **Expressed as a percentage, based on polymer weight**
  - Ex: 100g dry polymer x 0.2 = 20g plasticizer
- **Dependent on polymer and plasticizer**
- **Not every polymer needs a plasticizer**
  - Ex: Eudragit NE 30 D

Compressing Coated Beads

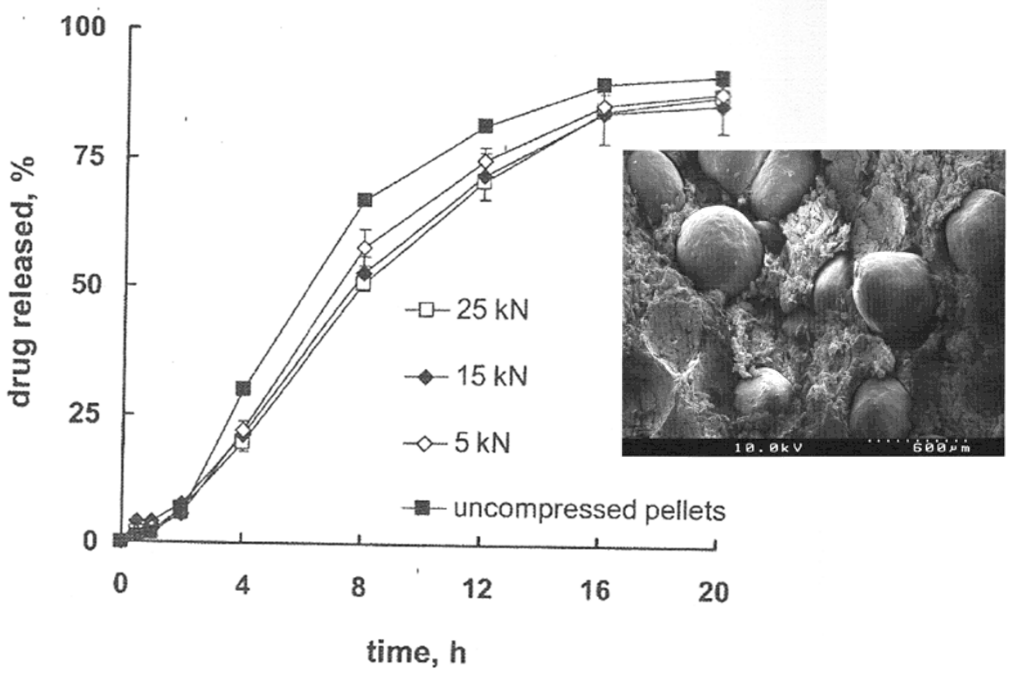
- **Coating must be mechanically strong to withstand compression**
  - Rupture of coating → faster release
  - Fusion of beads to form matrix → slower release
- **Polymer coating should be flexible, non brittle**
  - Eudragit NE; plasticized Eudragit RS/RL
- **Core should have some plasticity to deform**
- **Tableting excipients ('Cushioning' agents)**
  - Prevent rupture of film; minimize direct contact

Influence of Compressional Force During Tableting on Drug Release

Aquacoat ECD
(25% w/w TEC)



Kollicoat SR 30 D
(10% w/w TEC)

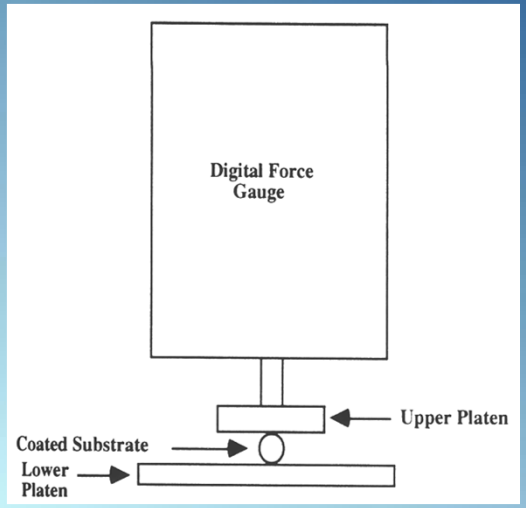


Propranolol HCl as model drug; 20% (w/w) coating level

Dashevsky et al, Int. J. Pharm., 2004

Mechanical Strength of Coated Beads

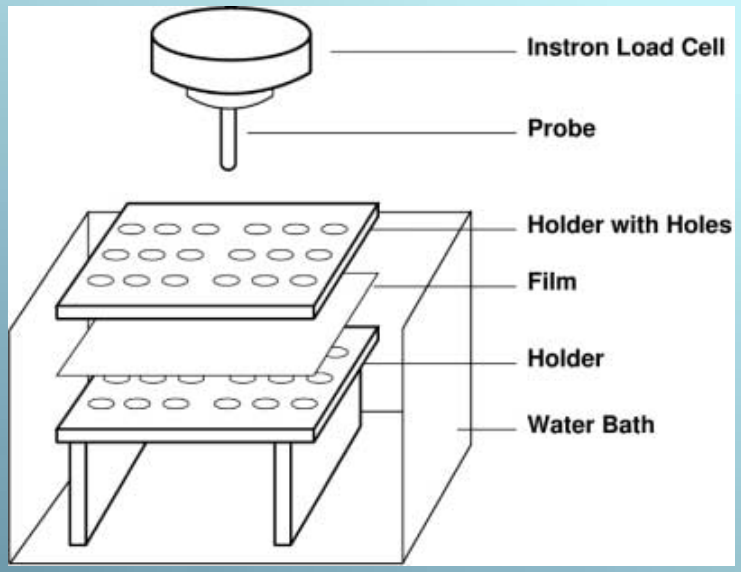
- **Individual beads**
- **Compression test**
  - Similar to tensile testing of free films
  - Uniform displacement rates applied
  - Record force and displacement values
    - Convert to stress and strain and graph data
- **Investigate coating, core, processing and storage conditions**
- **Qualitative adhesion information**



Felton et al, S.T.P. Pharma Sci., 1997

Mechanical Strength of a Film in the Hydrated State

- **Films in dry state may not predict behavior when in contact with biological fluids**
  - Plasticizing effect of water; Leaching of plasticizers
- **Puncture strength of hydrated films**



Bussemer, Peppas, and Bodmeier, Drug Dev. Ind. Pharm., 2003

Anti adherents

- **Prevent agglomeration during both coating and storage**
- **Examples**
  - Talc (25-200%, based on polymer weight)
  - GMS (2-10%, based on polymer weight)
- **Clog spray nozzle**
- **Affect polymer properties**

Pigments

- **Dyes, lakes, iron oxides**
- **Add color or opacity**
- **Critical pigment volume conc (CPVC)**
  - Insufficient polymer present to surround all insoluble pigment particles
- **Mottling due to migration of dyes**
- **Interactions with polymer or drug**
- **Clog spray nozzle**
- **Affect polymer properties**

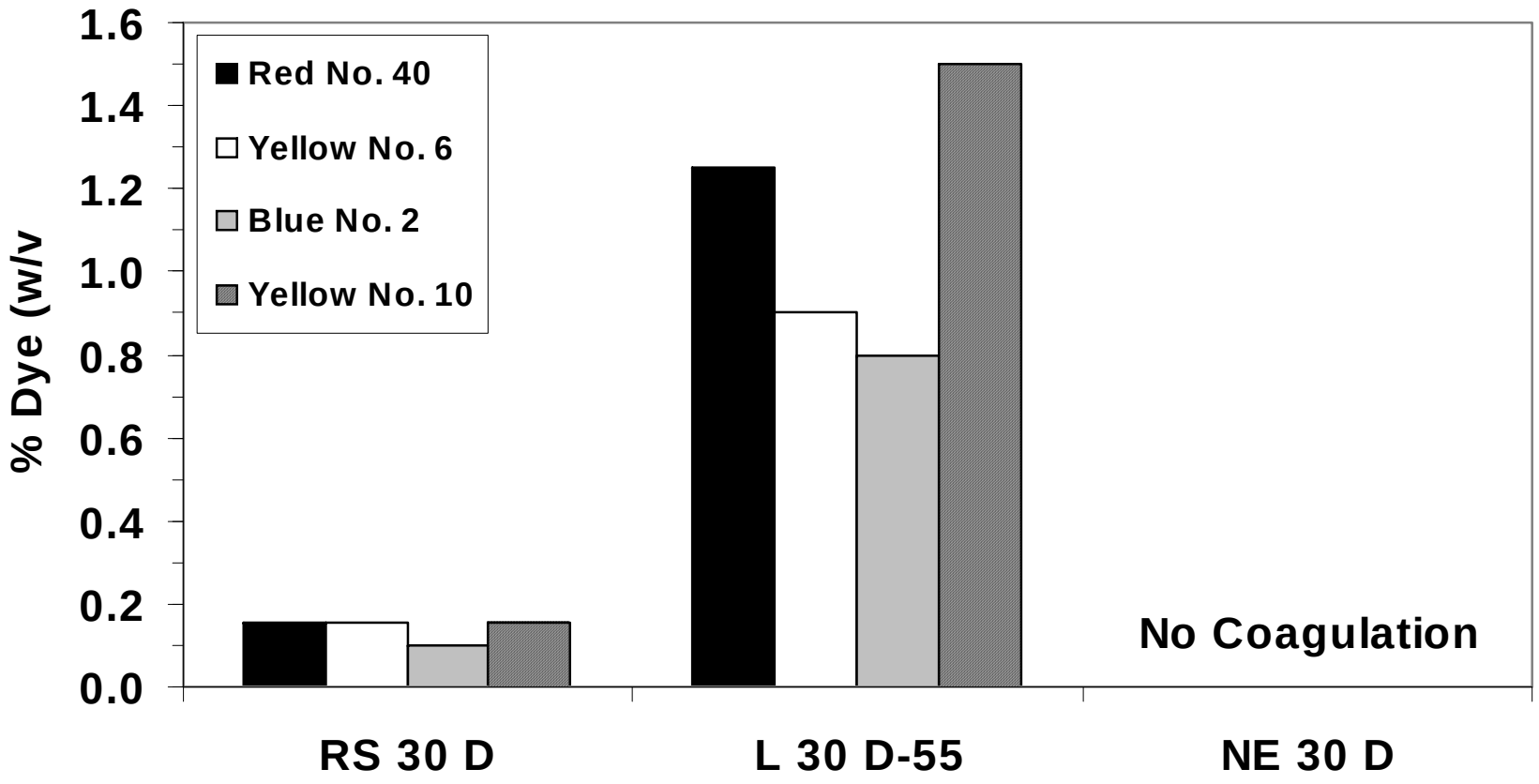
CPVC of HPMC Films
(Determined by gloss measurement)

Pigment	CPVC (% v/v)
Black iron oxide	7.0–8.5
Red iron oxide	8.5–10.0
Yellow iron oxide	10.0–12.0
Titanium dioxide	13.5–15.0
Aluminum lake yellow No. 6	12.0–13.5
Talc (surface area 2.99 m^2/g^a)	12.0–15.0
Talc (surface area 14.33 m^2/g^a)	25.0–35.0

[a]Determined by BET nitrogen adsorption.

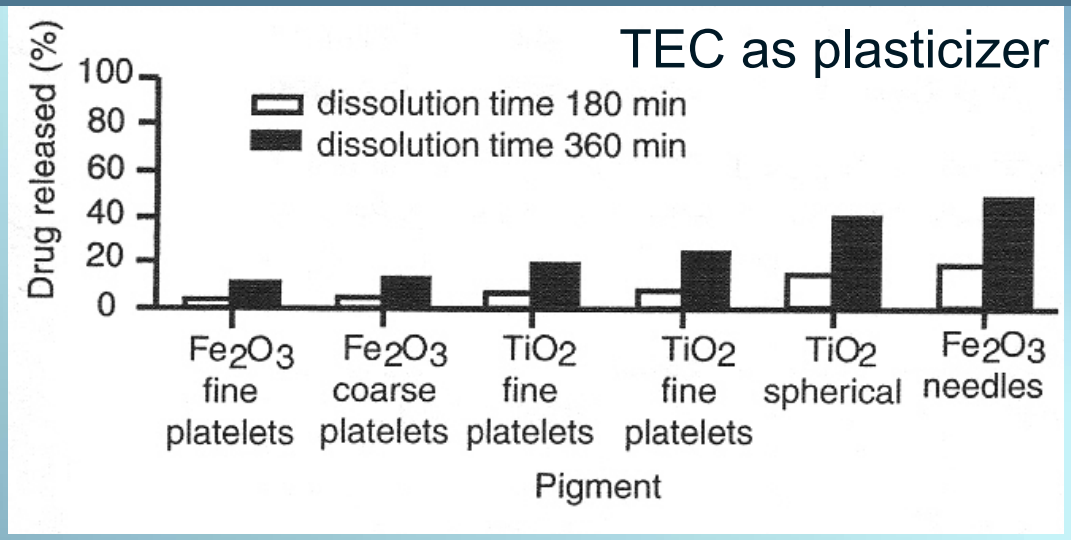
Felton and McGinity, Drug Dev. Ind. Pharm., 2002

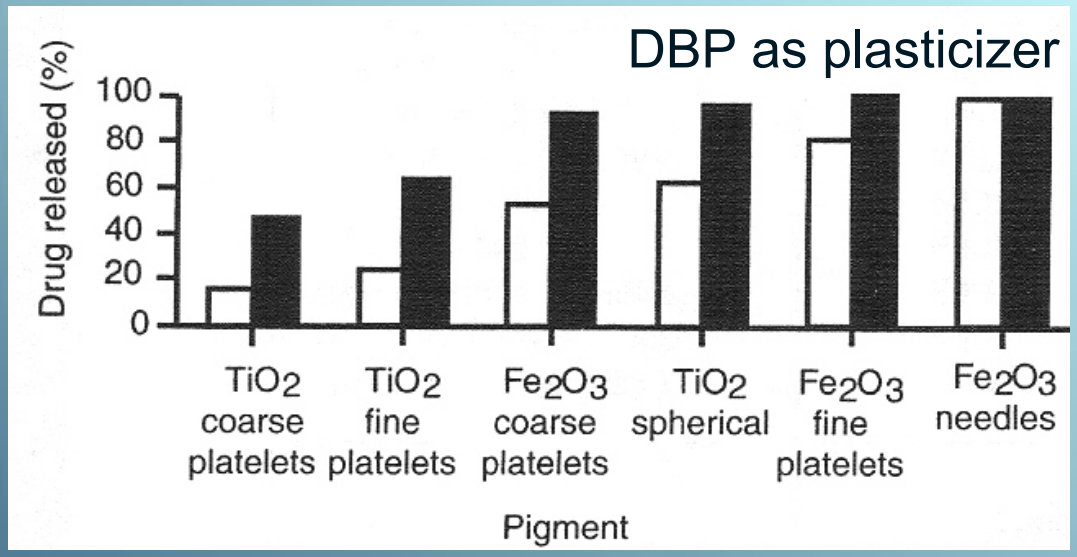
Dye Coagulation Concentrations for Eudragit® Dispersions



Nyamweya, Mehta, and Hoag, J Pharm Sci, 2001

Influence of Pigments in the Coating on Drug Release





Theophylline pellets

Eudragit RS 30 D

(pigment volume conc of 3cm^3/15g dry latex)

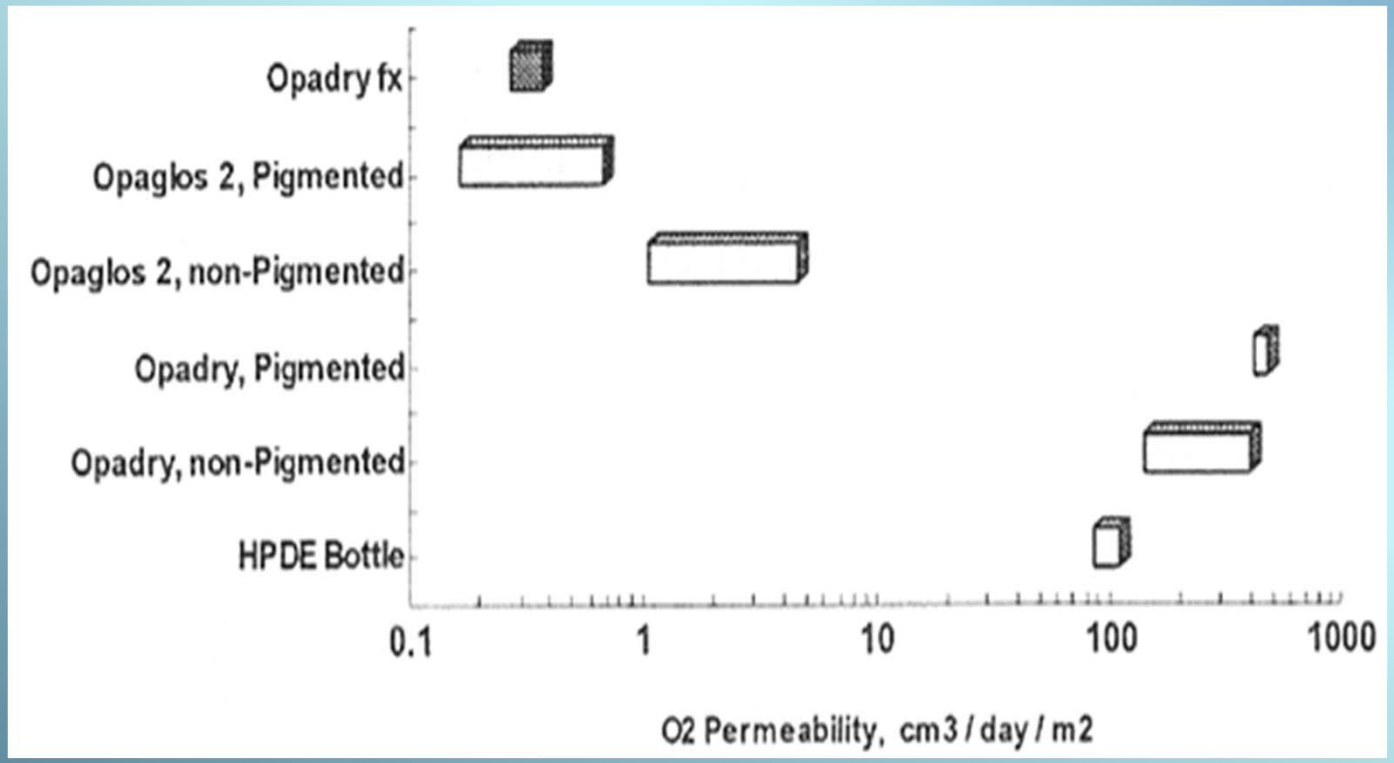
Maul and Schmidt, S.T.P. Pharma Sci., 1997

Surfactants

- Emulsify water–insoluble plasticizers
- Improve substrate wettability
- Stabilize suspensions
- Typical concentrations of 0.25–1%
- Can affect polymer properties and drug release

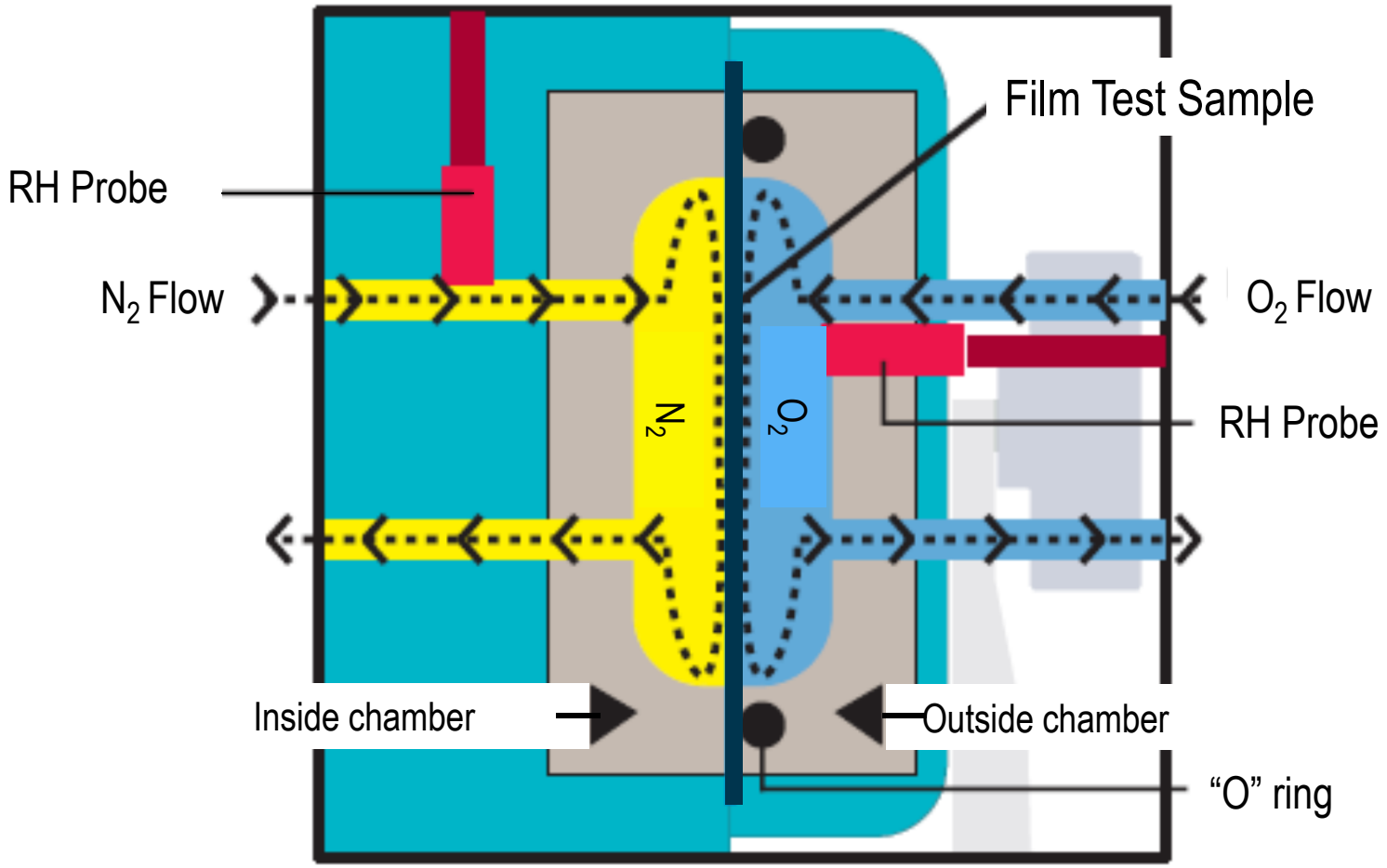
Protection Against Atmospheric Oxygen

- Opadry® fx (Colorcon)
- Cellulosic polymer, gloss enhancer, pigment(s)



Gulian et al, AAPS Annual Meeting, 2004

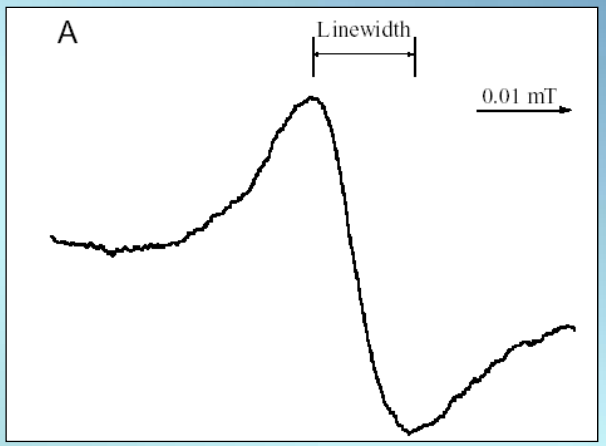
Oxygen Permeability of Free Films



From Mocon OX-TRAN 2/21 brochure

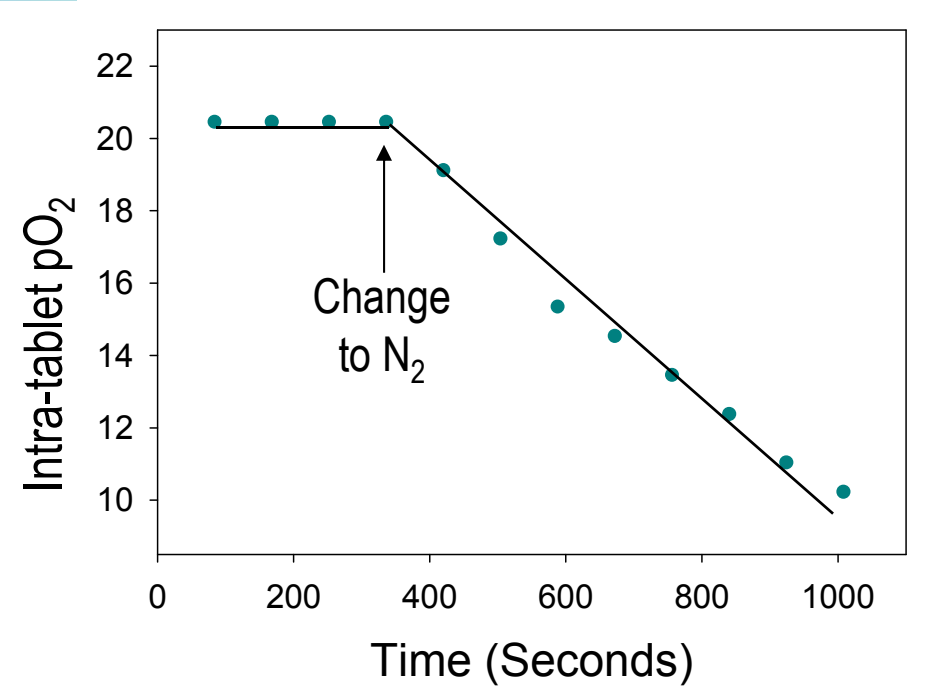
Oxygen Permeability of Applied Films

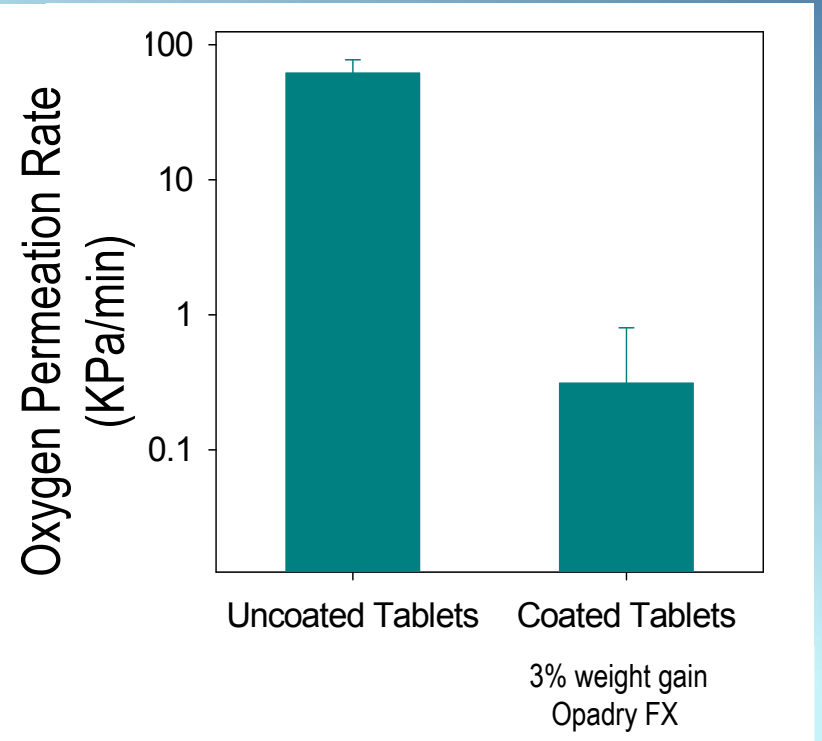
- **Electron Paramagnetic Resonance Spectroscopy (EPR)**
- **Lithium phthalocyanine crystal**
  - Oxygen sensitive crystal
  - Placed inside dosage form
  - Peak–to–peak linewidth derivative proportional to pO_2



- **pO_2 plotted vs time and calculate slope**

Oxygen Permeability of Applied Films



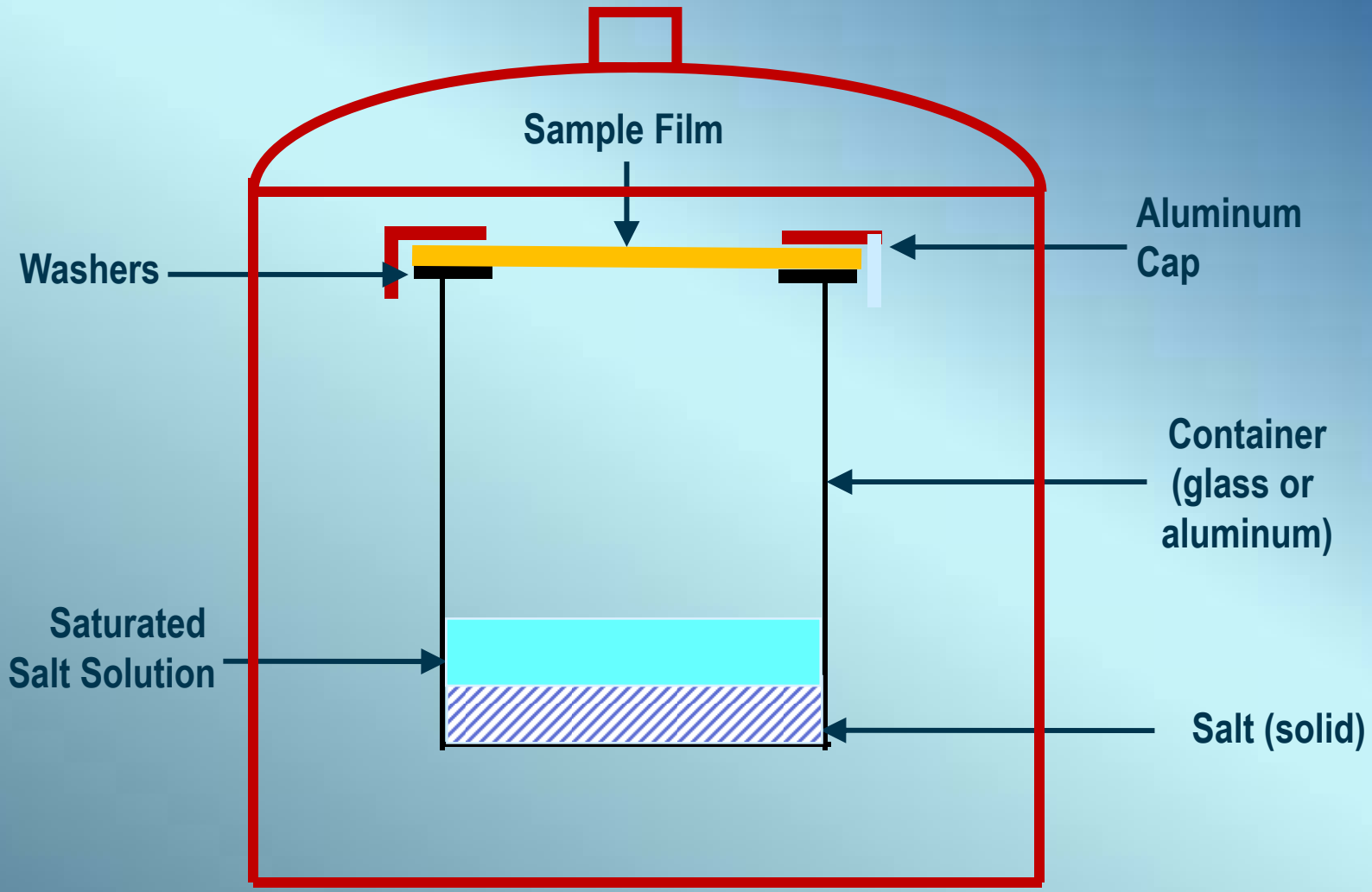


Felton and Timmins, Pharm. Dev. Technol., 2006

Water Vapor Permeability

- **Protect the drug from atmospheric moisture**
- **Quantify the effectiveness of the coating**
  - Water vapor transmission cells
    - Saturated solution in cell
    - Store in humidity–controlled environment
    - Follow weight change over time
  - Excipients in the coating and processing conditions can influence water vapor permeability

Water Vapor Transmission Cell Set Up



Calculate Water Vapor Permeability

Water Vapor Transmission Rate (WVT)

G = weight change

t = time

Slope of weight change vs time graph

$$WVT = \frac{G}{t}$$

Permeability Constant (P_{erm})

WVT = Rate of moisture transmitted/time

L = Film thickness

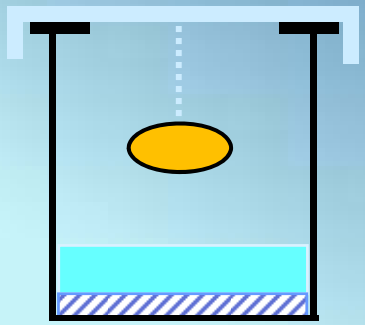
A = Area of the film exposed

ΔP = Vapor pressure gradient

$$P_{erm} = \frac{WVT \ x \ L}{A \Delta P}$$

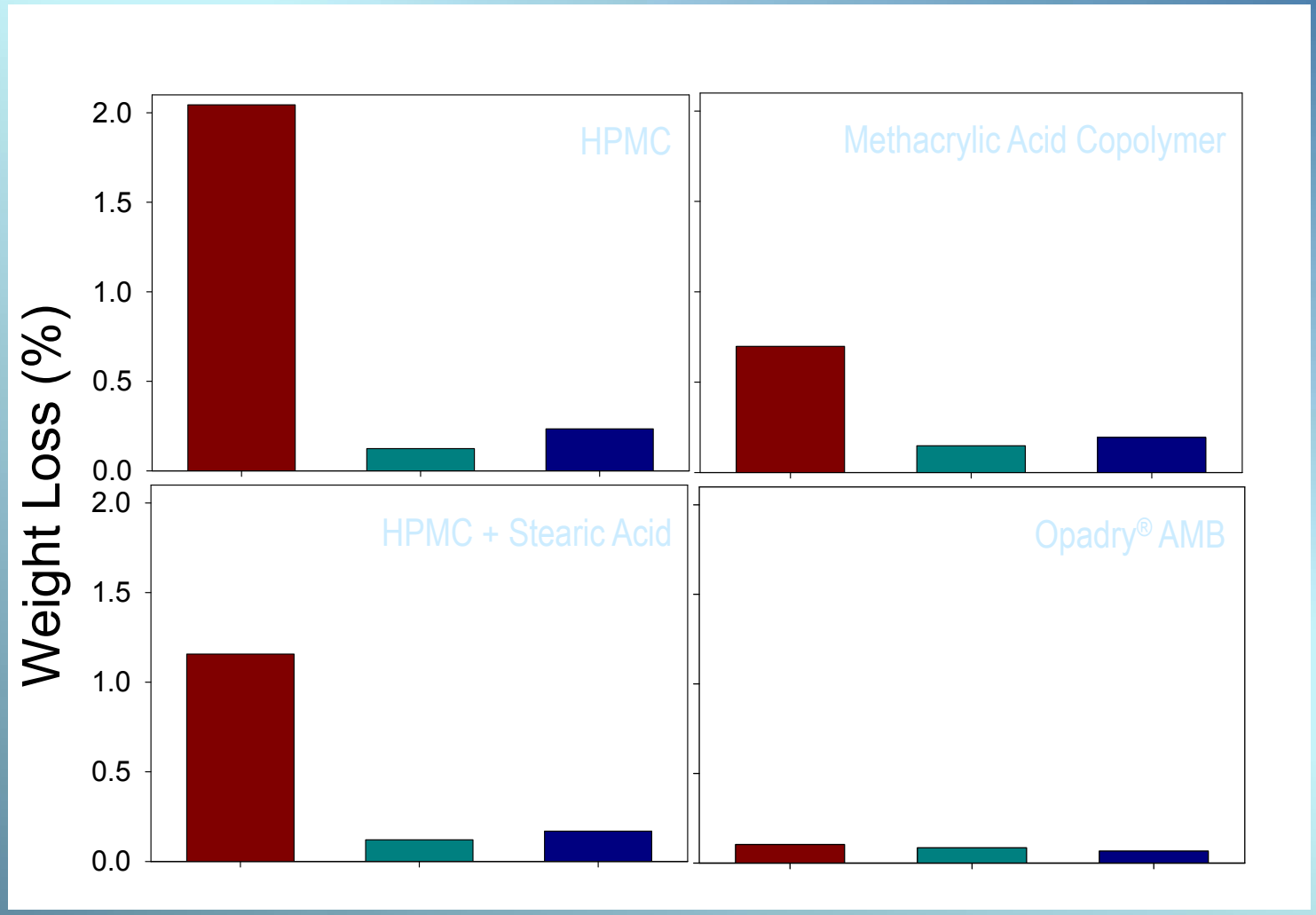
Water Vapor Permeability of Applied Films

- **Modification of free film apparatus**
  - Tablet suspended on wire loop
  - High (or low) humidity environment
  - Weigh tablets over time



- **Calculate WVT and P_{erm}**
- **Investigate influence of excipients in core on water vapor transmission**

Comparison of Moisture Barrier Coatings of Various Tablet Cores



(■) Standard; (■)Low Hygroscopicity; (■)Waxy Cores

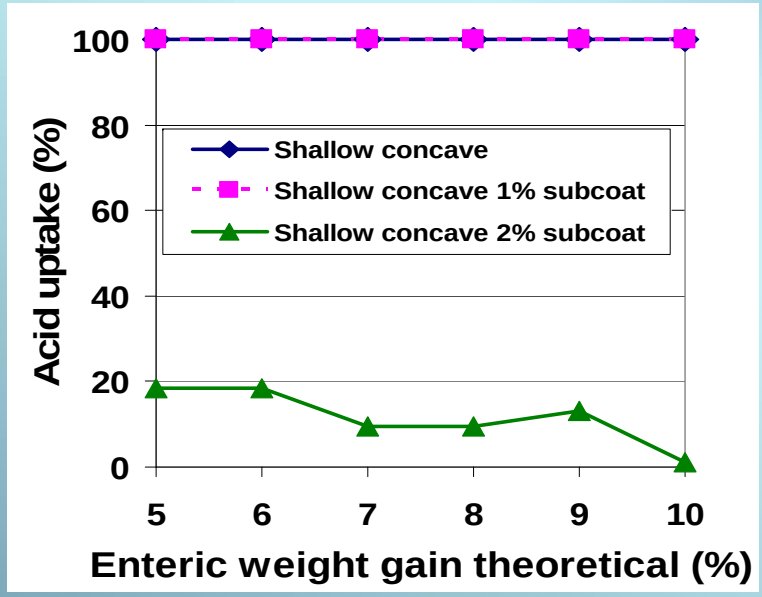
Colorcon Technical Data; Opadry AMB Sorption & Desorption Study; 2003

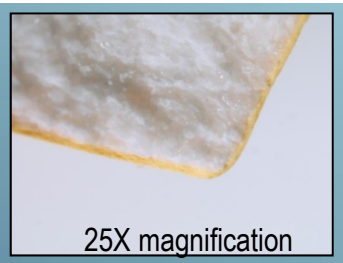
Substrate Considerations in Aqueous Film Coating Processes

- **Physical properties of dosage form**
  - Hardness, size/shape, surface properties, heat sensitivity
- **Chemical properties of the active**
- **Core-polymeric film interaction**
  - Swelling of the core, moisture penetration, surface dissolution, migration

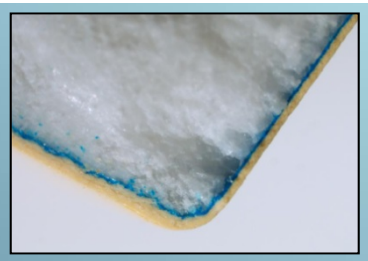
Shape Can Influence Coating Integrity

Shallow Concave



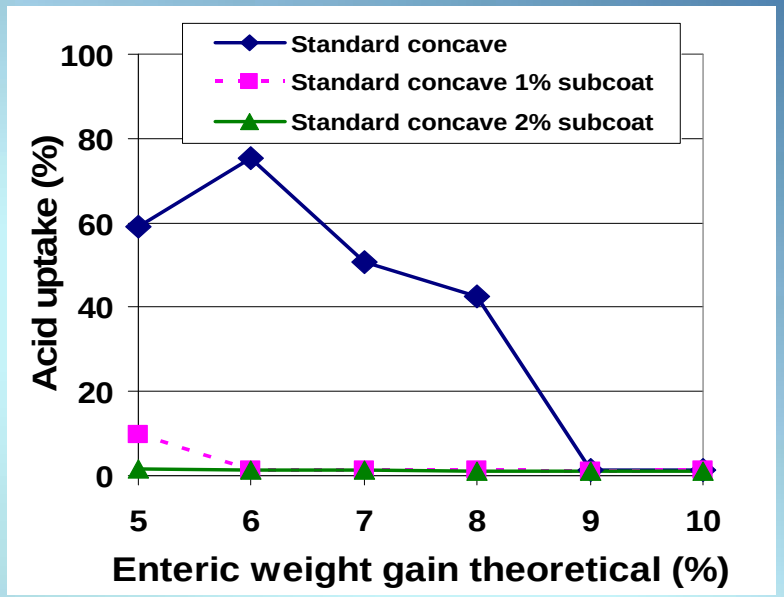


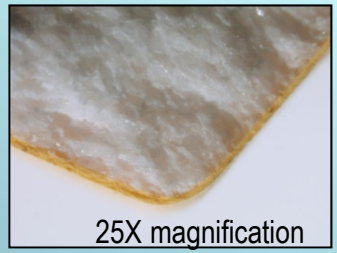
10% weight gain
No sub coat



10% weight gain
2% sub coat

Standard Concave





10% weight gain
No sub coat

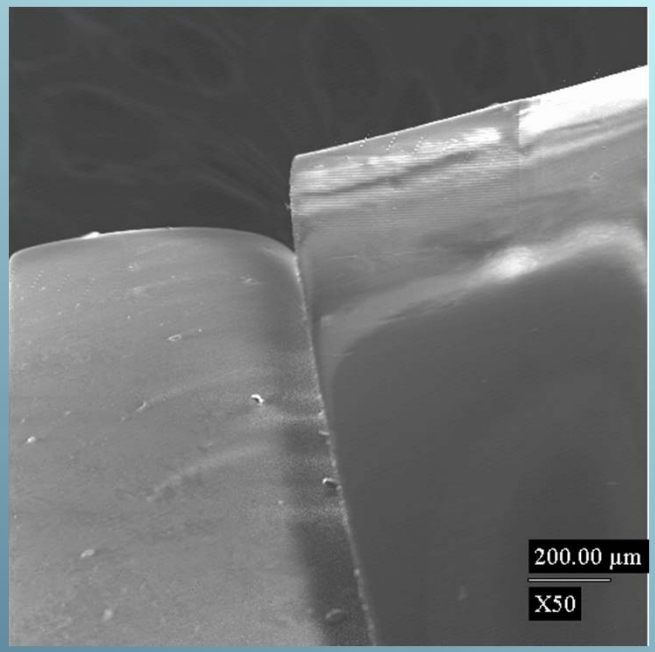
10% weight gain
2% sub coat

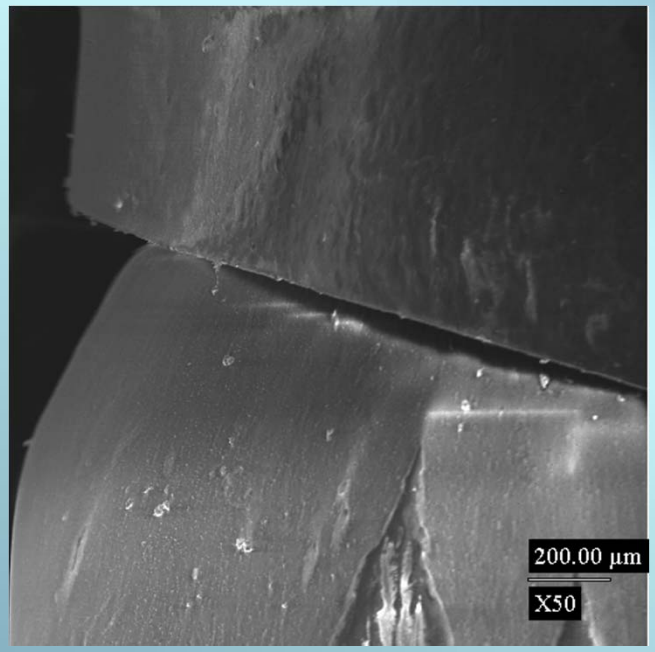
Acryl-Eze yellow enteric system; Opadry II blue subcoat

Cunningham et al, AAPS Annual Meeting, 2002

Coating Hard Shell Capsules

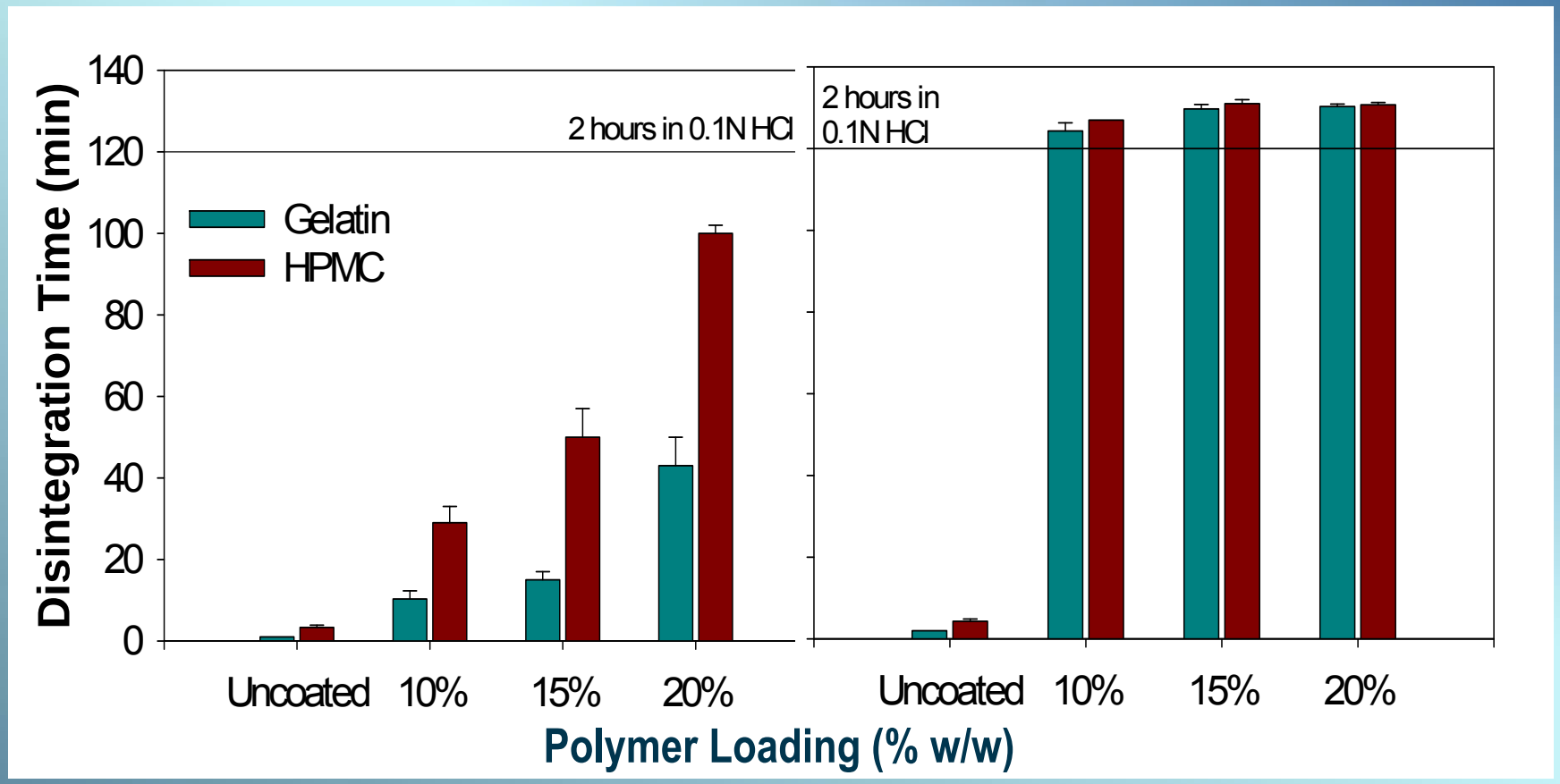
- Relatively smooth surface
- Residual moisture in shell
- Cap/body joint





Gelatin HPMC

Enteric Performance of Coated Capsules



Eudragit L 30 D-55, 20% TEC; coated in perforated pan; USP Disintegration test

Felton et al., AAPS Annual Meeting, 2002

Aqueous-based Coating of Soft Gelatin Capsules

- **Difficulties due to physical properties of gelatin and the dosage form**
  - Solubilization of gelatin
  - Bed temperature used during coating
  - Prewarming stage prior to coating
  - Adhesion & enteric properties affected by
    - Plasticizer in the coating
    - Fill liquid

Felton et al, Int J Pharm, 1995; Felton et al, Int J Pharm, 1996

Polymer Adhesion

- Good adhesion is a major prerequisite
  - Flaking or peeling of the coating
  - Accumulation of moisture at the interface
  - Compromise mechanical protection
- Related to
  - Film–tablet interfacial interactions
  - Internal stresses within the film

Estimation of Internal Stress

$$P = \frac{E}{3(1-v)}\left[\left(\frac{\Phi_s - \Phi_r}{1-\Phi_r}\right) + (\Delta\alpha_{cubic}\Delta T) + \left(\frac{\Delta V}{V}\right)\right]$$

Stress due to shrinkage of film | Thermal stress | Volumetric stress

P = Total stress

E = Elastic modulus of film

v = Poisson's ratio

Φ_s = Volume fraction of solvent at solidification point of film

Φ_r = Volume fraction of solvent in 'air dry' film

$\Delta\alpha_{cubic}$ = Difference in coefficient of thermal expansion between film and substrate

ΔT = Difference between Tg of film and temp during manufacturing and storage

ΔV = Volumetric change of substrate core

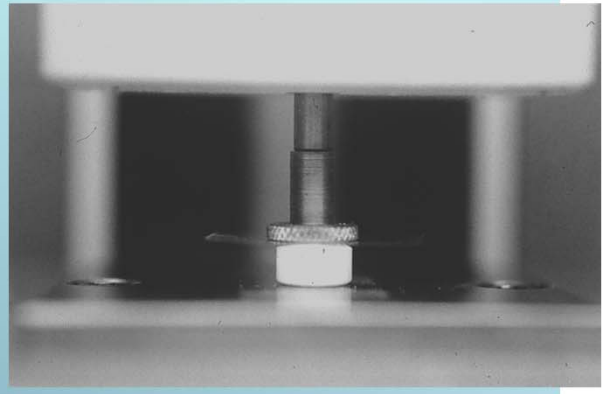
V = Original volume of substrate core

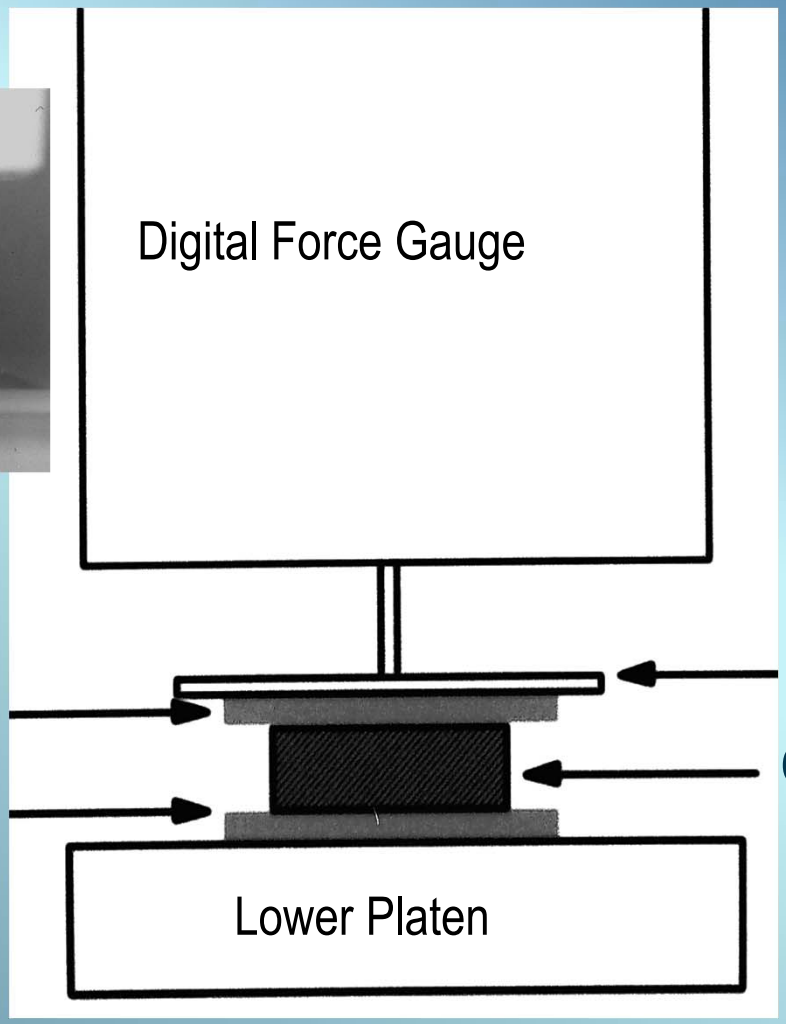
Croll, 1979; Sato, 1980; Rowe, 1983; Okutgen et al, 1995

Methods to Assess Adhesion

- **Compression testing-** qualitative information
- **Contact angle-** Indication of wettability
- **Peel test**
  - Modified tensile tester to peel film at 90° angle
  - Peel strength is dependent on the elasticity of the film and the uniformity of adhesion
  - Modification to predict tackiness of film during coating
- **Butt Adhesion test**
  - Entire film removed normal to surface of tablet
  - Eliminates variations due to the elasticity of the film
  - Less influenced by the uniformity of adhesion

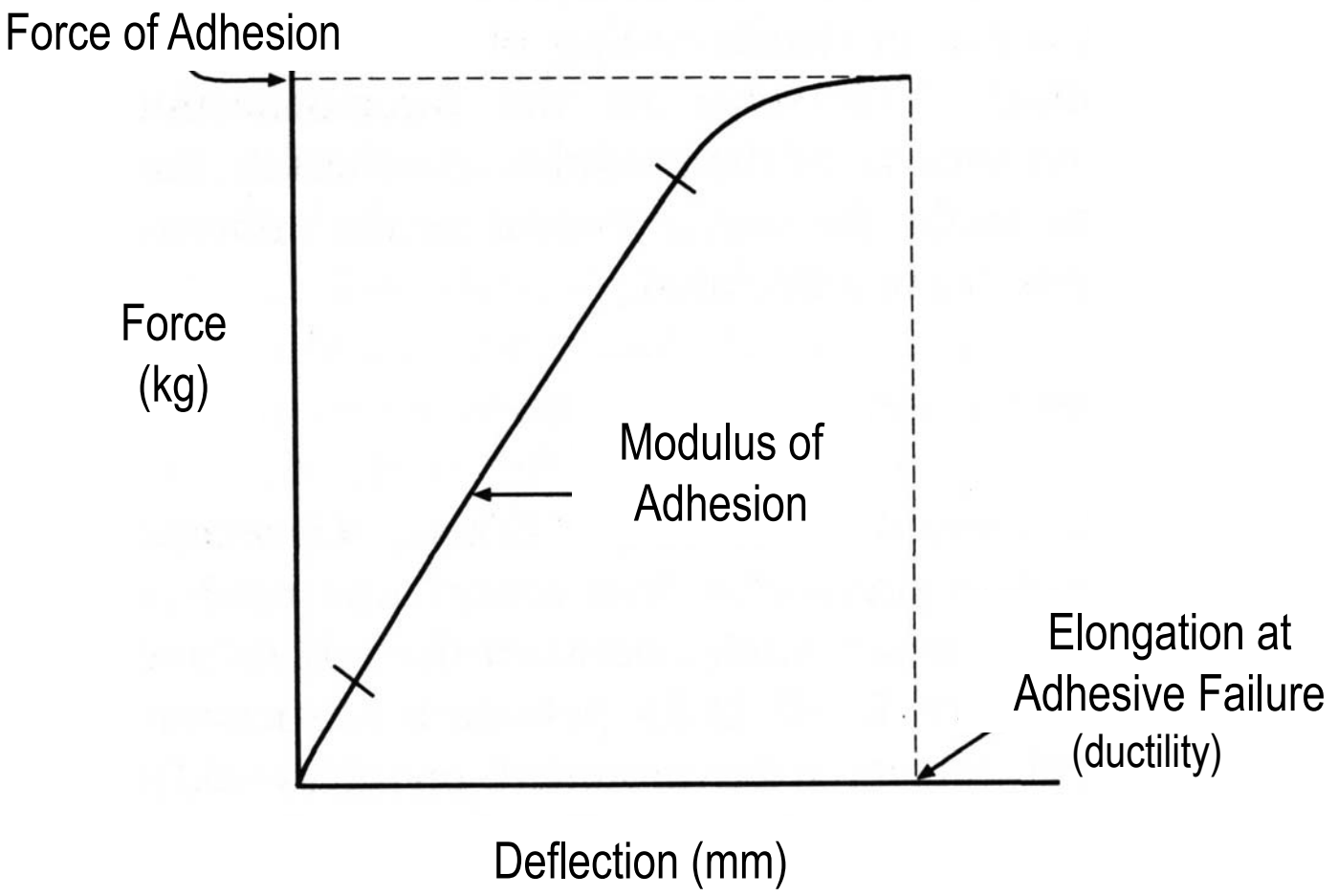
Butt Adhesion Test





Felton and McGinity, Pharm. Dev. Technol., 1996

Force–Deflection Profile

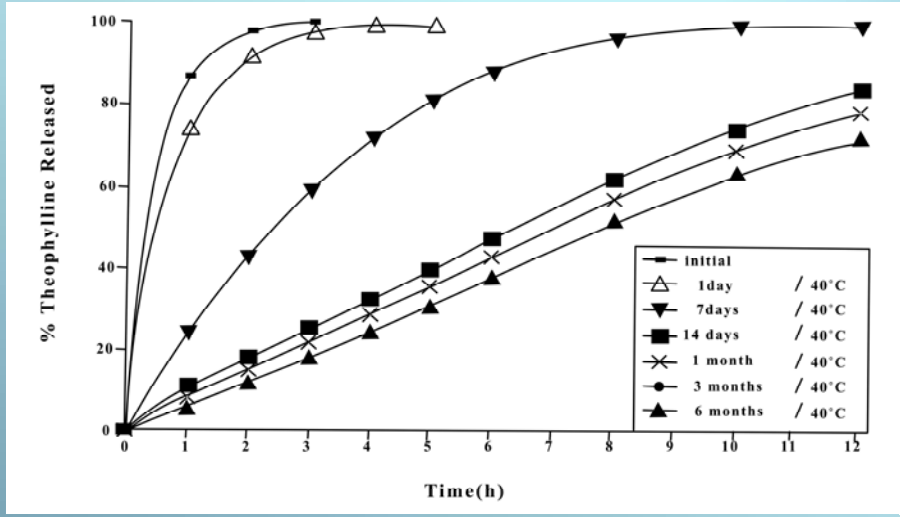


Adhesive Toughness = Area Under Curve
(work required)

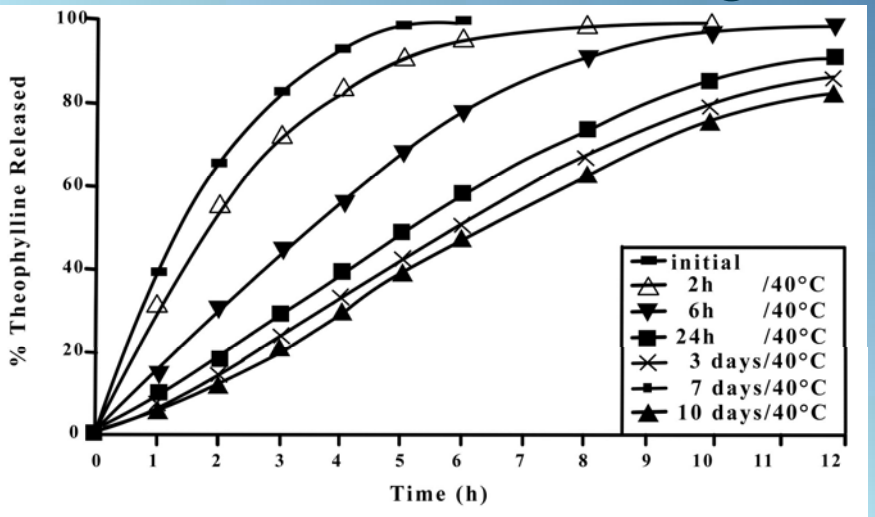
Felton and McGinity, Pharm. Dev. Technol., 1996

Changes in Drug Release Over Time

10% TEC in coating



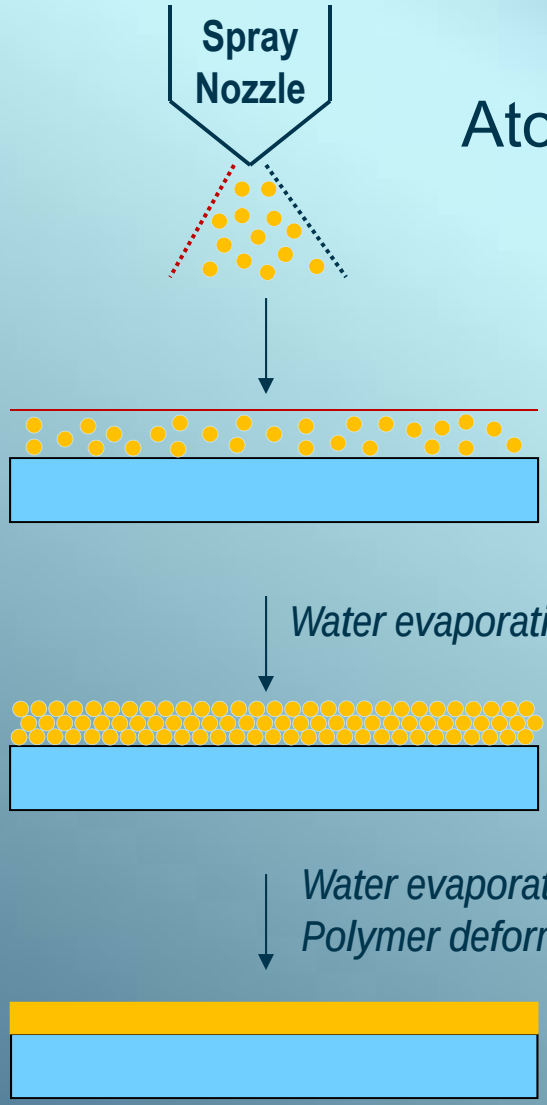
20% TEC in coating



Pellets coated with Eudragit RS 30 D
containing 5% Pharmacoat 505
Approximately 10% weight gain

Kucera, McGinity, and Felton, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

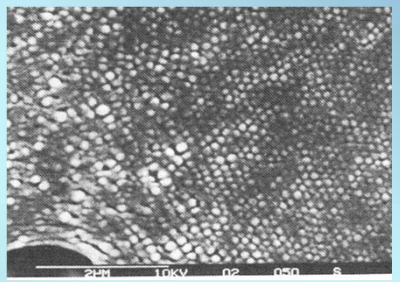
Film Formation from an Aqueous Polymeric Dispersion



Atomization of polymeric dispersion

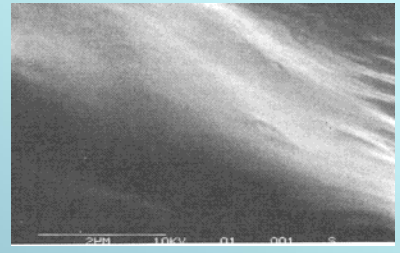
Polymeric dispersion deposited onto substrate

Close packed polymer spheres; water in voids



Coalescence

Continuous film



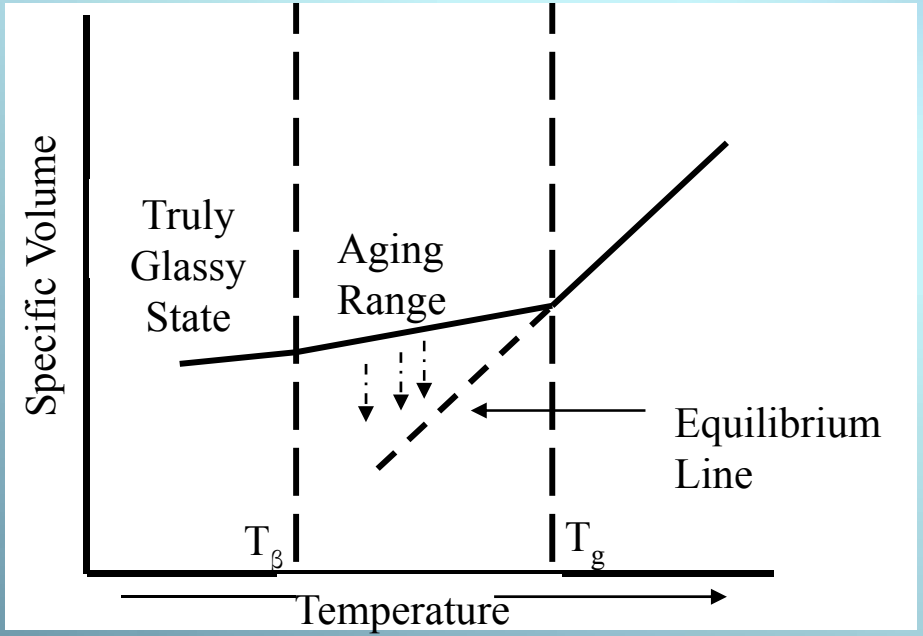
Lehmann, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Marcel Dekker, 1997

Variables Influencing Coalescence

- **Plasticizer**
- **Temperature**
  - **During coating: 10-20°C above the minimum film forming temperature**
  - **During storage (post-coating drying)**
    - **Ethyl cellulose: 60°C for 2 hours**
    - **Eudragit L 30 D-55: 40°C for 2 hours**
- **Humidity**

Physical Aging

- Amorphous polymers become more rigid, brittle, and dense with time
- Decrease in free volume over time



Kucera, McGinity, and Felton, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

Methods to Stabilize Drug Release

- Fully coalesce film after coating
  - Temperature and humidity
- Increase plasticizer concentration

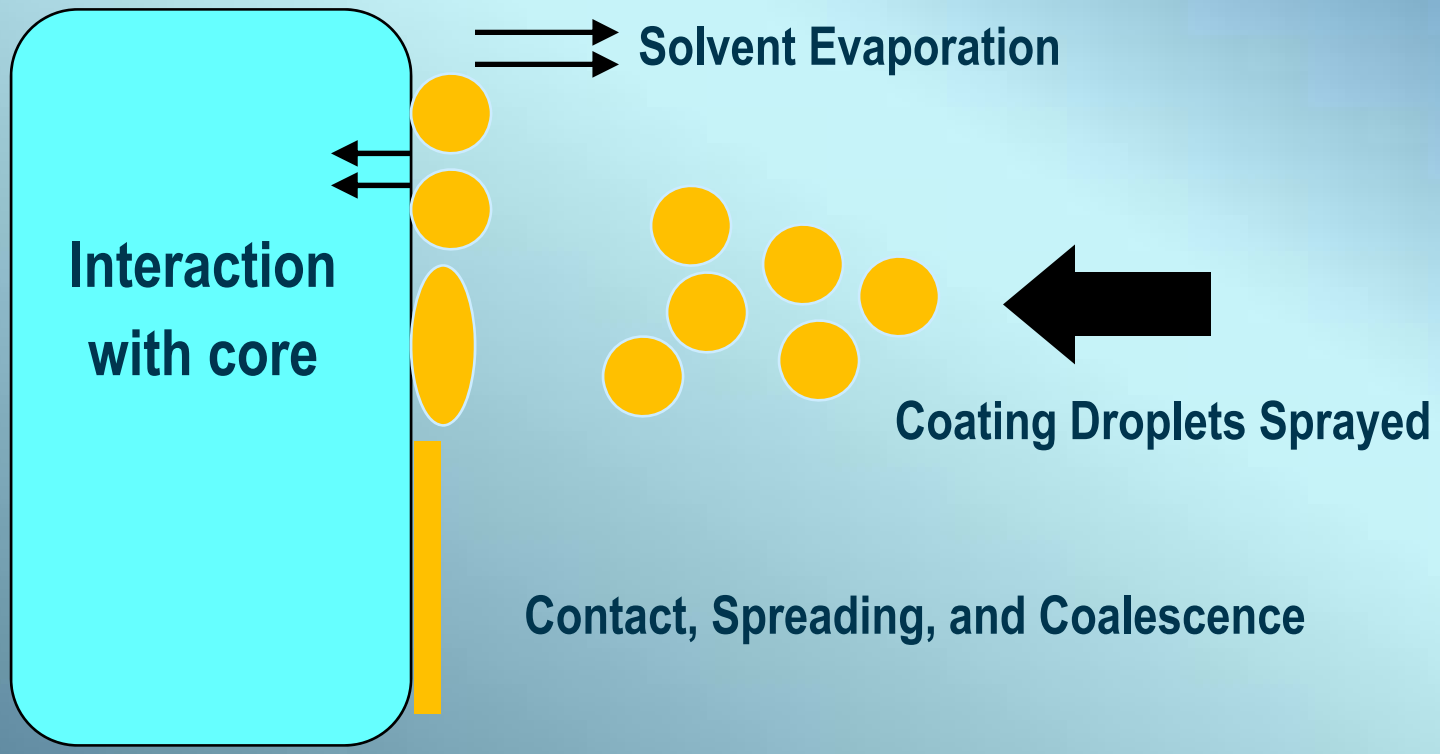
Related to coalescence

- Add polymer with high glass transition temperature
- Add high amounts of talc
- Add immiscible, hydrophilic excipients

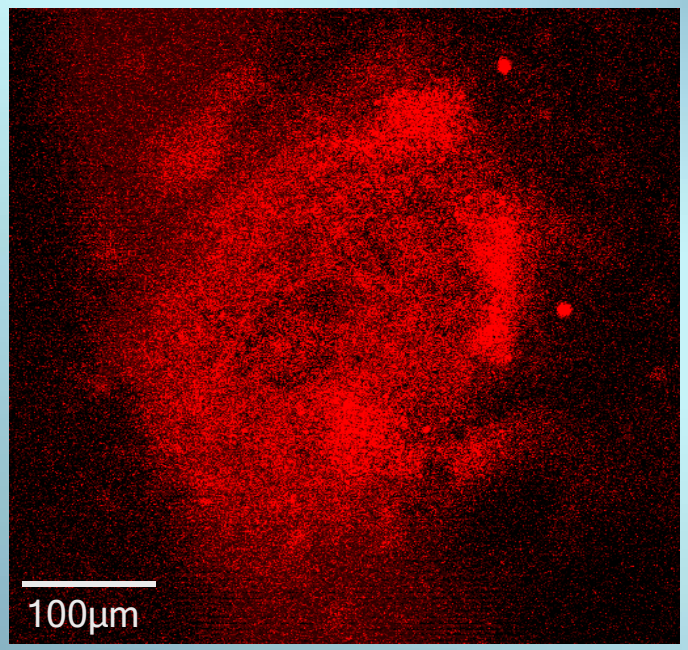
Related to physical aging

Physical Mixing at the Interface

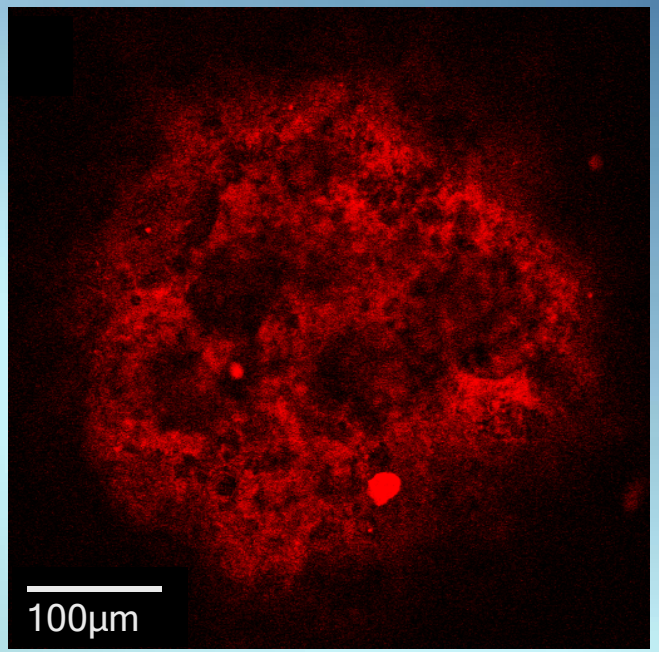
- **Dissolution of the outermost layer of the tablet**
  - Migration of drug/excipient into film
- **Affect polymer properties**



Investigation of Drug Migration



Surface of Uncoated Pellet

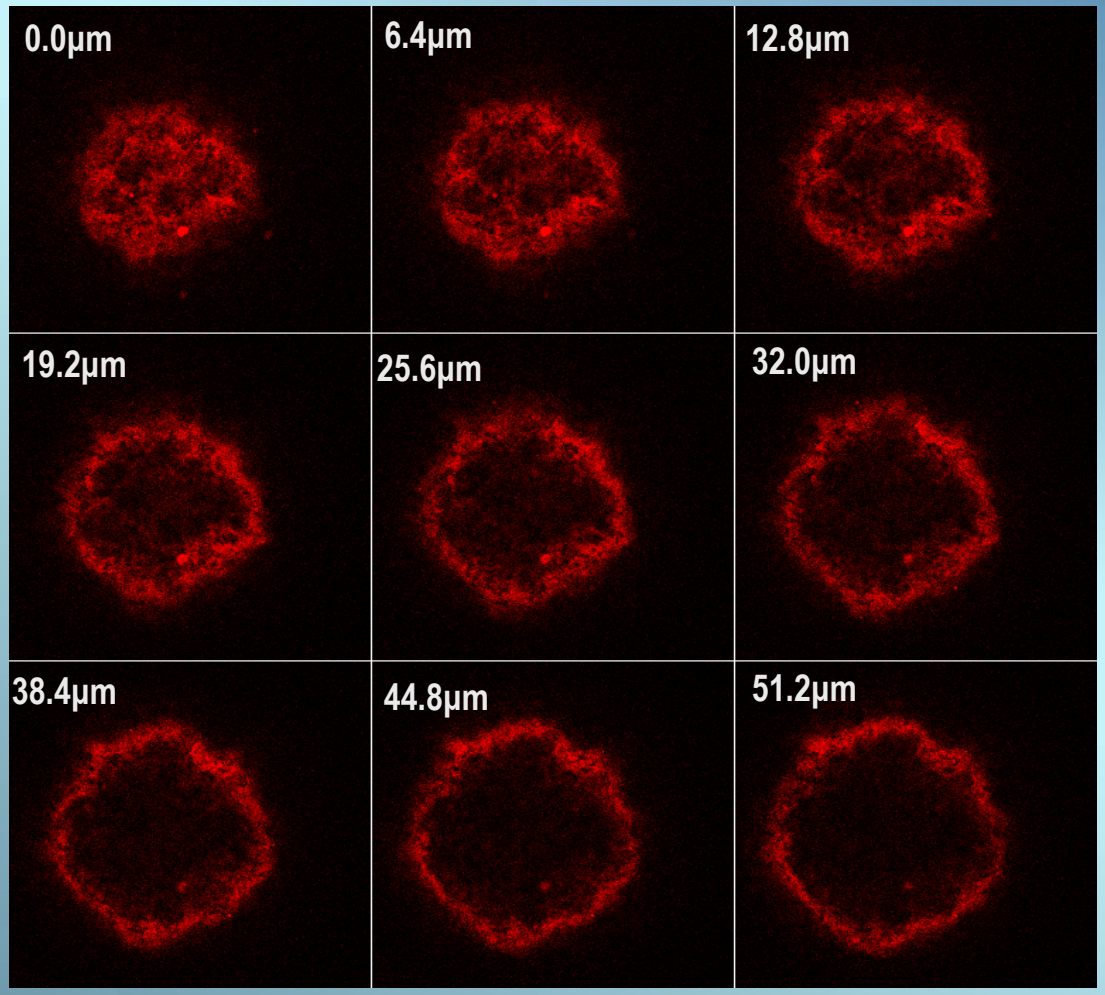


Surface of Coated Pellet

- **Confocal laser scanning microscopy**
  - Model drug: water soluble, fluorescent drug
  - Coating material: ethylcellulose in isopropyl/water

Felton and Yang, CRS Annual Meeting, 2005

Depth Profiling using CLSM



(XY plane: 921.4 x 921.4 µm, depth imaging interval : 6.4 µm)

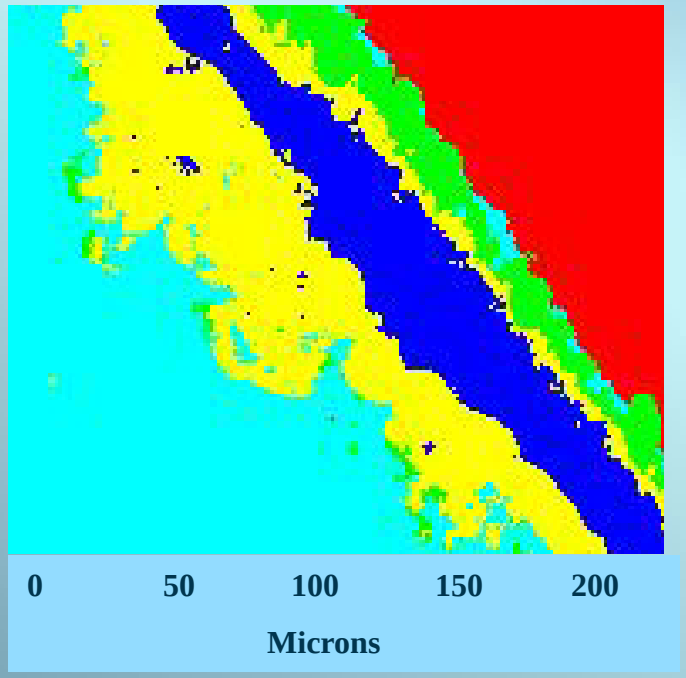
Felton and Yang, CRS Annual Meeting, 2005

X–Ray Photoelectron Spectroscopy (XPS)

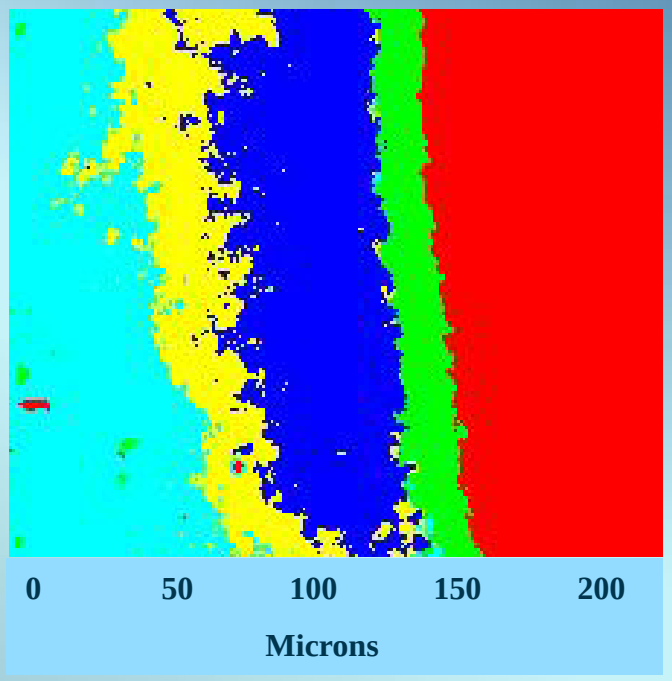
- Elemental analysis of solid surface
- Combined with intermittent ion bombardment for depth profiling
  - Quantify film-tablet interfacial thickness at single point
    - Felton and Perry, Pharm. Dev. Technol., 2002
- Combined with Principal Component Analysis and Classification
  - Create a visual image of the data
    - Variation in film-tablet interfacial thickness

XPS + Principle Component Analysis + Classification

15 PSI



20 PSI



Yellow (tablet/coating interface); Light blue (tablet); Dark blue (coating); Green (air/coating interface); Red (air)

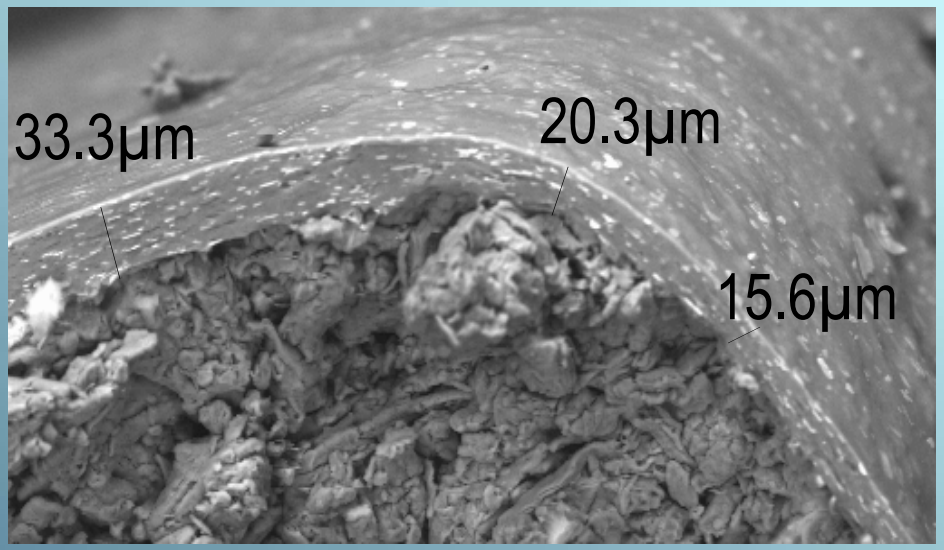
Barbash, et al, *Drug Dev Ind Pharm*, **2009**

Novel Solvent–Free Coating Systems

- **Dry powders deposited on substrate**
  - Dry powder particle coating
  - Electrostatic coating
- **Eliminates the use of solvents**
  - Reduce potential for surface dissolution and drug migration
  - No residual solvent issues
  - Suitable for hydrolytic drugs

Film Thickness and Uniformity

- **Assume all substrates coated uniformly**
  - Variation between batches
  - Variation between substrates in a given batch
  - Variation within individual substrates



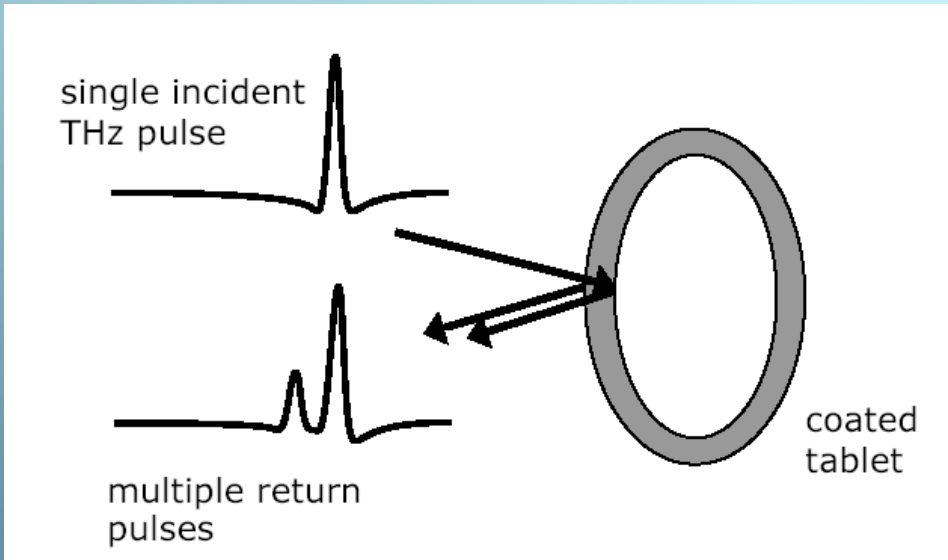
Felton et al., AAPS Annual Meeting, 2004

Laser-Induced Breakdown Spectrosopy

- **Technique to quantify film thickness**
  - Elemental analysis based on atomic emission from a plasma formed by high-energy laser
  - Construct tablet/coating with specific targets
  - Estimate thickness based on emission spectra
- **Measure different areas on tablet for uniformity of thickness**

Terahertz Pulsed Imaging

- Nondestructive technique to determine film thickness
- Wavelengths between microwave and IR



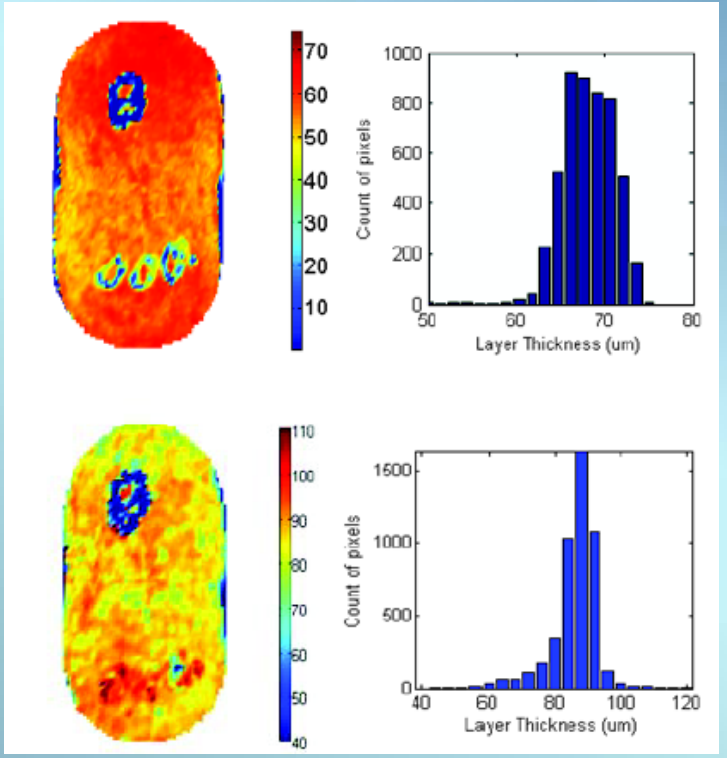
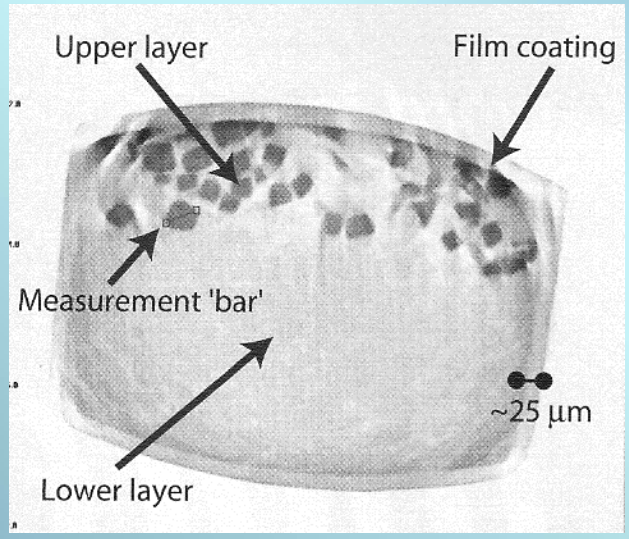
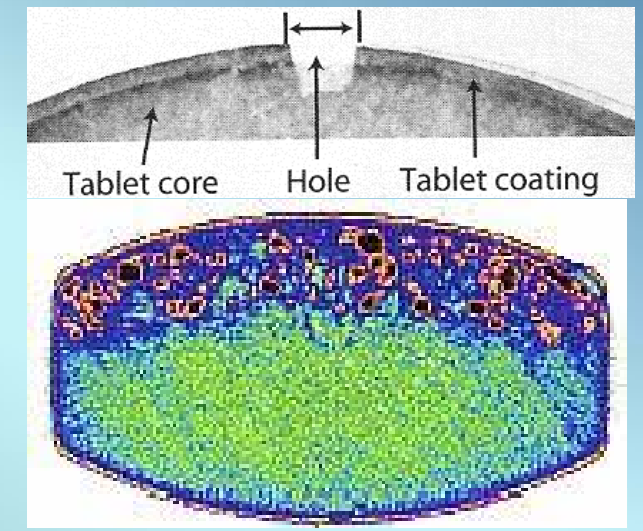


Image courtesy of TeraView

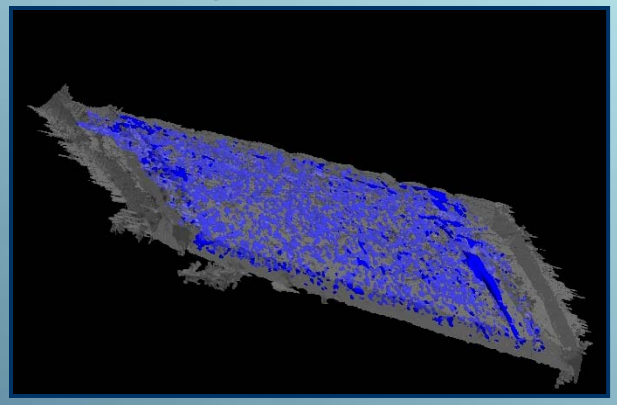
X-ray Microtomography

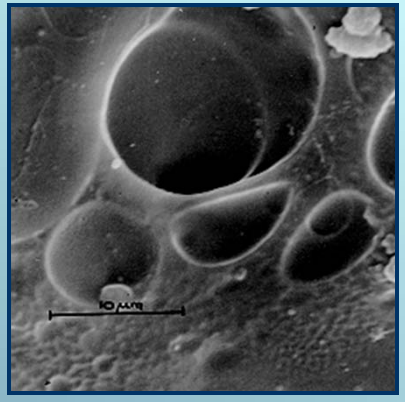
- **Visualize structural features in solids**





Hancock and Mullarney, Pharm. Tech., 2005





Images courtesy of Dr. Stuart Porter

Summary

- **Overview of the coating process**
  - Polymer and excipients
  - Film coalescence and physical aging
- **Critical polymer properties**
- **Characterization techniques**
- **Variables that influence polymer properties**
  - Coating: polymer, film thickness, excipients
  - Substrate: API, dosage form

Any Questions?

Overview of Film-Coating Processes, Process Scale-Up, & Troubleshooting

Stuart C. Porter, Ph.D.

Technical Lead,

NA Technical Services and Global Film Coating Technology

Ashland Specialty Ingredients

Overview of Presentation

Introduction to coating equipment:

- Pan-coating equipment.
- Fluid-bed coating equipment.

Overview of coating processes:

- Introduction to coating processes.
- Factors to consider when attempting to control coating processes.

Scale-up of film-coating processes:

- Scaling up pan-coating processes.
- Scaling up fluid-bed coating processes.

Troubleshooting in film coating:

- Introduction to troubleshooting issues.
- Review of factors that lead to problems in film coating.

A.

INTRODUCTION TO COATING EQUIPMENT

The Concept of the Coating Vessel

The coating vessel is central to the whole coating process, and:

- Acts as a container for the product being coated.
- Imparts motion to that product.
- Facilitates uniform application of the coating liquid.
- Facilitates the drying process.

Coating vessels can be divided into:

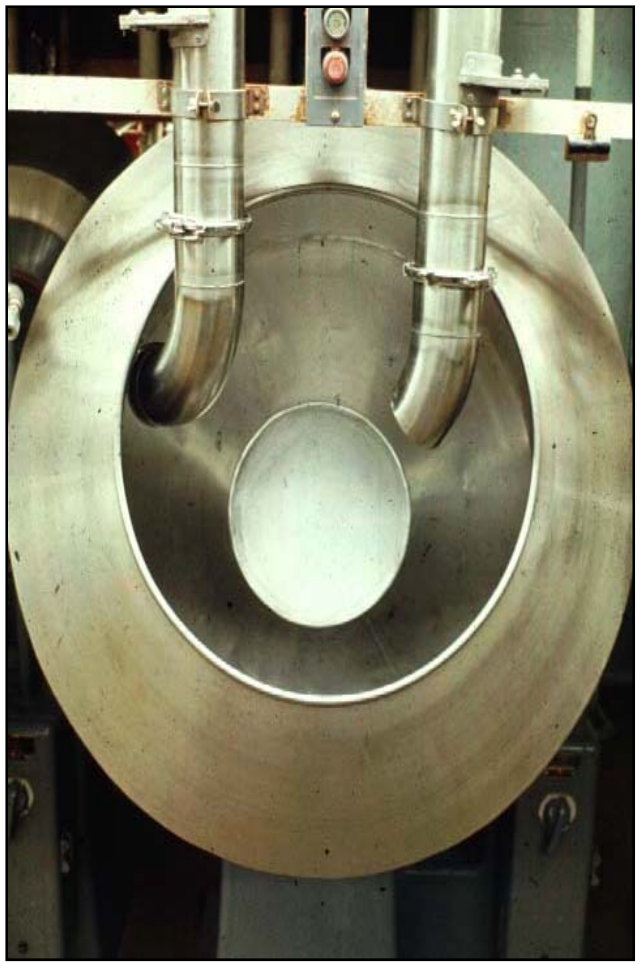
- Coating pans, and
- Fluid-bed processors.

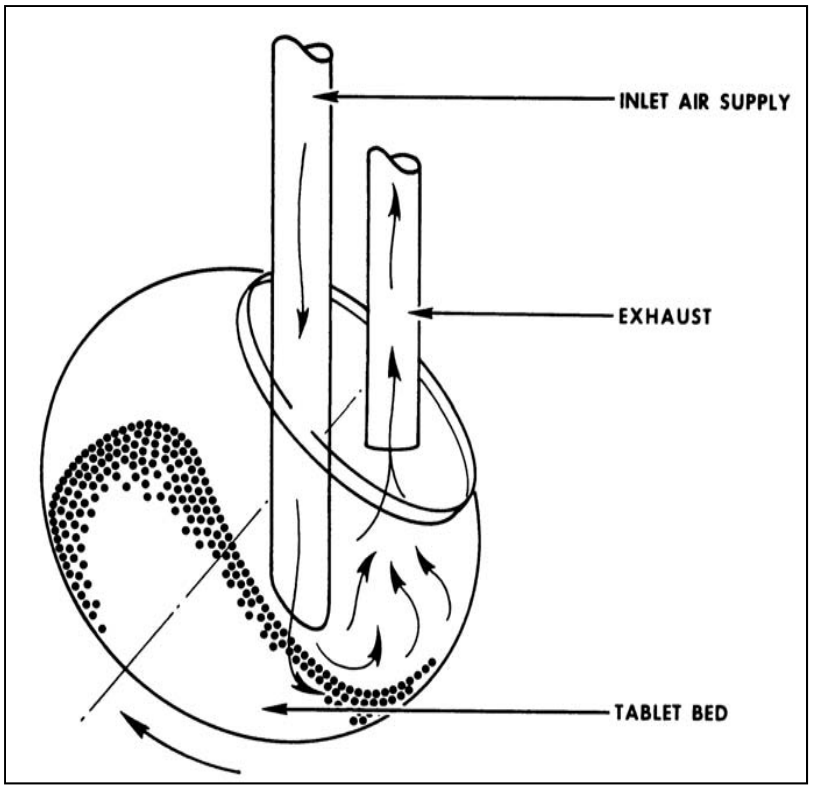
Ancillary Equipment Used in the Coating Process

- Air-handling equipment (blowers and heat exchangers.
- Liquid metering equipment (pumps).
- Dosing systems (e.g. spray guns).
- Coating liquid holding tanks.
- Process monitoring systems.
- Process control systems.
- Effluent treatment systems (e.g. dust collectors, solvent recovery equipment, etc.).

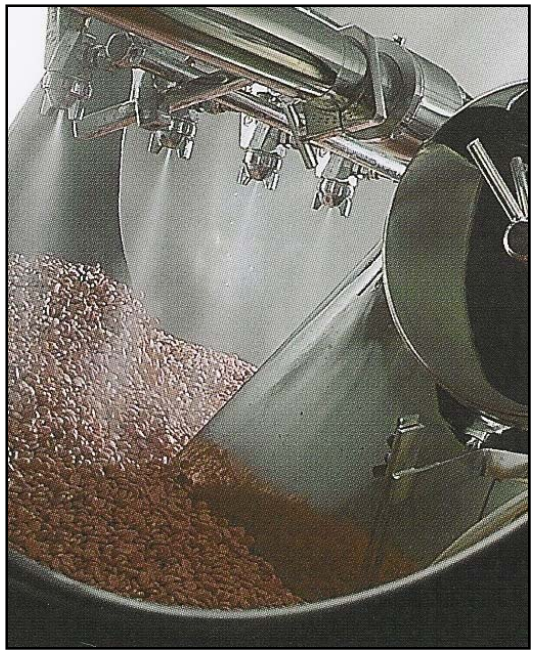
PAN COATING EQUIPMENT

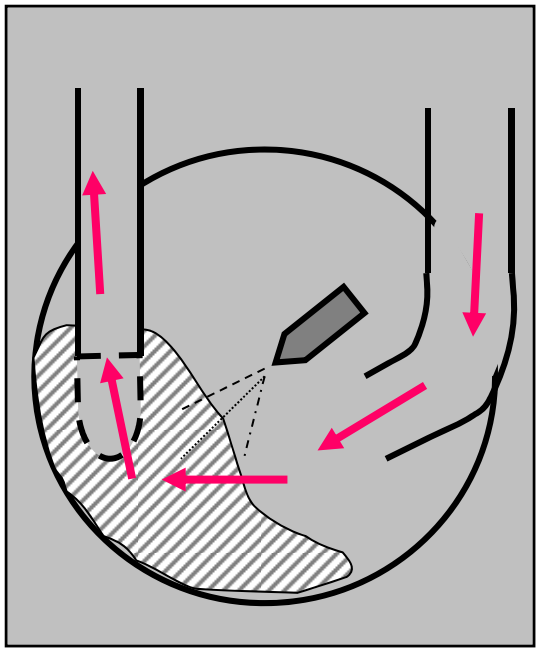
Conventional Batch Pan-Coating Equipment



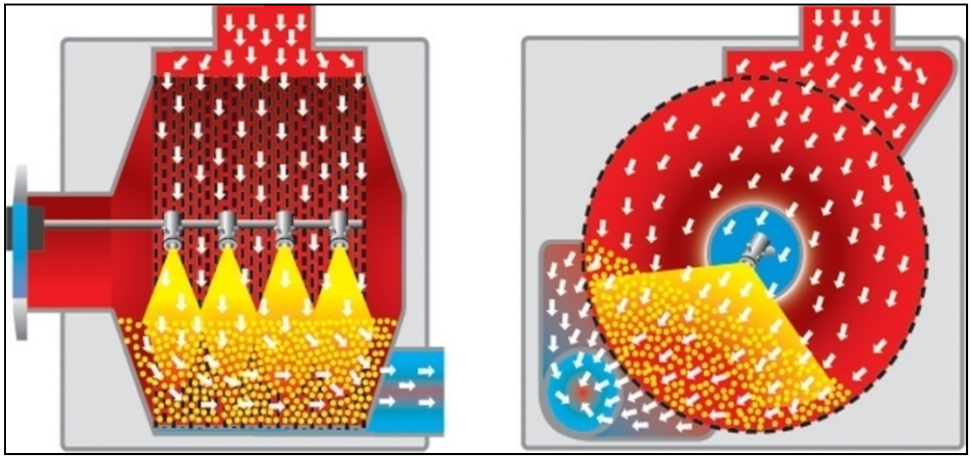


Upgraded Conventional Batch Pan-Coating Equipment

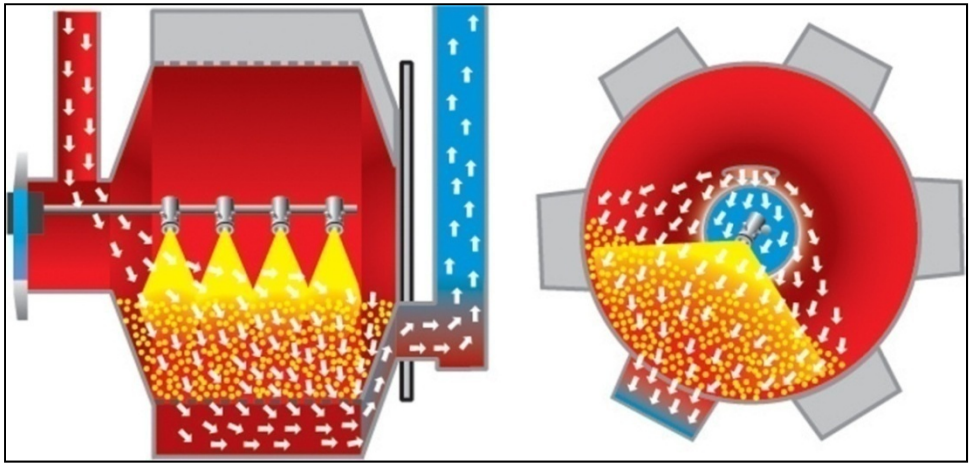




Side-Vented Pan Coating Equipment



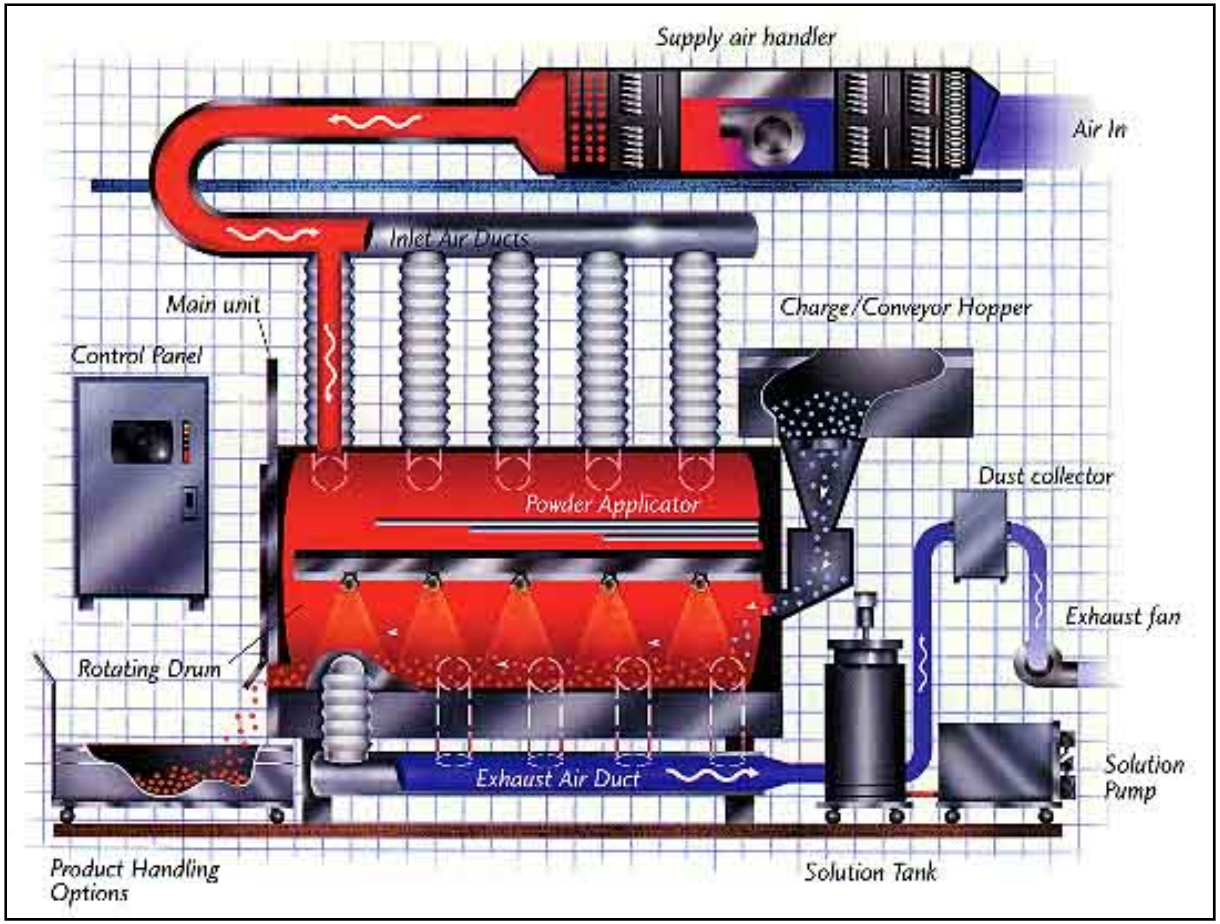
A. Fully Perforated Pan



B. Partially Perforated Pan

Courtesy of Vector Corporation

Continuous Pan-Coating Processes



Courtesy of Vector Corporation

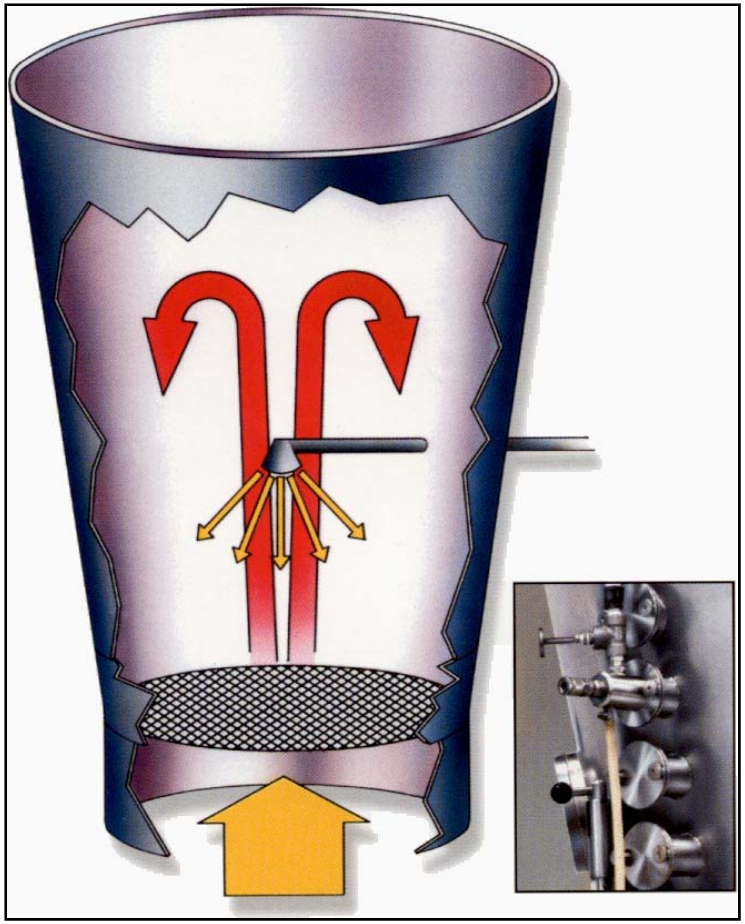
FLUID-BED COATING EQUIPMENT

Examples of Fluid-Bed Coating Equipment

Commonly, fluid-bed equipment is designed on the principle of one processing unit capable of accepting each of various inserts, including:

- Bottom-spraying unit (“Wurster” type).
- Top-spraying unit (granulator type).
- Tangential-spraying unit (rotor type).

Fluid-Bed Coating Equipment: Top Spray

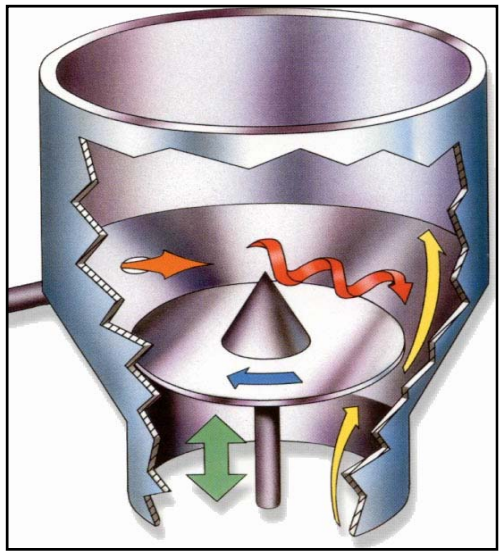


Courtesy of Glatt Air Techniques

Fluid-Bed Coating Equipment: Bottom Spray

Courtesy of Glatt Air Techniques

Fluid-Bed Coating Equipment: Tangential Spray



Courtesy of Glatt Air Techniques

Features of the Three Types of Fluid-Bed Coating Equipment

Method	Advantages	Disadvantages	Applications
Top Spray	• Large batch sizes. • Easy nozzle access. • Simple setup. • Excellent mixing.	• Limited weight gains. • Highest potential for spray drying.	• Film coating. • Taste masking. • Hot-melt coating.
Bottom Spray	• Moderate batch sizes. • Uniformly coated product. • Wide range of applications.	• Nozzles not easily accessible. • Tallest of three machines.	• Sustained-release coating. • Drug layering. • Taste masking.
Tangential Spray	• Easy setup. • Easy nozzle access. • High spray rates possible. • Batch size flexibility.	• Product subjected to high mechanical stress.	• Drug layering. • Pelletization. • Sustained-release and enteric coating.

B.

OVERVIEW OF FILM-COATING PROCESSES

Film Coating: A Process Under Control?

Process control in film coating presents many challenges because:

- The list of potential parameters that can affect product quality is quite extensive.
- The impact, on product quality, of key elements of the process is poorly understood, and often ignored.
- Technology transfer is often ineffectual, and the impact of equipment changes (during transfer from the laboratory to the pilot, and ultimately the full production scale) is underappreciated.

Process Control: What Needs to be Controlled?

There are several critical elements of the process to consider, namely:

- The drying process.
- The spray application process.
- Coating process efficiency.
- The uniformity of distribution of the coating.
- Pan loading.
- Process Endpoint.

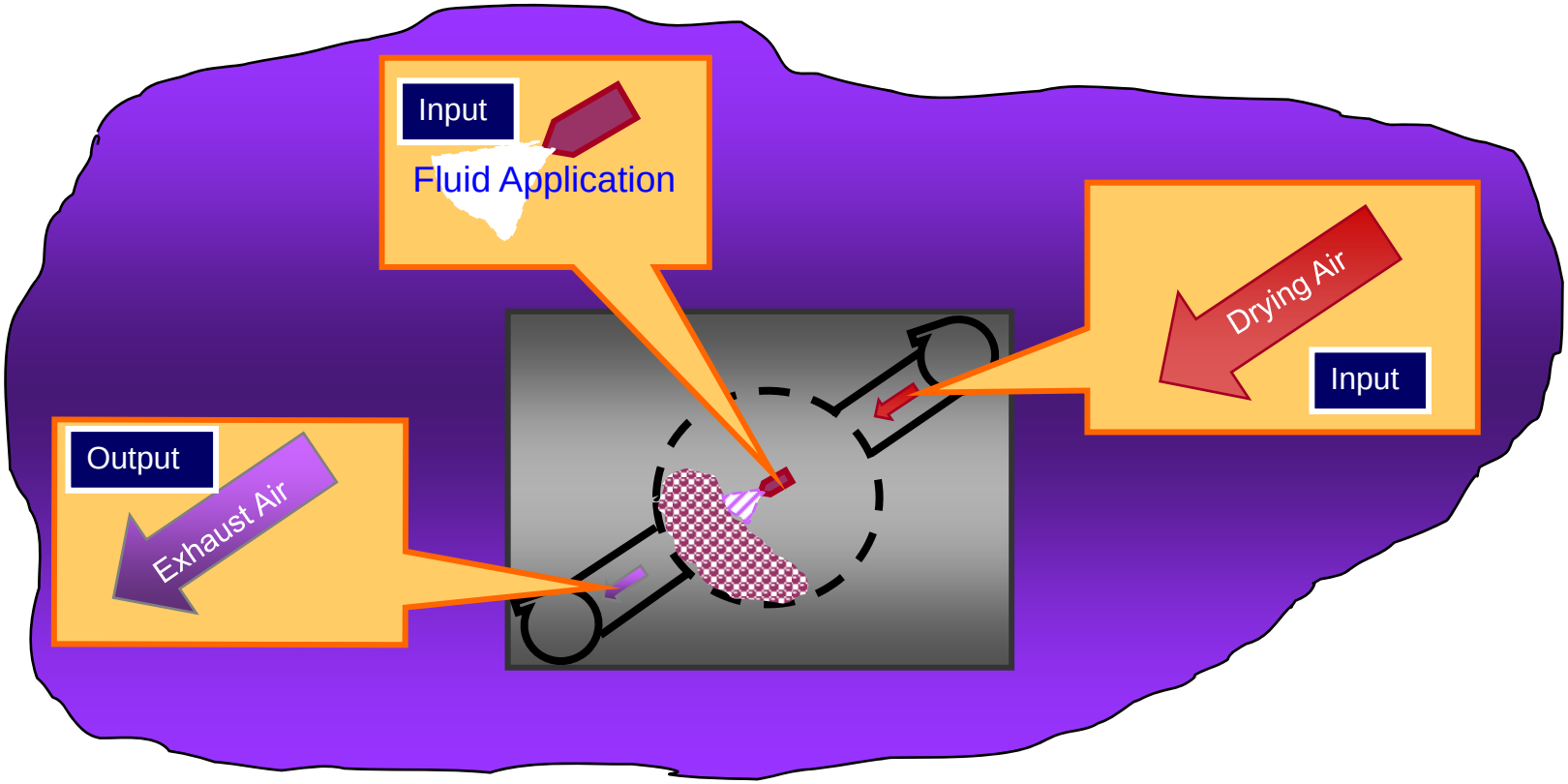
Examining the Drying Process

Process Control: What Factors Affect the Drying Process?

Removal of coating solvent will depend upon:

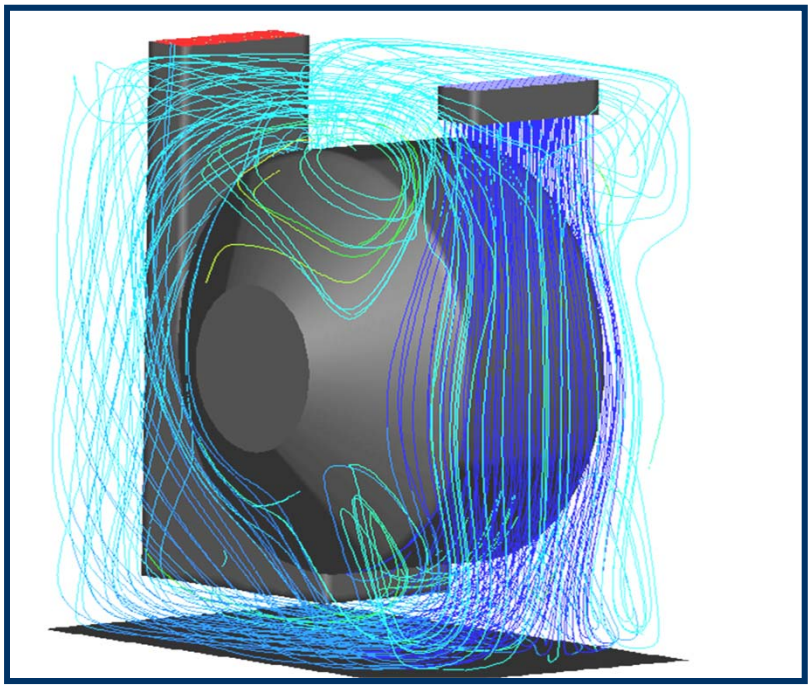
- Drying capacity of process air stream:
  - Mass, or volume, of air.
  - Temperature of air.
  - Moisture content of air.
- Surface area from which drying takes place:
  - Droplet size (controlled by atomization air pressure and coating solution properties) of coating liquid, and ultimately the diffusion rate of water to the surface of the droplet as viscosity increases.
  - Tablet surface area (impacted by pan fill, tablet size and shape).
- Rate at which solvent is introduced into the process:
  - Spray rate.
  - Solvent content of coating liquid.

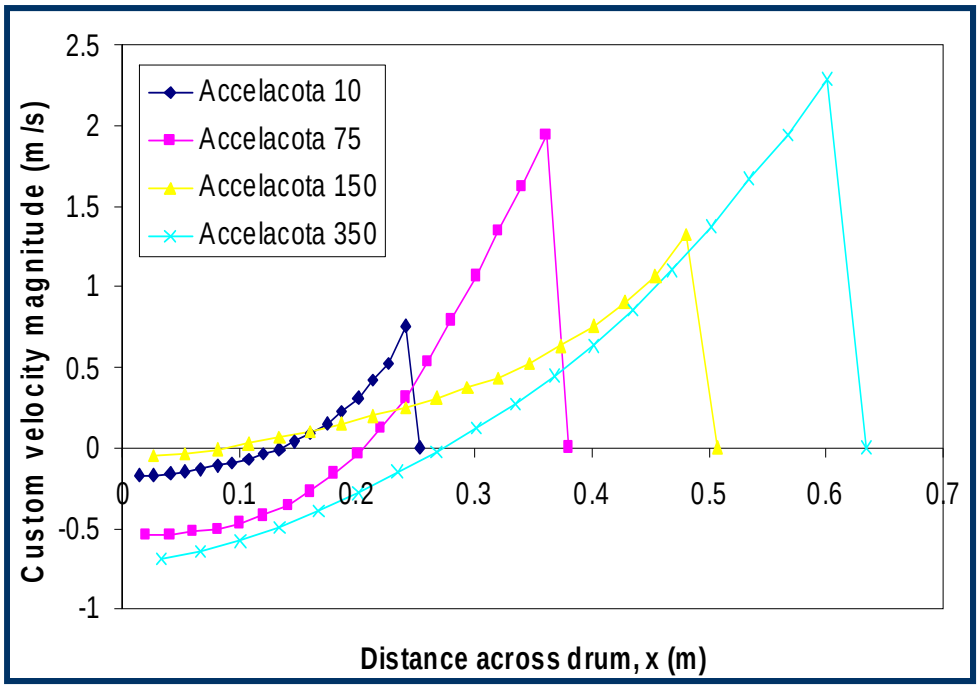
Thermodynamics Considerations



Modelling (CFD) Air Flow Within the Coating Pan

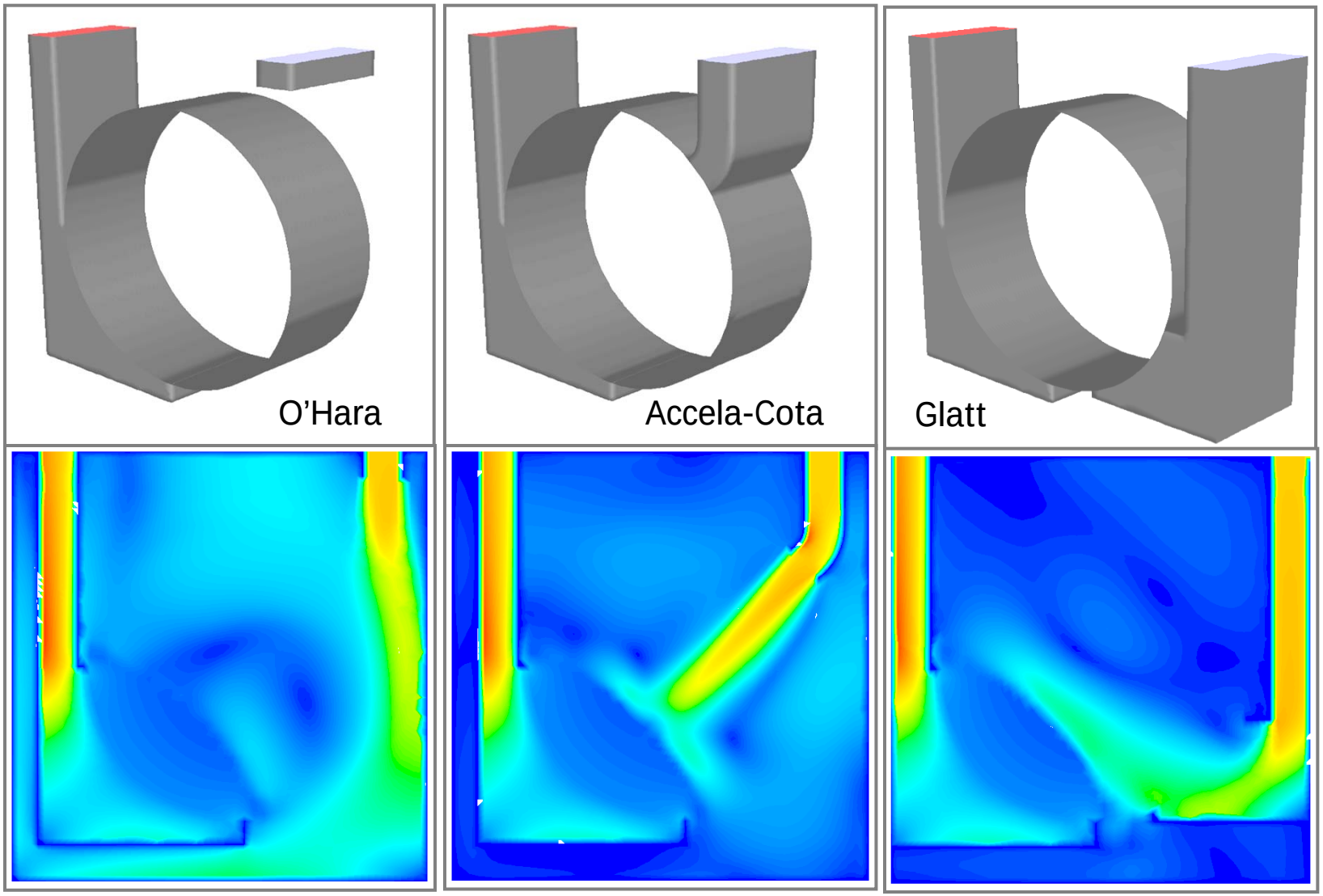
- Majority of the air circulates around the drum before entering.
- Circumferential velocities induced inside the drum.
- Absence of an intake plenum is responsible for this.





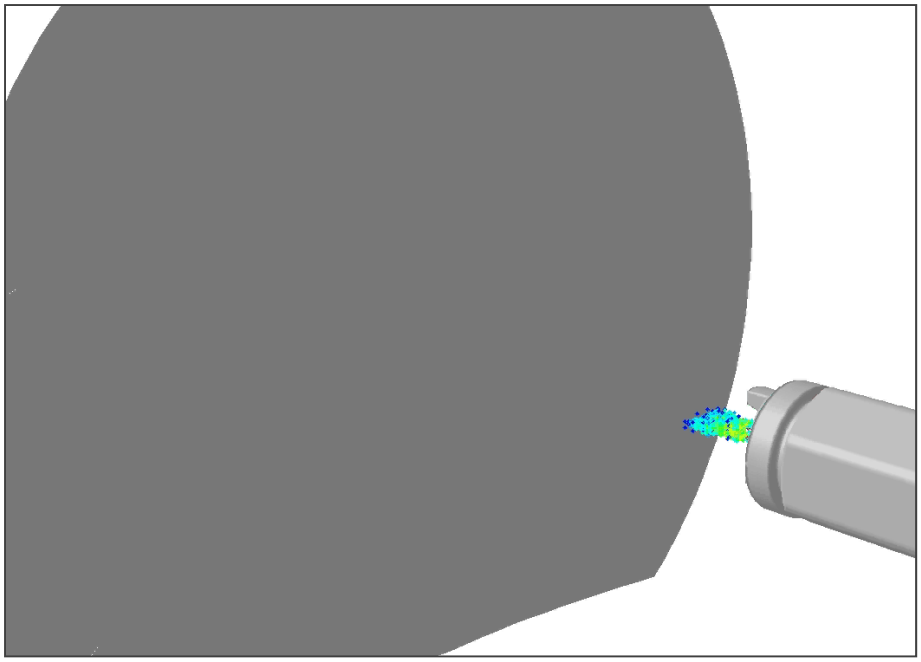
Far-Field : Scaling Drum Sizes

Side Vented Pan: Influence of Inlet Plenum Configuration on Airflow



Understanding Spray Dynamics

What Do We Mean by Spray Dynamics?



Spray dynamics essentially involves those factors that influence:

- Droplet size, and droplet size distribution.
- Droplet velocity.
- Droplet momentum at impact.
- Spray coverage (across the surface of the tablet bed).
- The relative “wetness” of droplets as they impact the surface of the tablet bed.

Process Control: What Factors Affect Spray Dynamics?

In the context of critical process elements, key issues to consider are:

- The impact of the drying process.
- The relationship between spray rate, liquid viscosity, coating liquid solids content *and* the driving force for atomization (atomizing and pattern air pressure and volume).
- Gun-to-bed distance (which is affected by equipment set-up and tablet charge).

The Myths Surrounding Spray Application of Coating Liquids

Common myths include:

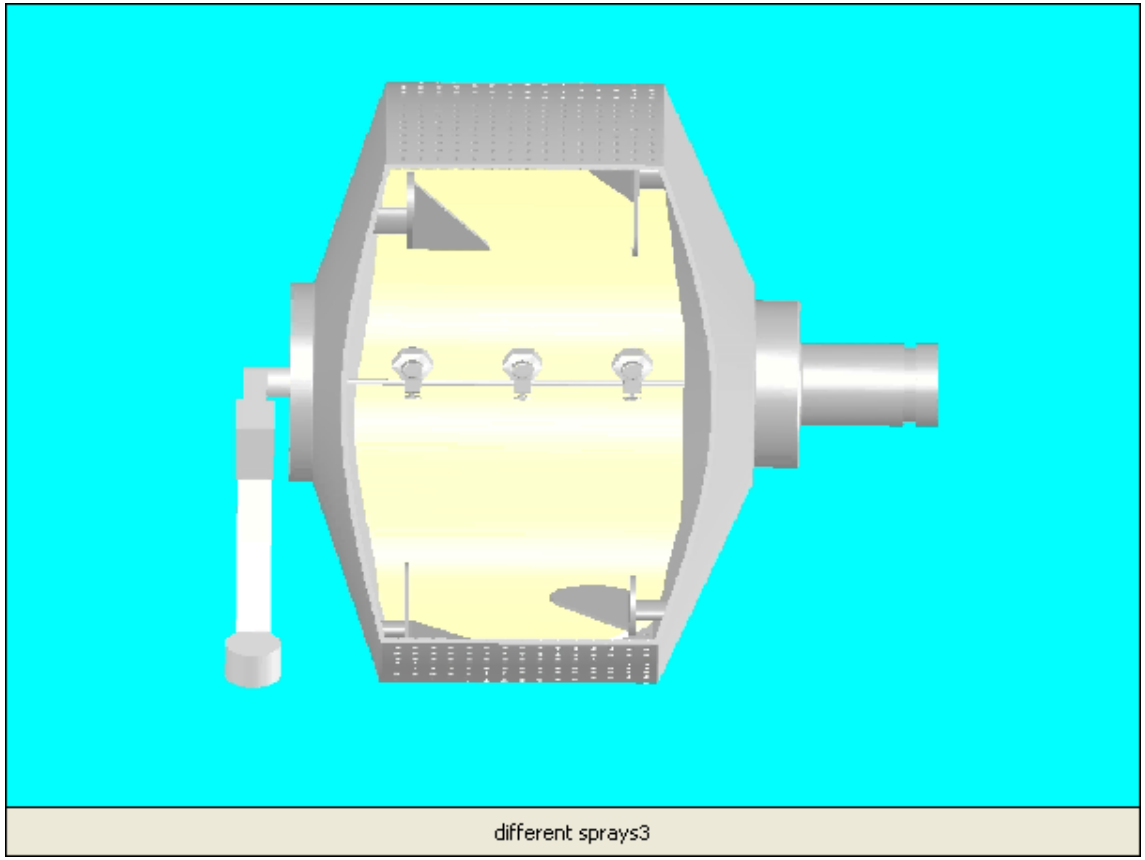
- **Atomized droplets get smaller (because of solvent evaporation) the further they travel from the spray nozzle. In fact, they get LARGER, because of droplet collisions.**
- **Larger droplets create rougher coated tablets, while smaller droplets produce a smoother finish. Intuitively, this seems like a correct assumption, and generally there is some truth to it. However:**
  - Smaller droplets, because of the larger surface area of the total atomized liquid in this state, can facilitate faster evaporation of solvent while the droplets are in flight, creating a more rapid viscosity build, and hence less ability to spread on impact.
  - Larger droplets, if they remain more fluid, because of their greater momentum, can deform more easily and spread out on impact (the so-called “splat effect”).
- **All spray guns are the same. In fact, there is a lot of published data to show that spray guns differ considerably. Major differences, under similar atomization conditions, include:**
  - Significant differences in droplet size distributions.
  - Significant differences in droplet velocities.
  - Significant differences in bed coverage

Pan Film Coating: Setting Up Spray Equipment

Key issues to consider are:

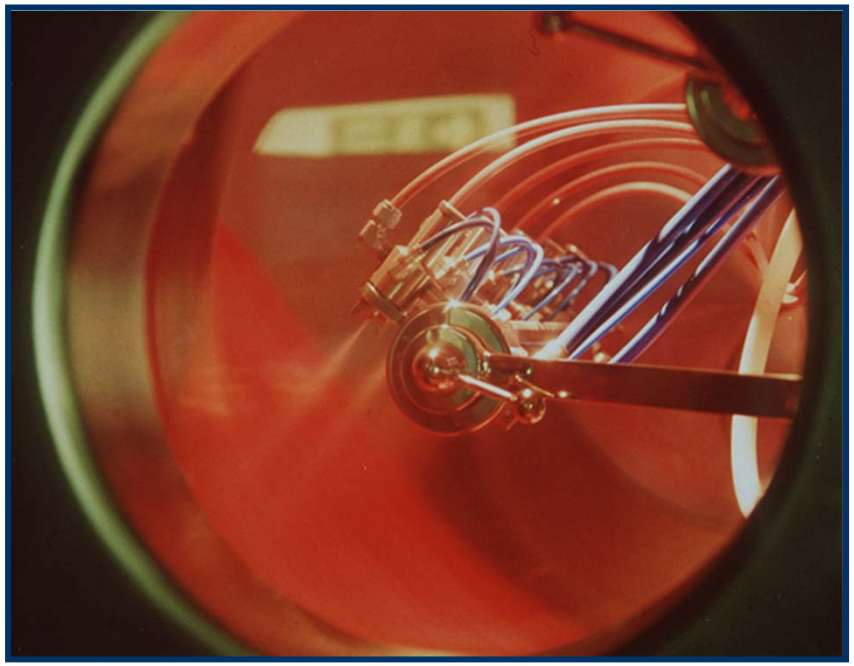
- Establishing the correct gun-to-bed distance and separation.
- Establishing the correct location of the guns above the surface of the tablet bed.
- Ensuring that all spray guns are spraying at the same rate.
- Establishing appropriate atomizing and pattern air (pressure and volume)

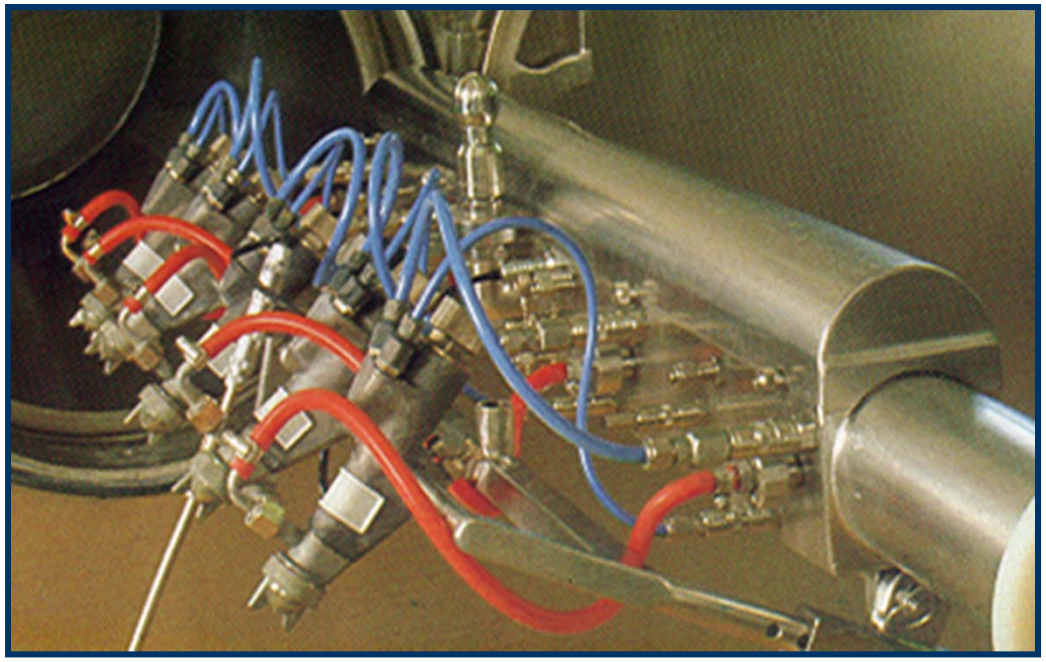
Example of Typical Gun Set-Up in a Coating Pan



different sprays3

Examples of Multiple Spray Gun Arrangements





Calibration of Spray Guns

All coating processes on the manufacturing scale will use multiple spray-guns. It is critical to ensure that each spray gun is delivering coating fluid at the same rate.

Some points to remember:

- Always check the accuracy of delivery through each gun at the commencement of each batch process.
- When doing checks on fluid delivery, it is better to do so with the atomizing air switched ON (most spray guns exhibit a siphoning effect when the air is on, and thus the spray rate will be different than when the air is off, and it is also worth remembering that if the volume of air consumed by each gun is different, this can lead to different spray rates).
- Check the accuracy of all flow devices (such as mass flow controllers) frequently to make sure that the information being provided is accurate, and that they are operating within calibration limits.

Understanding the Impact of Process Efficiency

Why Is Coating Process Efficiency Important?

Efficiency has an impact on:

- Amount of coating that must be applied to reach a target weight gain.
- Coating process time and economics.
- Quality (roughness and gloss) of the applied coating.
- Coating structure, and thus coating functionality.

Coating Process Efficiency: What Is Achievable?

Two major issues are:

- ❖ Actual coating process efficiency.
- ❖ Variability in coating process efficiency.

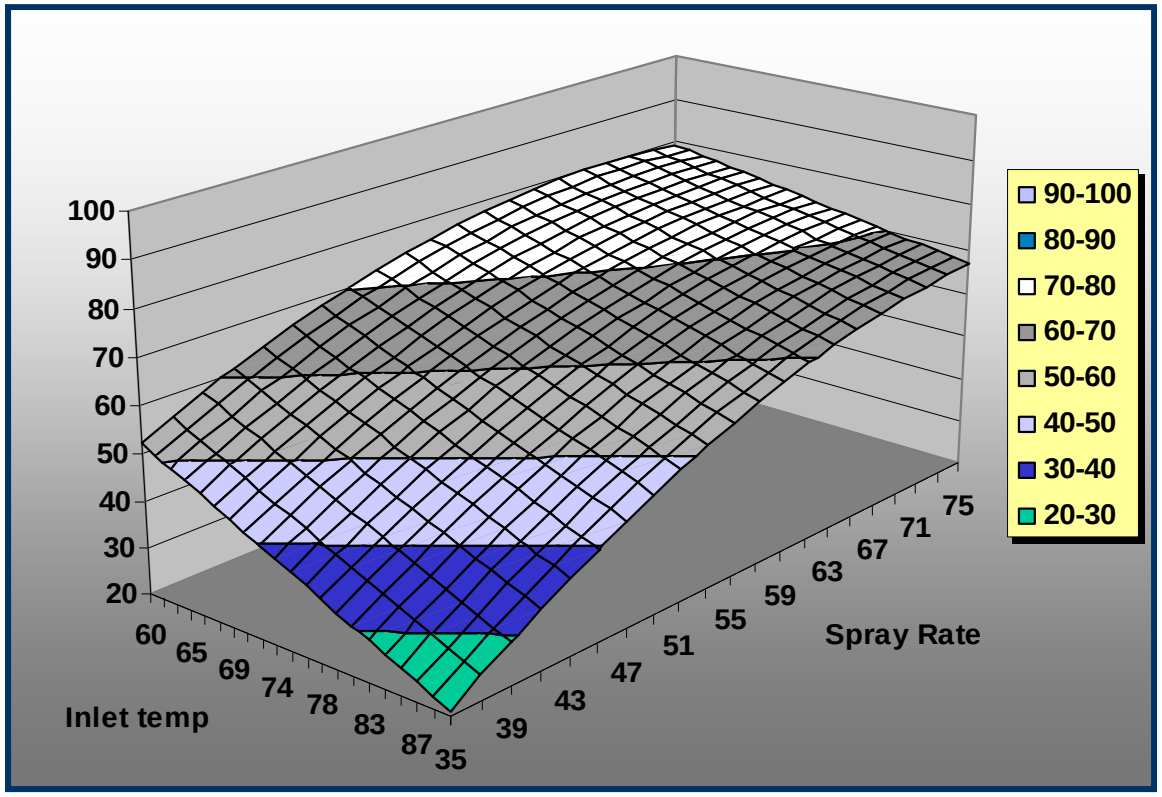
Target process efficiencies >97% (+/- 2%) are achievable, and corrective action should be taken when process efficiencies < 90% are attained, or when variability exceeds +/- 5%

Process Control: What Factors Affect Coating Process Efficiency?

Process efficiency is generally affected by:

- The drying process (including air movement within the coating process).
- Spray dynamics.
- Gun-to-bed distance (which is affected by equipment set-up and tablet charge).
- Tablet charge (including tablet size and shape).

Factors Affecting Process Efficiency



The Importance of Coating Uniformity

The Importance of Achieving Good Coating Uniformity

Coating Uniformity Influences:

- The amount of coating that needs to be applied to achieve visual uniformity (which, in turn, has cost implications).
- Drug release from a modified-release product (when the coating is part of the release-control mechanism).
- Product stability (particularly when the coating is being used as an environmental barrier to improve stability).
- Drug content uniformity (when the coating is being used as a carrier/adherent for the API).

General Factors that Impact Coating Uniformity in a Pan-Coating Process

Key factors are:

- **The dwell time of tablets in the spray zone, which is impacted by tablet speed (and hence, pan speed).**
- **The mixing of tablets in the coating pan, which is, in turn, influenced by:**
  - **Pan speed.**
  - **Pan design.**
  - **Tablet size and shape.**
  - **Baffle design.**
  - **Pan loading.**
  - **Air flow.**
- **The rate at which the coating is deposited, which is influenced by:**
  - **Spray rate.**
  - **Coating suspension solids.**
  - **Coating process efficiency.**
- **Uniformity of distribution of the coating, which is impacted by:**
  - **The number of spray guns used.**
  - **Types of spray gun used.**
  - **Atomization and spray pattern conditions used**

The Criticality of Pan Loading

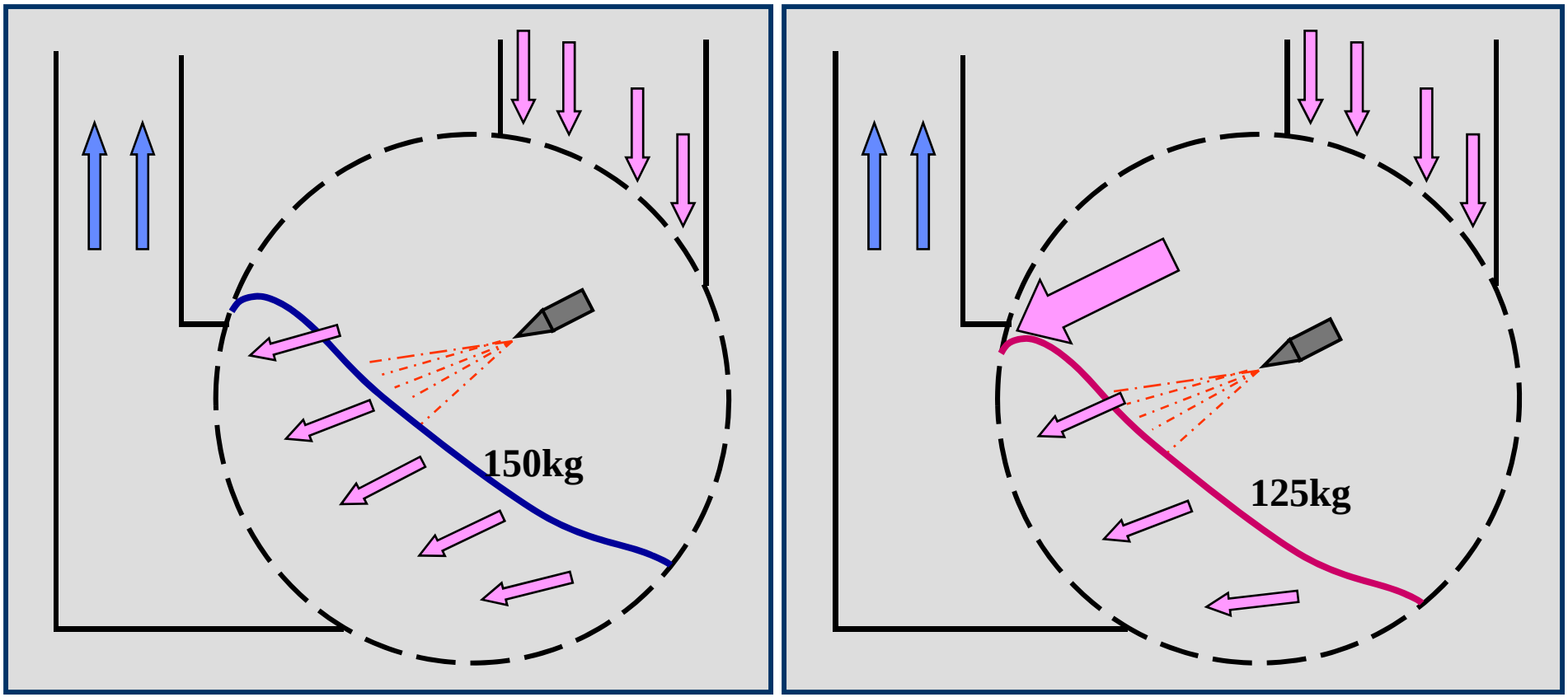
Process Control: Pan Loading?

On the production scale, pan loading is a contentious issue because it is a parameter not usually determined by pan capacity, but more by tablet manufacturing batch size.

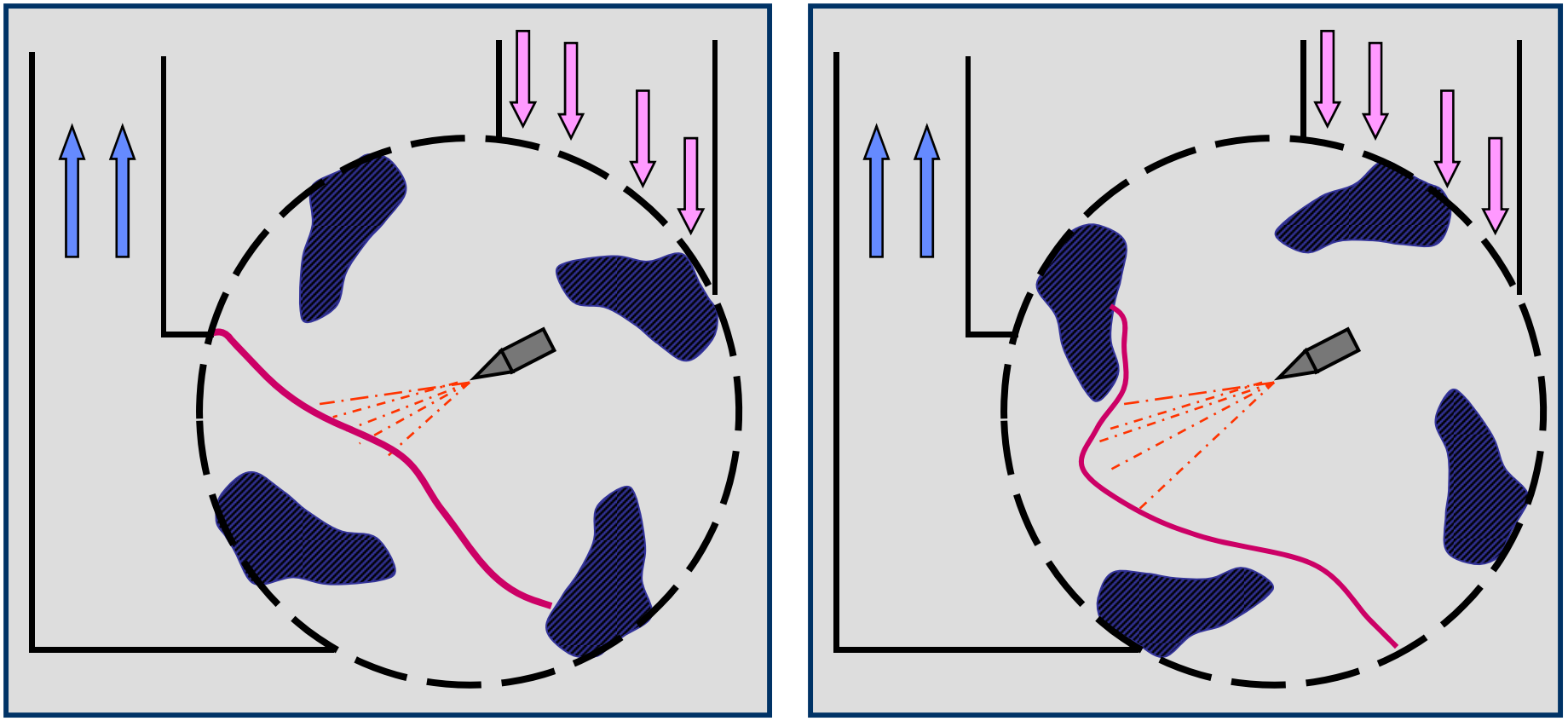
As a potential process variable, it can impact:

- **The drying process.**
- **Spray dynamics.**
- **Coating process efficiency.**
- **Uniformity of distribution of the coating.**
- **Coated tablet quality.**

Pan Loading: Potential Impact On Airflow



Pan Loading: Potential Impact On Spray Coverage



Determining Process Endpoints

Ensuring the Same Amount of Coating is Deposited for Each Batch

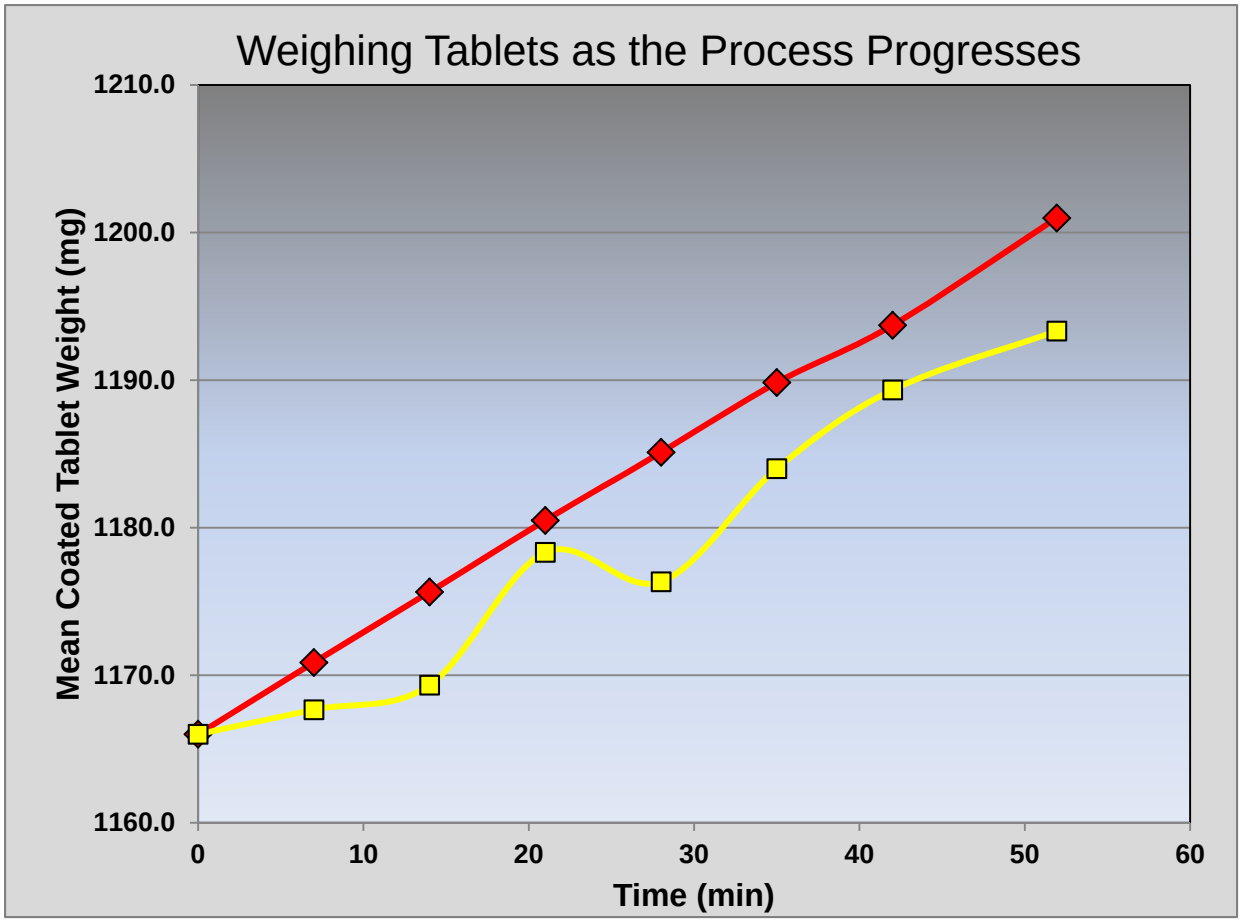
Critical issues to consider here are:

- Using accurate methods to determine process end point, or
- Optimizing the process so that process variability is under control, thus ensuring that when a fixed amount of coating suspension is applied, the same target weight gain is achieved each time.

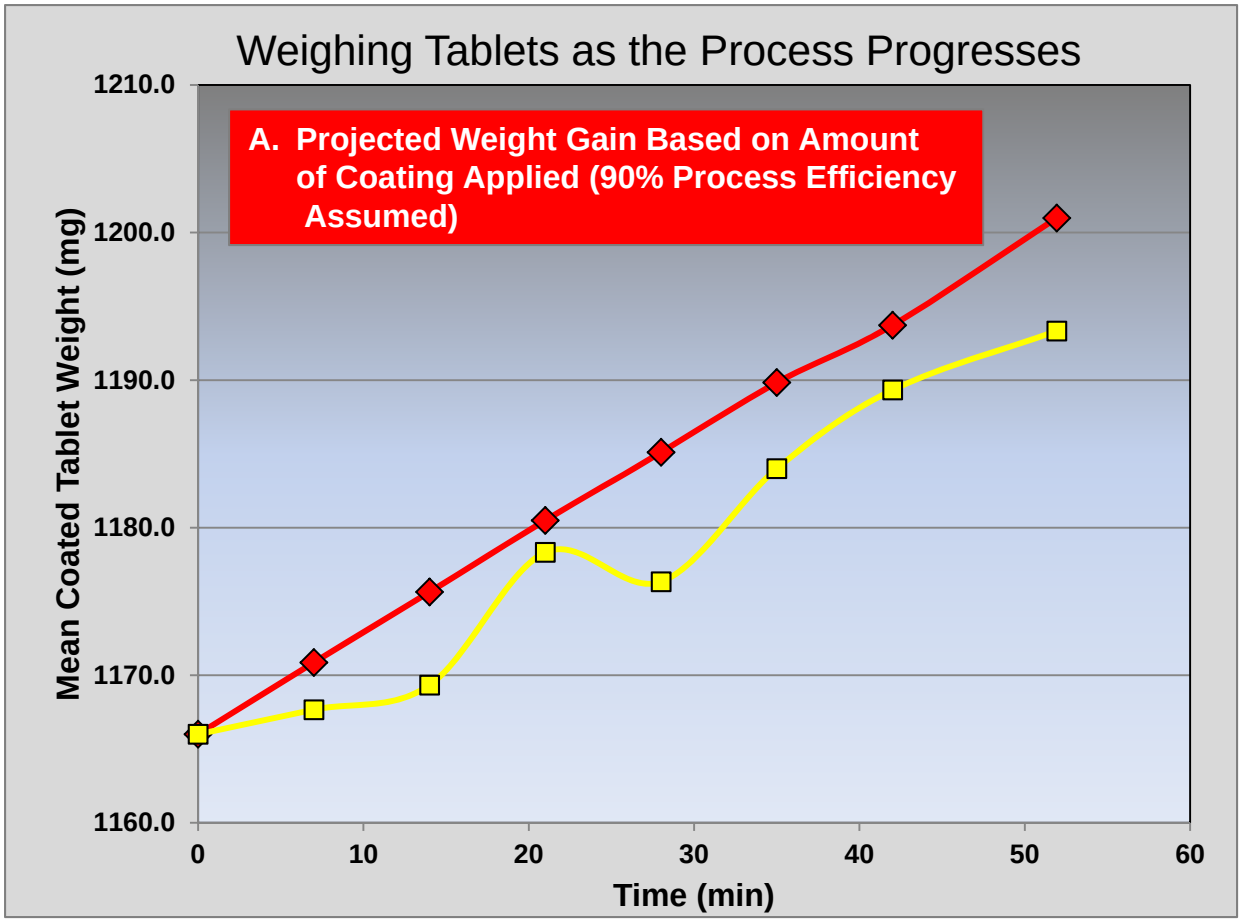
How Not to Determine Process End Point

Weighing Tablets as the Process Progresses

How Not to Determine Process End Point



How Not to Determine Process End Point



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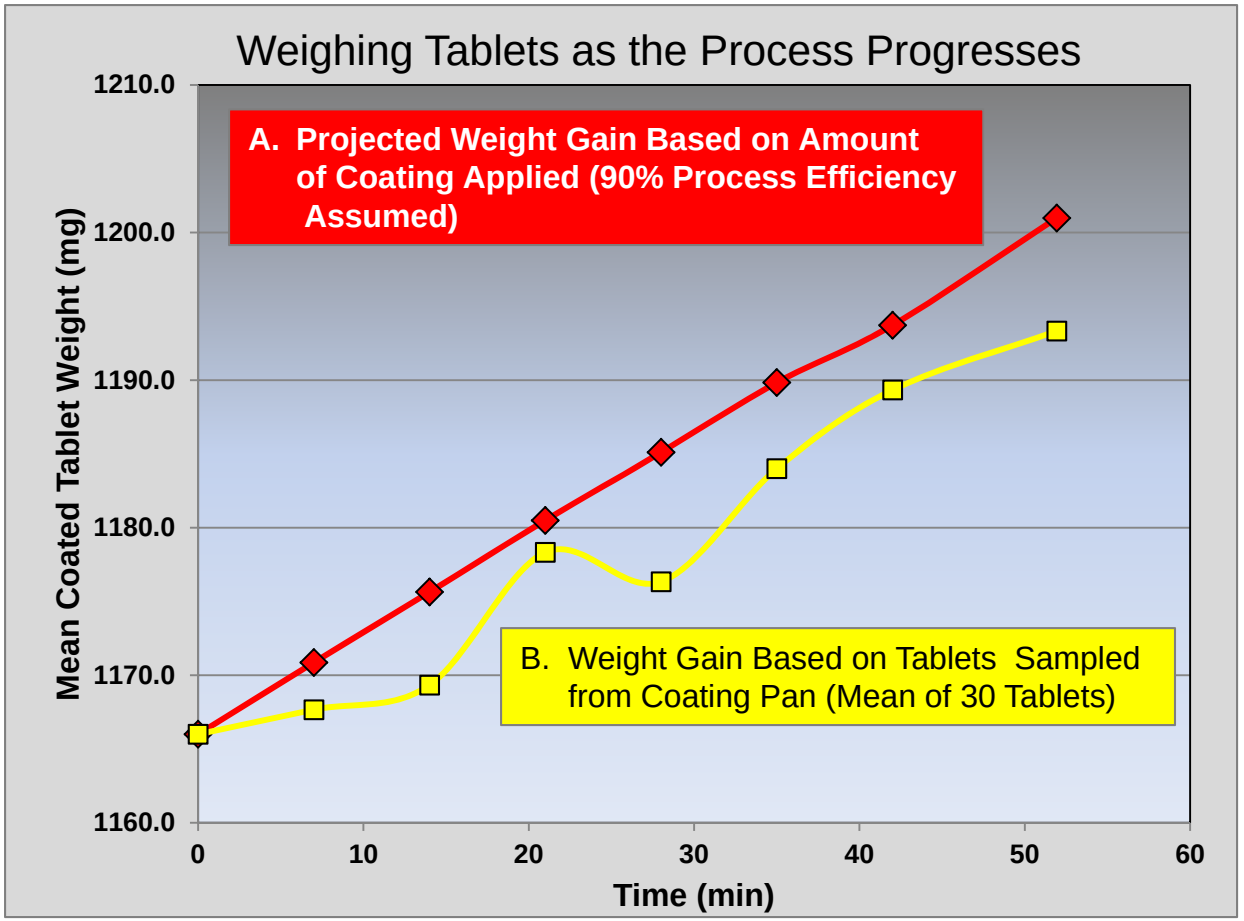
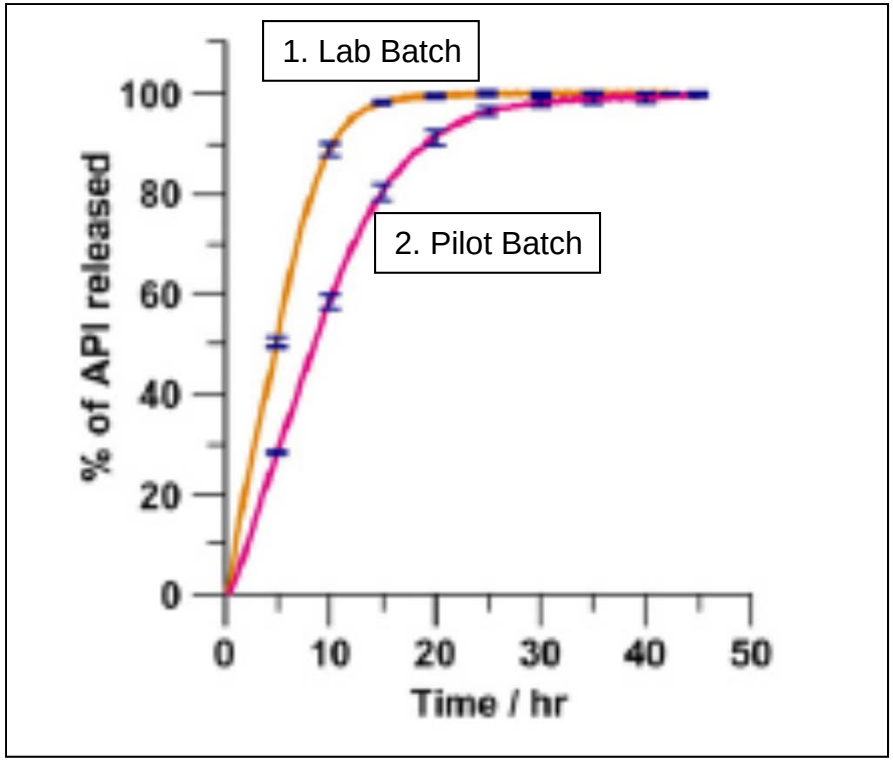


The Shortcomings of Conventional Process Monitoring Techniques

Dissolution Results for a Modified-release Coated Product



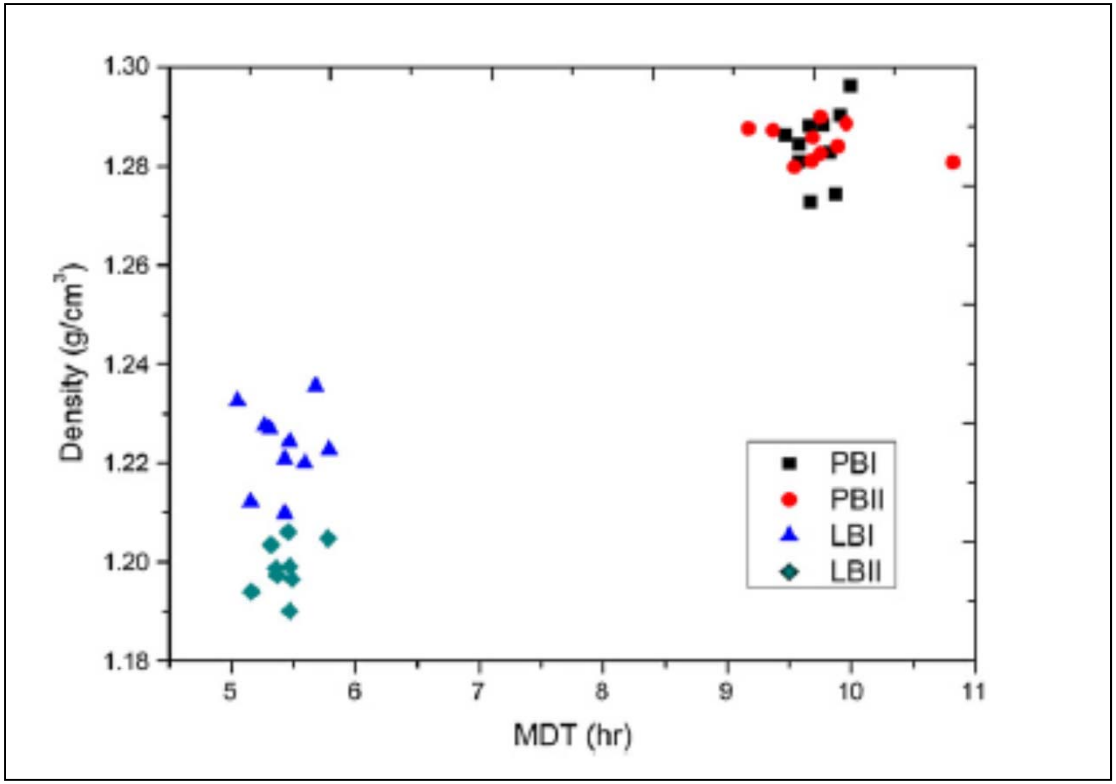
Lab batch weight gain = 42.52 mg

Pilot batch weight gain = 42.54 mg

Ho, et al, Journal of Controlled Release, 127, pp79-87, (2008)

The Shortcomings of Conventional Process Monitoring Techniques

Application of terahertz Analysis to Evaluate a Modified-release Film Coating to Tablets



Ho, et al, Journal of Controlled Release, 127, pp79-87, (2008)

Effective Means to Determine the Endpoint of Film-Coating Processes

- **Control process efficiencies, and then apply the precise amount of coating needed to reach a target endpoint.**
- **Use effective means of monitoring the process to determine endpoint, such as:**
  - On-line nIR
  - On-line Terahertz
  - On-line Raman spectroscopy.

C.

SCALING UP COATING PROCESSES

Introduction to Process Scale Up

Scale Up: What Is Typically Involved?

Simplistically, this process involves:

- **Taking a laboratory-scale process (hopefully one that has been appropriately optimized) and transferring the processing technology firstly to the pilot scale and, ultimately, to full production scale.**
- **Further optimizing the process on the larger scale to take into account those issues whose influence could not have been easily predicted during earlier process development activities.**

Film Coating: Predicting Scale-Up Issues

Process parameters that are usually fixed for the purposes of determining process conditions on scale-up include:

- **Product and coating formulations.**
- **Solids content of coating suspension.**
- **Amount of coating applied (although improvements in coating process efficiency on scale-up may require theoretical levels to be adjusted).**
- **Inlet air temperatures (although these may be adjusted to accommodate other limitations, such as uncontrollable changes in inlet air humidity and limitations on heater capacity).**

Typical Changes that Occur on Scale-Up

These include dealing with:

- **Increased batch sizes.**
- **Increased attritional effects.**
- **Increased spray rates.**
- **Increased number of spray guns (or a change from a single-headed to multiple-headed nozzles).**
- **Changing spray dynamics.**
- **Increased drying air volumes.**
- **Increased processing times per batch.**

The Robustness Factor

We must ensure that:

- **The formulations (core and coating) used are sufficiently robust to meet the needs of the operation. This requirement is all the more important when viewed in terms of the increased (but often ill-defined) stresses to which the product is subjected on scale-up.**
- **Critical elements of the coating process, and their impact on final product quality (in the broadest sense), have been determined and taken into account during process optimization.**

Key Product & Process Attributes to Consider

Coated Product Attributes		Coating Process Characteristics
Aesthetic	Functional	
High gloss	Drug release characteristics meet target requirements	High, and reproducible, coating process efficiency
Smooth coating		
Good color uniformity	Coated product meets stability requirements	High uniformity of distribution (on a weight basis) of the coating from tablet-to-tablet or particle-to-particle
Absence of edge chipping		
Absence of film cracking	Effective taste-masking is achieved (if required)	
Absence of logo bridging		
Absence of twinning	Coated product meets dose strength requirements	High productivity
Absence of picking		

Potential Consequences of Inadequate Product & Process Development

Once the product and process has been transferred to Operations, these may result in the need to:

- **Discard batches (often determined on the basis of balancing recovery costs with the inherent value of the batch).**
- **Reprocessing batches.**
- **Sorting batches to remove defective material.**

Factors to be Considered

The scale-up process may well involve using coating systems that employ:

- **Organic-solvent-based polymer solutions.**
- **Aqueous polymer solutions.**
- **Aqueous polymer dispersions.**
- **Hot-melt systems.**

And processes that utilize:

- **Coating pans.**
- **Fluid-bed processors.**

Scaling Up Pan-Coating Processes

Parameters to Consider

- **Drying air volume.**
- **Pan speed.**
- **Pan loading.**
- **Number of spray guns used.**
- **Gun to tablet-bed distance.**
- **Spray rate.**
- **Spray gun dynamics.**

Determining Spray Rate on Scale-Up

Film coating, especially the aqueous process, is a thermodynamic process. If the equipment features and climatic conditions are similar in the production environment to those used on the lab scale, then this equation can be used as a simple rule of thumb:

$$S_2 = (S_1 \times V_2) / V_1$$

Where: S_1 **and** S_2 **are the respective spray rates, and** V_1 **and** V_2 **the respective air flow volumes, for the lab and production scales.**

For more complex situations, it may well be worthwhile applying the concepts outlined, inter alia, by Glen Ebey [*Pharm. Technol. 11 (4), p 40 (1987*)].

Scaling Up a Pan-Coating Process: Case Study

Process Characteristics:

- Process involved application of enteric coating to aspirin tablets.
- During the development of the process on the laboratory scale, a statistical D.o.E. approach was used that was designed to examine, and identify, critical process parameters that would influence the functionality of the final coated product.
- Once process development work was completed, the knowledge obtained was used to define process conditions to be used on the larger processing scale(s).

Process Operating Parameters Employed

Process Parameter	Coating Process Conditions Used		
	24” Accela-cota	48” Accela-cota	60” Accela-cota
Inlet air volume (cfm)	250	1800 – 2000	2300 – 2700
Exhaust air volume (cfm)	300	1900 – 2100	2400 – 2800
Inlet air temp. (°C)	75 – 84	70 – 80	70 – 80
Exhaust air temp. (°C)	38 – 41	40 – 45	40 – 45
Spray rate (g min^{-1})	60 – 70	400 – 500	650 – 700
# spray guns used (*)	2	3	5
Gun-to-bed distance (in)	5-7	8-12	10-12
Atomizing air pressure (psi)	35 – 40	60 –80	50 –70
Pan loading (kg)	12	135	300
Tablet bed prewarm (°C)	45 – 50	45 – 48	45 – 48
Pan speed (rpm)	14	6	4
Enteric coating suspension solids content (% w/w)	15.0	15.0	15.0
Quantity of enteric coating applied	10.0	10.0	10.0

(* Binks 605; 66SS fluid nozzle; 66SH air cap)

Enteric Test Results for Aspirin Tablets Coated in Scale-Up Processing Studies

Batch Size (kg)	Disintegration Test			Dissolution Test (% Drug Released)	
	% Failures After 2 hours in 0.1 N HCl Solution		DT in buffer, pH=6.8	After 2 Hours in 0.1 N HCl	After 90 min in Buffer, pH = 6.8
	Enteric Test (ET)	Stressed Enteric Test (SET)			
12	0	0	8:05 ± 0:32	0	104.5
135	0	0	7:04 ± 0:52	0	91.5
300	0	0	6:32 ± 1:00	0	105.2

Scaling Up Fluid-Bed Coating Processes

Factors That Differentiate Fluid-Bed Coating Processes from Pan-Coating Processes

- Nozzle positions are usually fixed.
- Round (or cone-shaped) spray patterns are usually used.
- There is greater flexibility in batch capacity, especially with the tangential-spray process.
- Atomizing air can contribute greatly to both product movement and attrition.
- Since the fluidizing air is required both for creating movement and effecting drying, these two process requirements have significant interdependence (thus, as the batch weight increases, an increase in fluidizing air may be required to maintain movement, a change that also influences the rate of solvent removal).

Scaling Up Fluid-Bed Processes: Parameters to Consider

Process parameters that are likely to change on scale-up include:

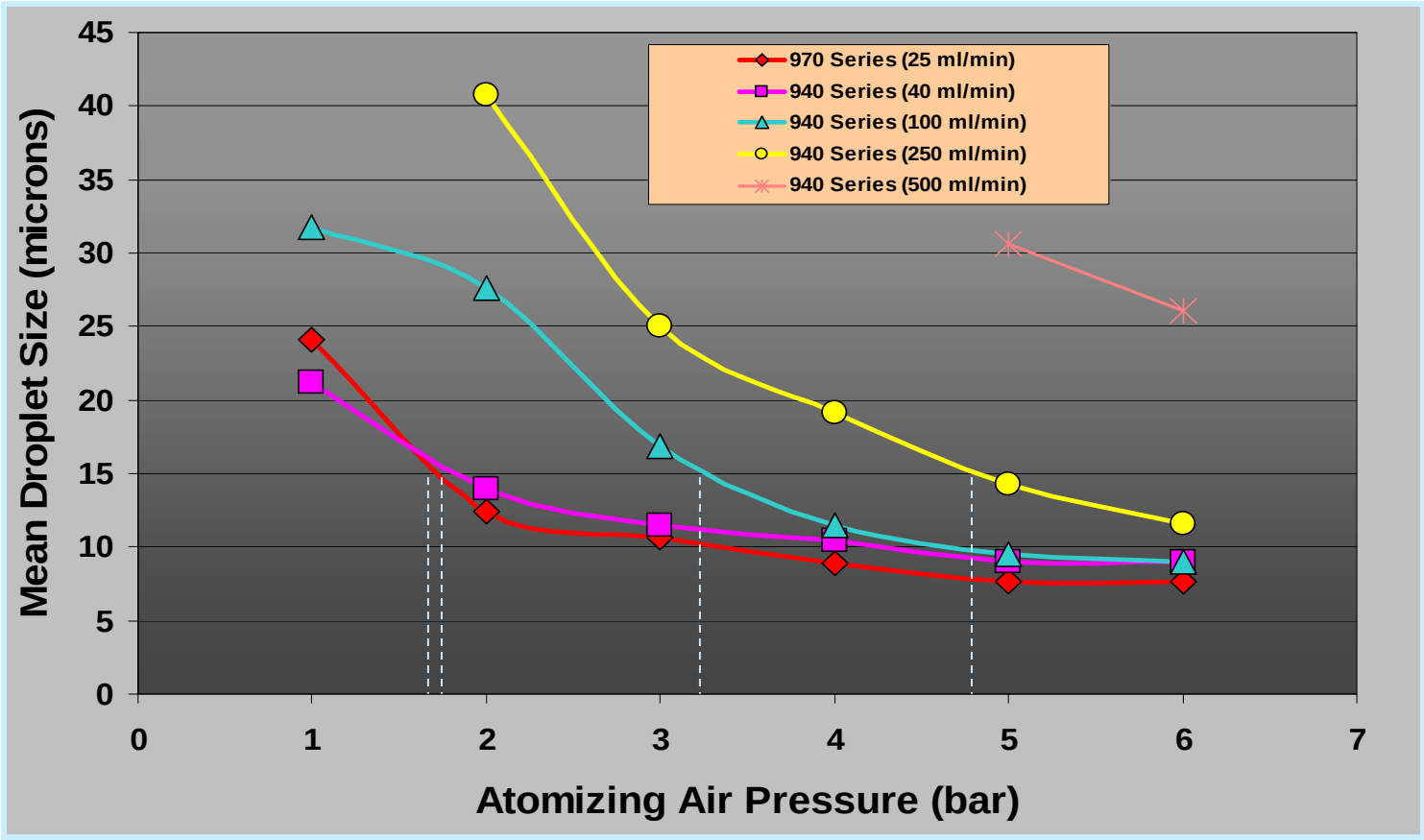
- **Batch size.**
- **Drying/ fluidizing air volumes.**
- **Spray nozzle dynamics (including nozzle type and atomizing air pressure/volume).**
- **Spray and evaporation rates.**

Spray Nozzle Considerations in Fluid-Bed Processes

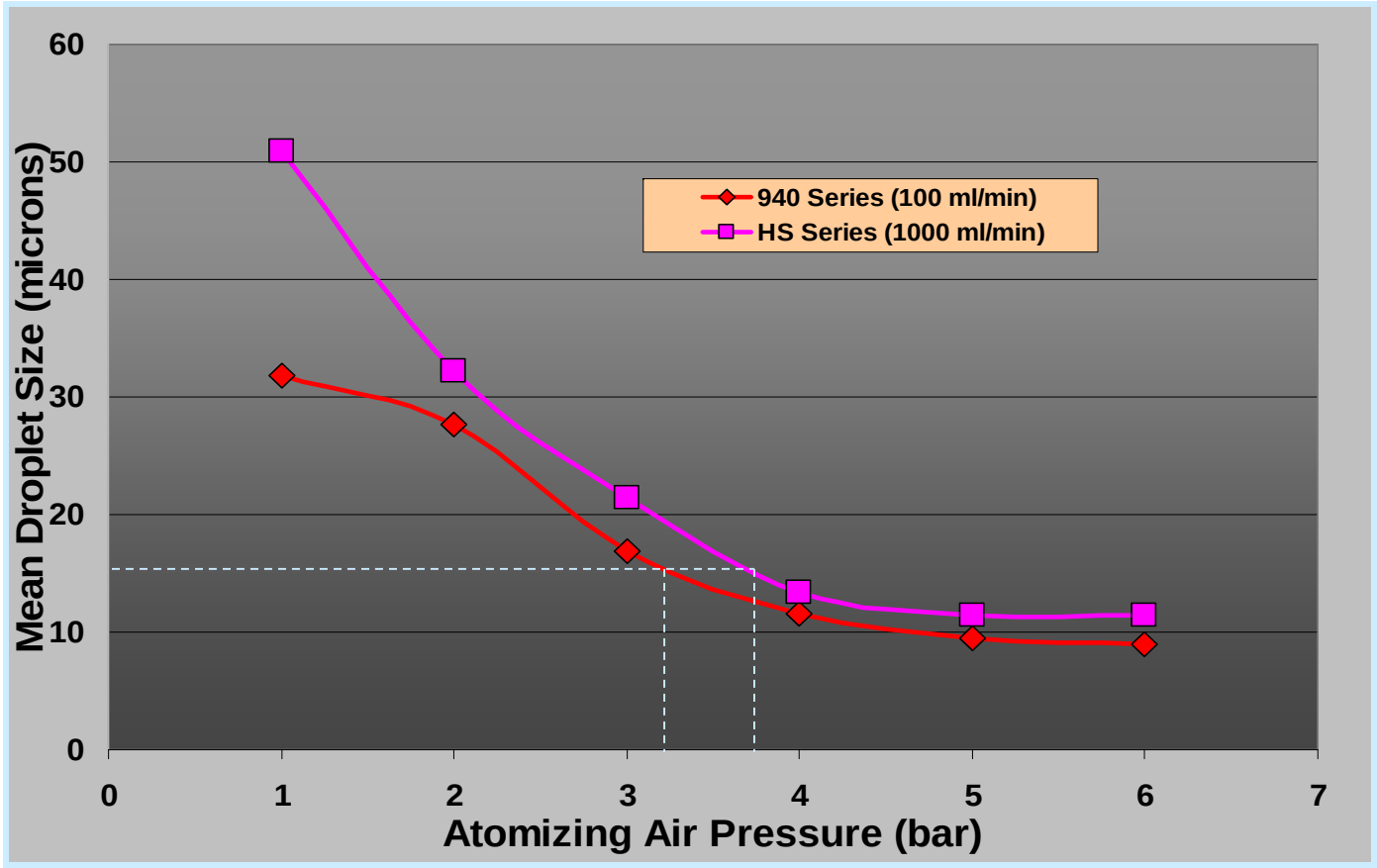
Some challenges to be faced with the fluid-bed processes:

- **The product being coated is usually a multiparticulate, with sizes in the range of 50μm to 1-3mm.**
- **In order to provide a discrete coating (instead of agglomerating), the coating liquid must be atomized into a much finer form than the particles that are being coated.**
- **In order to maintain atomizing efficiency, on scale-up, atomizing air pressures may well have to be increased to levels where the atomization air velocity can contribute significantly to increased product attrition.**
- **In order to meet these atomizing requirements, it may well be necessary to change the type, or model, of gun when moving to a larger scale process.**

Spray Nozzle Considerations in Fluid-Bed Processes



Wurster Pellet Coating Process: Benefits of Using Specialized Nozzles



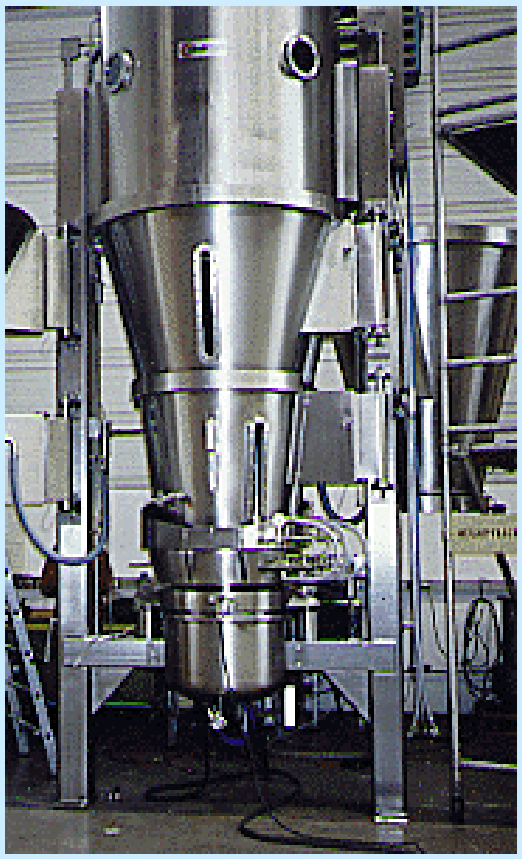
Scale-Up Features of Wurster Process

A. 7” Wurster

Typical batch load: 4.0kg
Number of spray guns: one
Number of partitions: one
Partition diameter: 89mm

B. 18” Wurster

Typical batch load: 40.0kg
Number of spray guns: one
Number of partitions: one
Partition diameter: 219mm



C. 32” Wurster

Typical batch load: 180.0kg
Number of spray guns: three
Number of partitions: three
Partition diameter: 219mm

Scaling Up a Fluid-Bed Process: Case Study

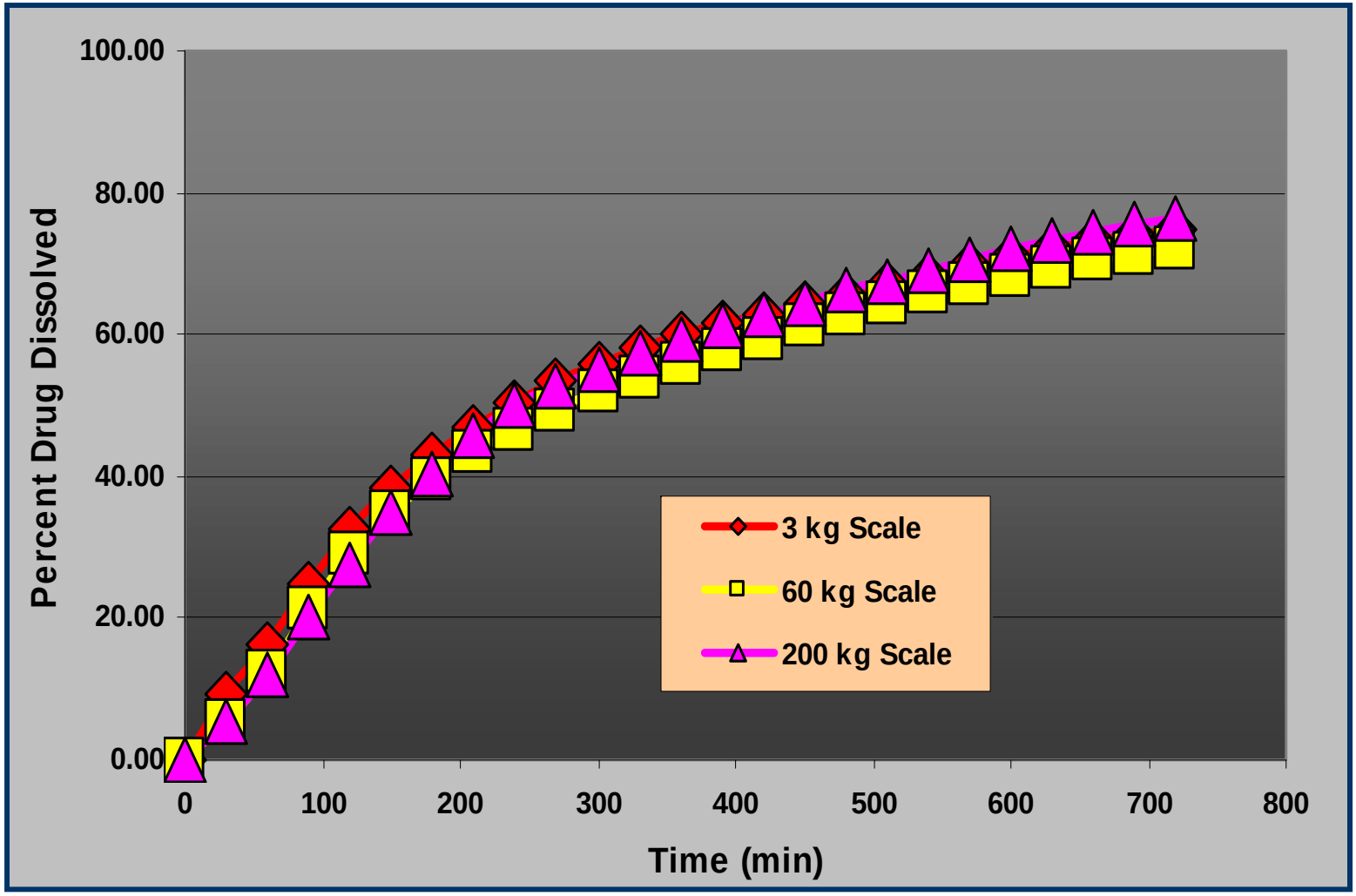
Process Characteristics:

- Process involved application of modified-release coating to CPM pellets using a Wurster process.
- During the development of the process on the laboratory scale, a statistical D.o.E. approach was used that was designed to examine, and identify, critical process parameters that would influence the functionality of the final coated product.
- Once process development work was completed, the knowledge obtained was used to define process conditions to be used on the larger processing scale(s).

Details of Coating Process Conditions Used During Scale-Up of Wurster Process

Process Parameter	Process Conditions		
	GPCG 3	GPCG 60	GPCG 200
Batch size (kg)	3	70	200
Fluidizing air ($m^3\ h^{-1}$)	140 – 180	1360 – 1530	NA
Inlet temp. (°C)	64 – 67	60 – 66	72 – 75
Exhaust temp. (°C)	40 – 45	39 – 41	47 – 51
Product temp. (°C)	41 – 47	40 – 46	43 – 46
Atom. Air press. (bar)	1.5	2.0	2.0
Solids content of coating dispersion (% w/w)	15.0	15.0	15.0
# spray guns	One (Schlick 970, 1.2mm)	One (HS, 1.5mm	Three (Schlick 940, 1.5mm)
Spray rate ($g\ min^{-1}$)	25 – 28	210 – 306	500 - 650
Amount coating applied (% w/w)	10.0	10.0	10.0

Release of CPM from Pellets Coated with an Aqueous EC Dispersion (10% w/w)



Process Scale-Up: the Path to Success

Several factors that must always be considered:

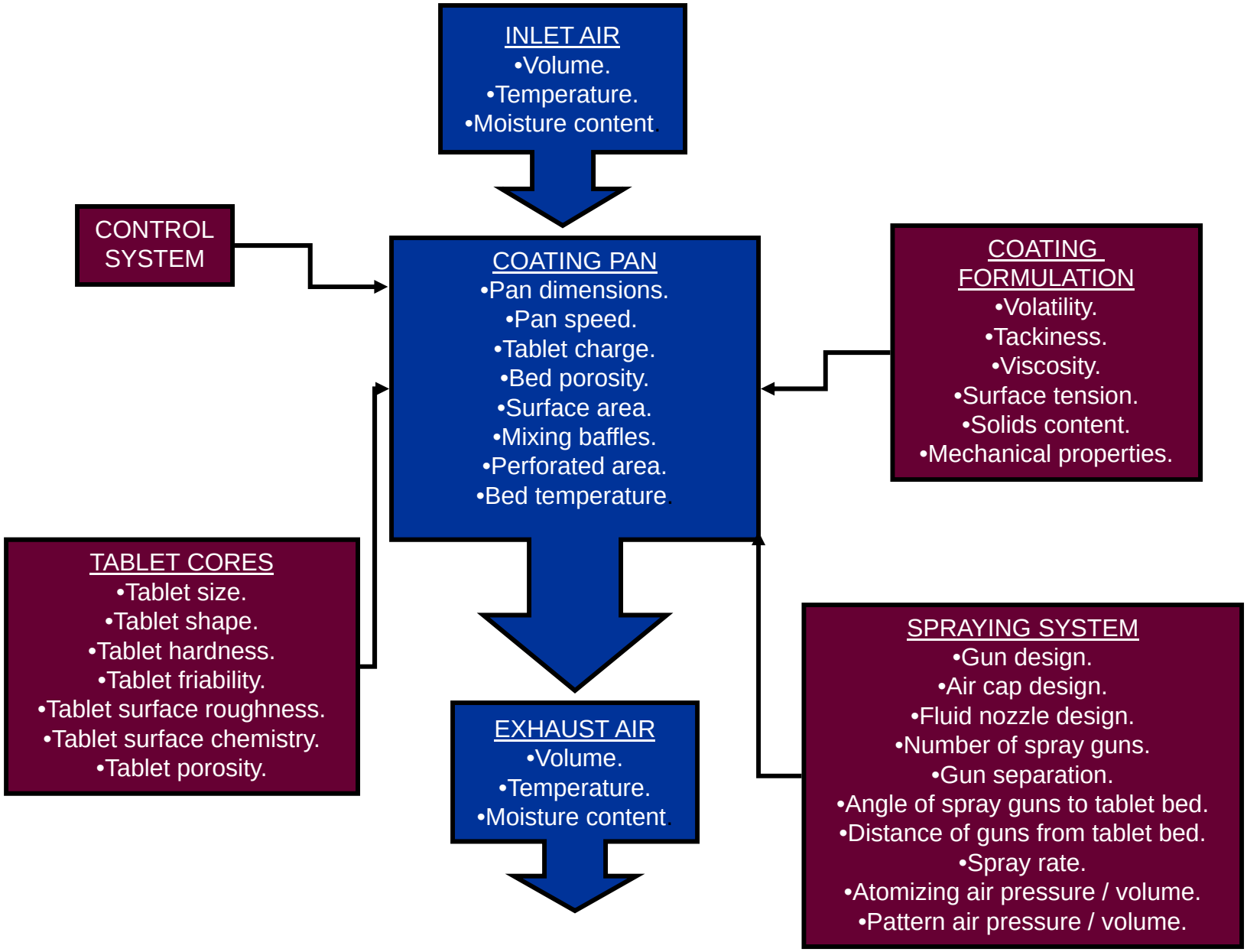
- During process development, design an optimized process that is based on detailed knowledge of the influence, on ultimate product quality, of all of the critical process factors.
- During the development of that optimized process, be cognizant of those issues that are important in the manufacturing plants.
- Ensure that effective technology transfer takes place from the laboratory, into the pilot plant, and, ultimately, into the production plant.

D.

TROUBLESHOOTING IN FILM COATING

Troubleshooting: Points to Consider

- **Troubleshooting is basically a “reactive” process, since it deals with something that has already gone wrong.**
- **When dealing with an existing, marketed product, the troubleshooting process is constrained by many regulatory issues.**
- **The best solution to “fixing problems” is to avoid them in the first place.**

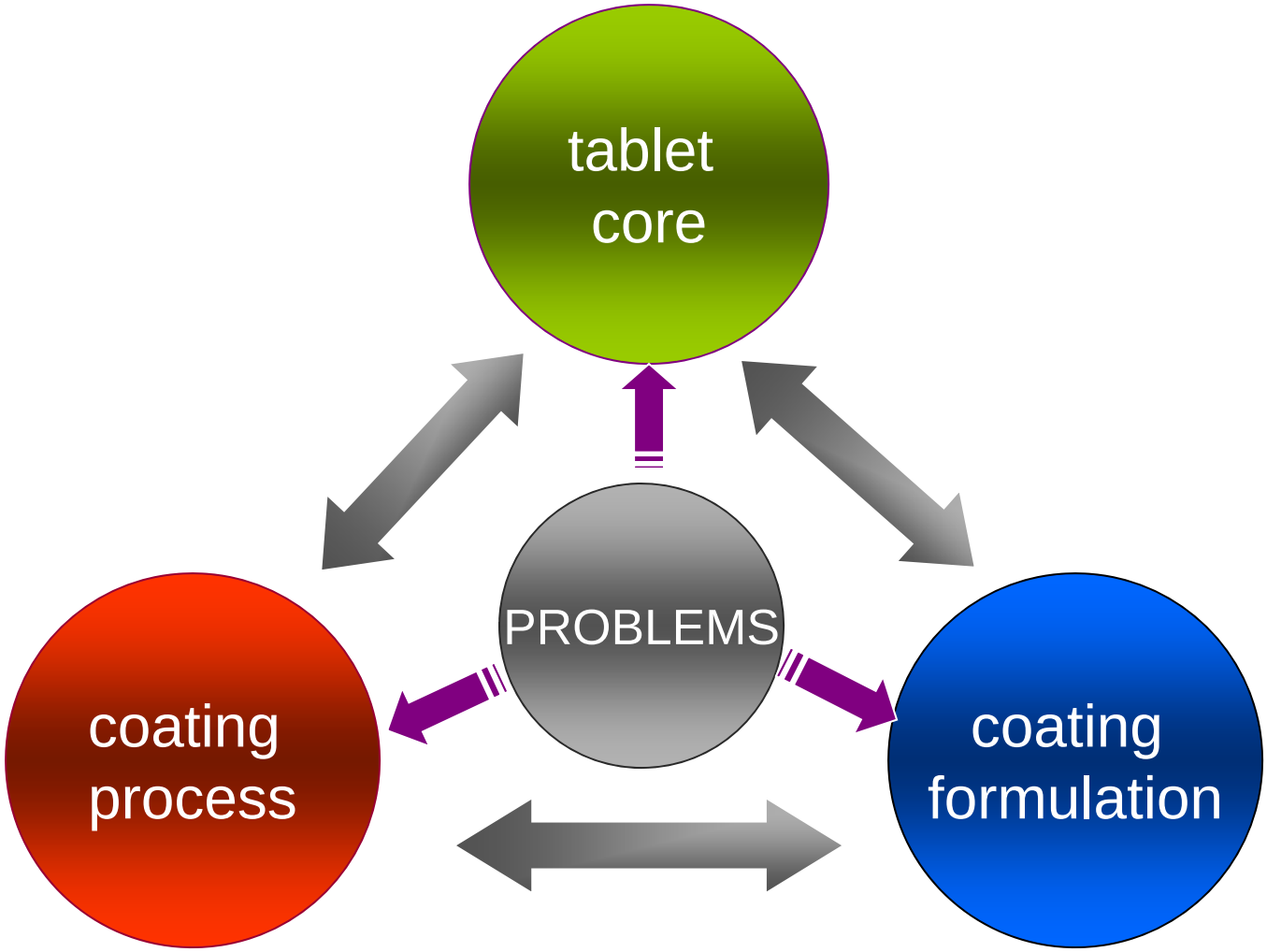

INLET AIR
•Volume.
•Temperature.
•Moisture content.
CONTROL SYSTEM
COATING PAN
•Pan dimensions.
•Pan speed.
•Tablet charge.
•Bed porosity.
•Surface area.
•Mixing baffles.
•Perforated area.
•Bed temperature.
COATING FORMULATION
•Volatility.
•Tackiness.
•Viscosity.
•Surface tension.
•Solids content.
•Mechanical properties.
TABLET CORES
•Tablet size.
•Tablet shape.
•Tablet hardness.
•Tablet friability.
•Tablet surface roughness.
•Tablet surface chemistry.
•Tablet porosity.
EXHAUST AIR
•Volume.
•Temperature.
•Moisture content.
SPRAYING SYSTEM
•Gun design.
•Air cap design.
•Fluid nozzle design.
•Number of spray guns.
•Gun separation.
•Angle of spray guns to tablet bed.
•Distance of guns from tablet bed.
•Spray rate.
•Atomizing air pressure / volume.
•Pattern air pressure / volume.

Classification of Coating Problems

These generally involve those affecting:

- **Coated product visual quality.**
- **Coated product functionality.**
- **Coated product stability.**
- **Processing efficiencies and costs**

Basis for Problems



Why Do Problems Occur All Too Frequently?

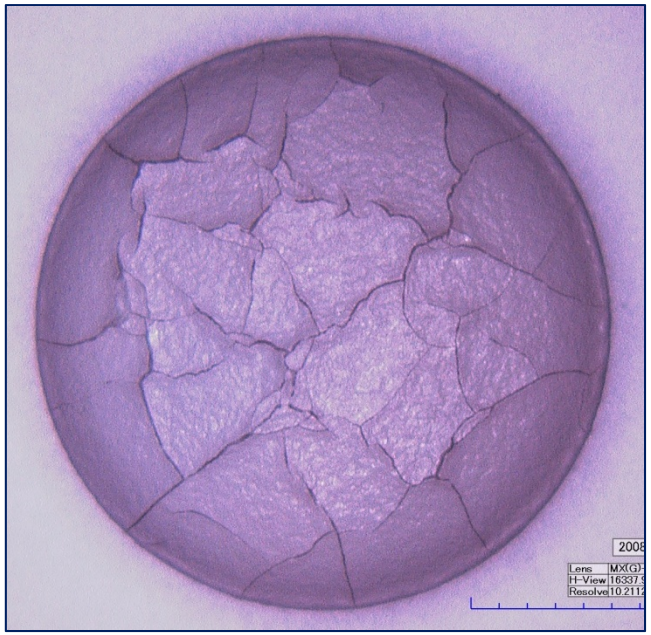
Often, problems arise because:

- The tablet core formulation is not robust.
- The coating formulation is not adequate for the product being coated, or for the coating process being used.
- Ineffective technology transfer (from laboratory to production site) has occurred.
- There is little appreciation for the influence of raw material variability, or inherent variations in the coating process, on ultimate product quality.
- Poor maintenance of process monitoring equipment results in decisions being made on the basis of inaccurate information.

IDENTIFYING PROBLEMS

Identifying Problems: Pictorial Determination

Identifying Problems: Pictorial Determination



Approaches to problem resolution:

Core

- Thermal expansion.
- Expansion due to moisture pick-up.
- Expansion due to post compaction strain recovery.

Coating

- Poor film strength.
- Poor film elasticity.

Coating process

- Excessive heat.
- Poor drying.
- Excessive mechanical agitation (tumbling).

Identifying Non Appearance-Related Problems

Identifying appearance-related problems is relatively easy because:

- Visual feedback is immediate.
- The magnitude of the problem is also often immediate.

Identifying non appearance related problems (such as those associated with chemical stability or drug release) is more difficult because:

- The existence of the problem is often not readily apparent.
- Determination is often on the basis of some analytical procedure that evaluates only a small sample (relative to the batch size in question) of tablets.
- Sampling, and the relevance of the samples selected to the characteristics of the whole batch, becomes a critical issue.

COMMON APPROACHES TO RESOLVING PROBLEMS

Focusing on the Core Formulation

General considerations:

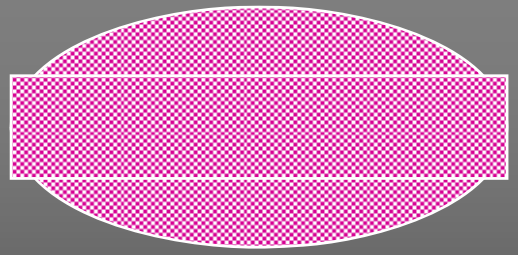
- Achieving physical robustness:
  - Mechanical strength.
  - Friability.
  - Resistance to dimensional changes.
  - Film adhesion.
- Maintaining chemical / functional robustness:
  - Role of amorphous, hydrophilic materials.
  - Low melting point ingredients.

Focusing on Core Design Issues

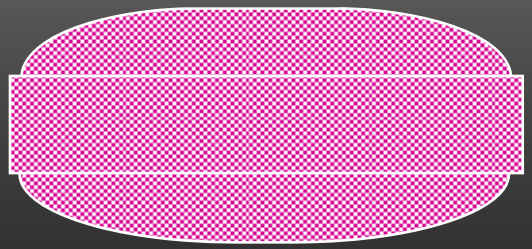
General considerations:

- Core shape, and how it influences:
  - Resistance to surface erosion.
  - Tablet movement, and hence coating uniformity
  - Resistance to twinning.
- Intagliations (“logos”), in terms of:
  - Placement.
  - Design.

Minimizing Surface Erosion Through Core Design



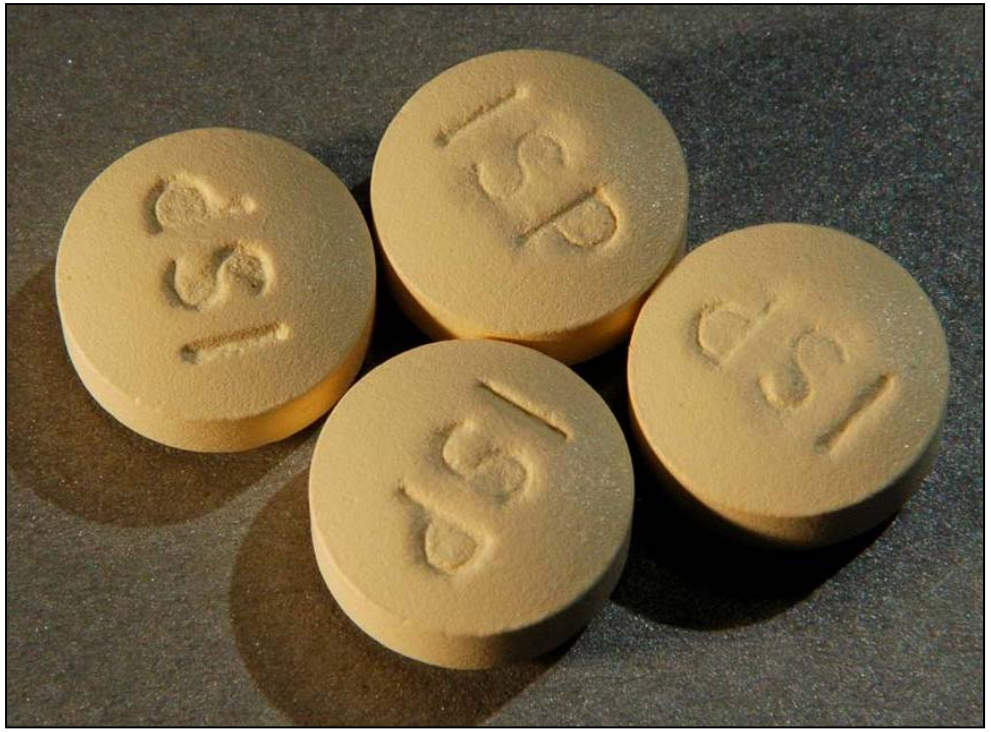
1. “Land” of tablet is pronounced, & edge is almost 90º



2. “Dual radius” punches are used, allowing edges to be minimized and thus become more damage resistant

Using Tablet Shape to Reduce Twinning

The Potential Impact of Logo Design and Placement on Core Erosion



Using Appropriate logo Placement to Minimize Erosion

1. Conventional Logo Placement

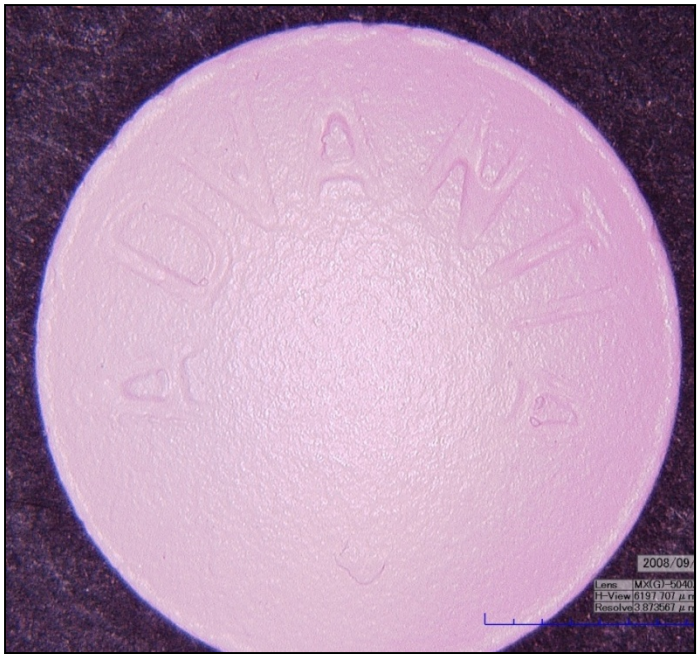
2. Appropriate Logo Placement for Tablets Made with Soft Crowns

Focusing on the Formulation of the Coating

Some general considerations involve addressing:

- Mechanical properties
  - Tensile strength.
  - Elastic modulus.
  - Adhesion.
- Internal stress:
  - Managing stresses.
- Spraying characteristics:
  - Sprayable solids.
  - Solution/suspension viscosity.

Modifying the Coating Formulation to Resolve Logo Bridging Problems



A. Original Coating Formulation
Adhesion Value – 30 kPa

B. Modified Coating Formulation
Adhesion Value - > 130 kPa

Focusing on the Tabletting Process

Some points to consider:

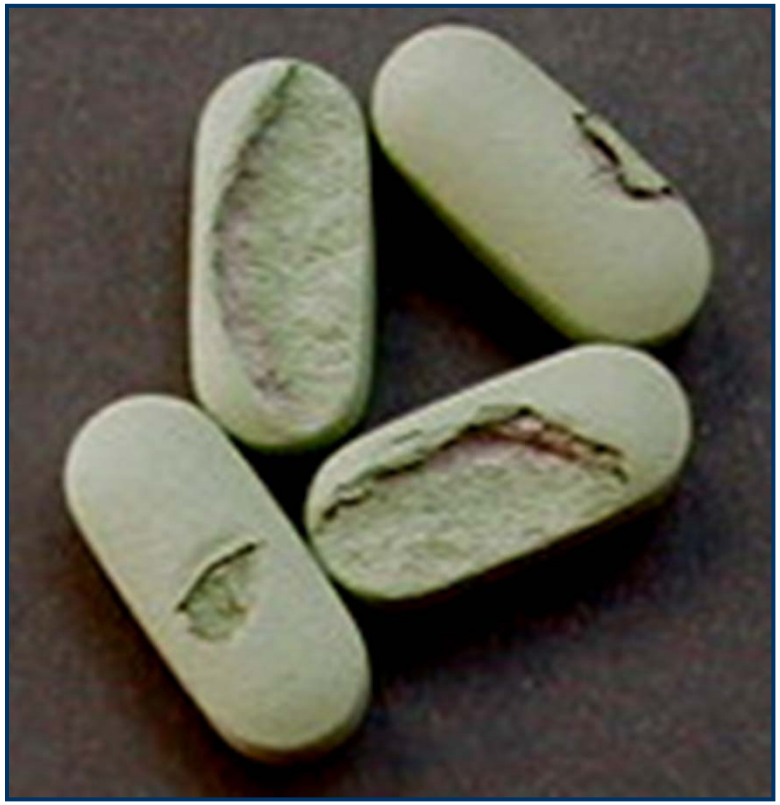
- **Blending of critical ingredients:**
  - **Lubricant such as magnesium stearate**
  - **Deagglomeration of superdisintegrants.**
- **Influence of processing on tablet robustness:**
  - **Influence of compaction force on tablet mechanical strength, and friability.**
  - **Compaction and time dependent changes, such as plastic deformation and post-compaction strain recovery.**
- **Influence of the compaction process on tablet porosity**
  - **Influence on film adhesion.**
  - **Influence on dissolution.**

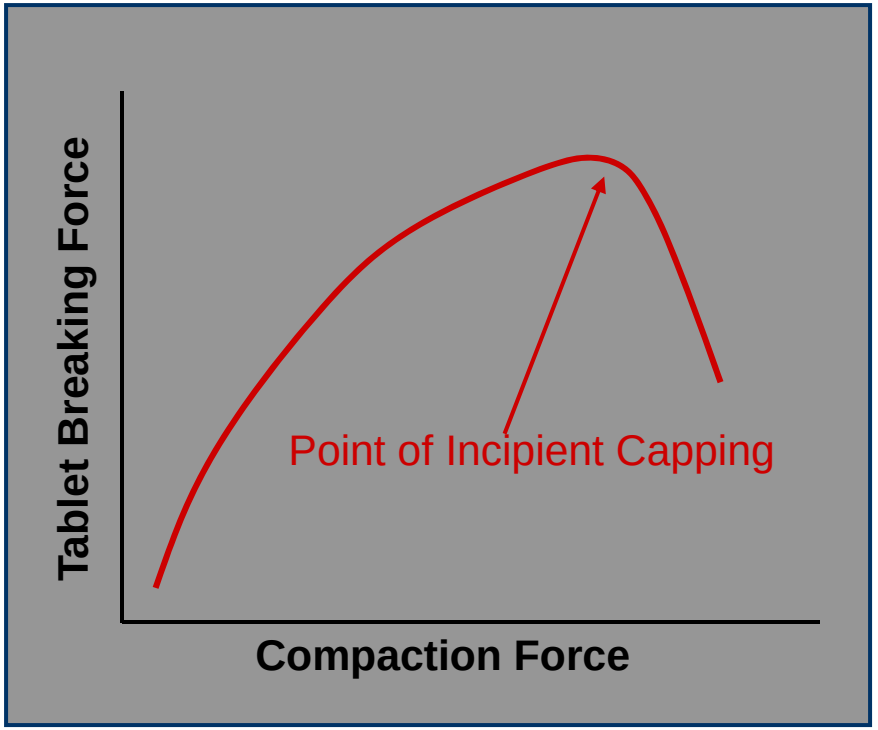
Example of impact of failure to Assure Effective Deagglomeration of Superdisintegrants

Tablet pitting due to:

- Poor distribution of disintegrants, and
- Overwetting during the application of the coating.

Capping: A Problem Often Associated Excessive Compaction Forces





Focusing on the Coating Process

Some general points to consider:

- Influence of pan speed on:
  - Core erosion.
  - Uniformity of distribution of the coating.
  - The drying process.
- Controlling the drying/spraying process:
  - Consequences of overwetting:
    - Tablet stability.
    - Tablet quality.
  - Consequences of over drying:
    - Tablet quality.
    - Process efficiency.
- Influence of coating solution/suspension solids on:
  - Tablet aesthetics.
  - Tablet stability.
  - Uniformity of distribution of the coating.

Common Tablet Defects Derived from Overwetting

1. Picking & Sticking

2. Twinning

3. Excessive Film Roughness

4. Tablet Swelling & Film Cracking

Common Tablet Defects Derived from Excessive Drying During Application of the Coating

Infilling of Logos

Excessive Roughness

Film Cracking

Common Visual Defects Derived from Poor Uniformity of Distribution of the Coating

1. Tablet-to-Tablet Color Variation

2. Variable Logo Bridging

Summary of Troubleshooting Issues

- **Troubleshooting is often a fact of life with film-coating operations.**
- **Identifying coating problems is a key issue in resolving the problem.**
- **Troubleshooting initiatives with post-marked products will always be constrained by regulatory issues.**
- **Employing a proactive approach to formulation and process design should always be a first consideration in order to eliminate, or, at least, minimize, the downstream impact of troubleshooting.**

Questions ?

Module 8:
TECHNOLOGY TRANSFER

Technology Transfer or Knowledge Transfer For Products and Processes:

Which Expedites the Process Most?

Dr. Russ Somma
SommaTech, LLC
Affiliate of IPS
Somerset, NJ

Technology Transfer or Knowledge Transfer?
OBJECTIVES

- ✓ To understand the process for developing a market formulation and requisite supportive data for technology transfer.
- ✓ To highlight requirements for submissions against the current move in industry to QbD NDAs.
- ✓ To understand the use of SUPAC as a tool to clarify transfer projects and leverage new submissions.
- ✓ To outline activities which should be done before entering manufacturing and attempting market entry.
- ✓ To identify the data needed to address regulatory concerns as well as providing a pragmatic baseline for PAT requirements.
- ✓ To provide an introduction to new industry aspects against the backdrop of the sectors of QbD relating to Design Space, Knowledge, and Control Strategy.

Technology Transfer or Knowledge Transfer?
OUTLINE

- Technology transfer and the requirements needed to effect this seamlessly.
- Leveraging these points to understand the aspects in the context of PAT.
- Drawing a parallelism to precepts of QbD.
- Knowledge and creating an understanding of what is critical
- Gathering the data needed to establish parameters and how this relates in the context of Design Space.
- Control aspects and putting a strategy in place for a design space.
- Using SUPAC as a tool to provide clarity and a common understanding for transfer but also for establishing a design space.
- Identifying the time critical aspects for transfers and setting out a pragmatic strategy balanced against what is to be transferred.

Technology Transfer or Knowledge Transfer?

We can no longer think of “tech transfer” in the traditional sense.

- The literature refers to technology transfer as a business strategy for enhancing R&D and commercialization.
  - *The transfer dimension has been refined.*
- Our role has traditionally been generating information for products and processes.
  - *How we generate and manage this information must be refined to create a knowledge store.*

Technology Transfer or Knowledge Transfer?

FDA instructs investigators to look for a series of product information during PAIs which may be interpreted as a *Knowledge Store*. The title of these data may vary but the information needed may be listed as:

- Drug substance characterization
- Process procedures
- In-process tests
- Finished product specifications
- Dissolution profiles
- Stability

Technology Transfer or Knowledge Transfer?

What has not changed is that technology transfer must deliver a product and process which are validated.

The objectives for validation are:

- *Demonstrate control over the process and finished product.*
- *Ensure compliance to internal and external requirements.*
- *Generate a knowledge base for the product as well as accommodate any further business needs.*

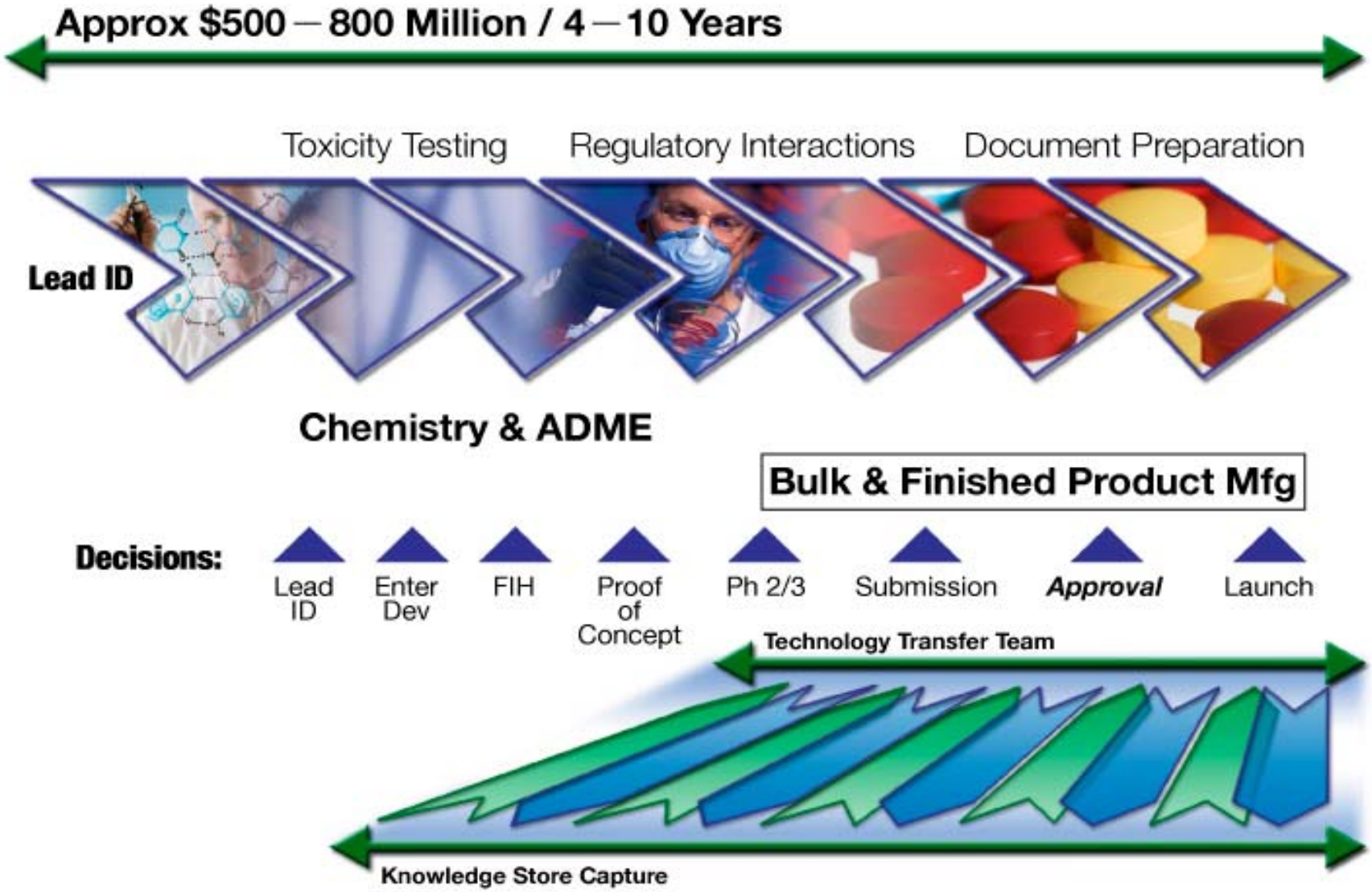
Technology Transfer or Knowledge Transfer?

Technology = Knowledge = Continuous Improvement

This relationship is implicit when we consider:

- *Process introduction is the start toward business efficiency.*
- *Validation is just one segment of this continuum.*
- *Well planned technology/knowledge transfer accelerates corporate learning.*

Drug Development and Technology Transfer



Technology Transfer or Knowledge Transfer?

Manage Process Validation as a Continuum

1. Utilize a DOE mentality for development batches to identify parameters and interactions for all process steps.
2. Early stages for formulation and process steps are established as the basis for refinements.
3. Subsequent pilot scale batches further add to the knowledge base for process steps and parameters used.
4. Product introduction at or near commercial scale at the launch site to further enhance the data base (Bio Batch).
5. Accumulated process knowledge forms a sound strategy to carry out the validation campaign.

Technology Transfer or Knowledge Transfer?

The continuum may be thought of as several components:

1. Conventional Aspects
   - Development Reports, Stability Reports
   - Validation Protocol, Validation and Scale-Up Reports
2. Enhancements
   - Proven Acceptable Ranges
   - Quality Risk Analysis
   - Process Comparability

Technology Transfer or Knowledge Transfer?

Process development should be used as a platform to establish proven acceptable ranges starting early in the development cycle.

Proven acceptable ranges:

- Provide a historical database for the product.
- May start at a broad range during the early stages which are subsequently tightened.
- Require a systematic reporting method which is referenced during pilot scale, scale-up and validation.
- Become a part of the knowledge store for the product and basis for statistical process control.

Technology Transfer or Knowledge Transfer?

Proven acceptable ranges (continued):

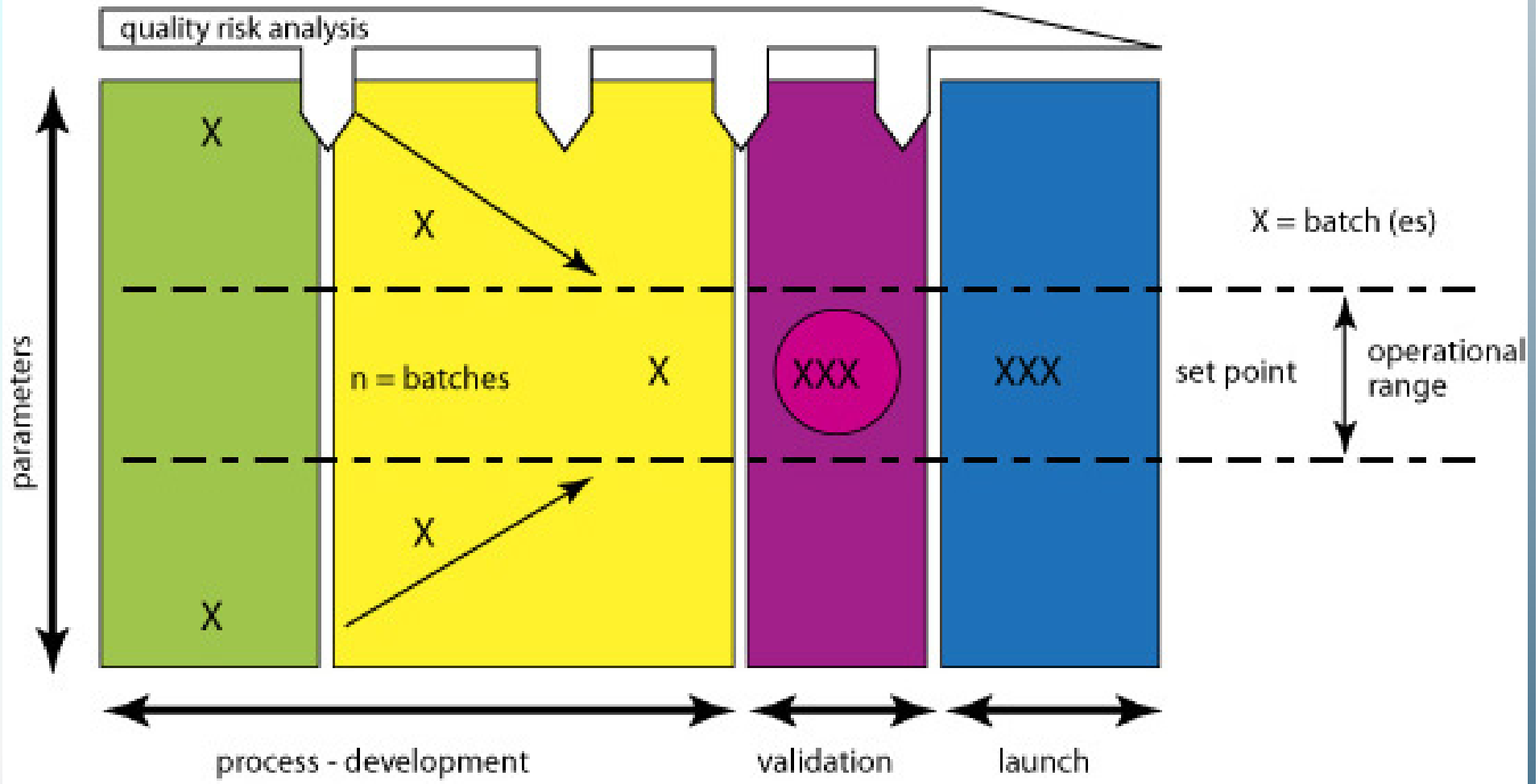
- Establish a chart for all process steps and controllable parameters.
- Brief description of the process step and controlled parameter.
- The engineering units which are recorded.
- The anticipated result for exceeding the proven acceptable range.
- Risk evaluation of exceeding the range is it major or minor.

Technology Transfer or Knowledge Transfer?

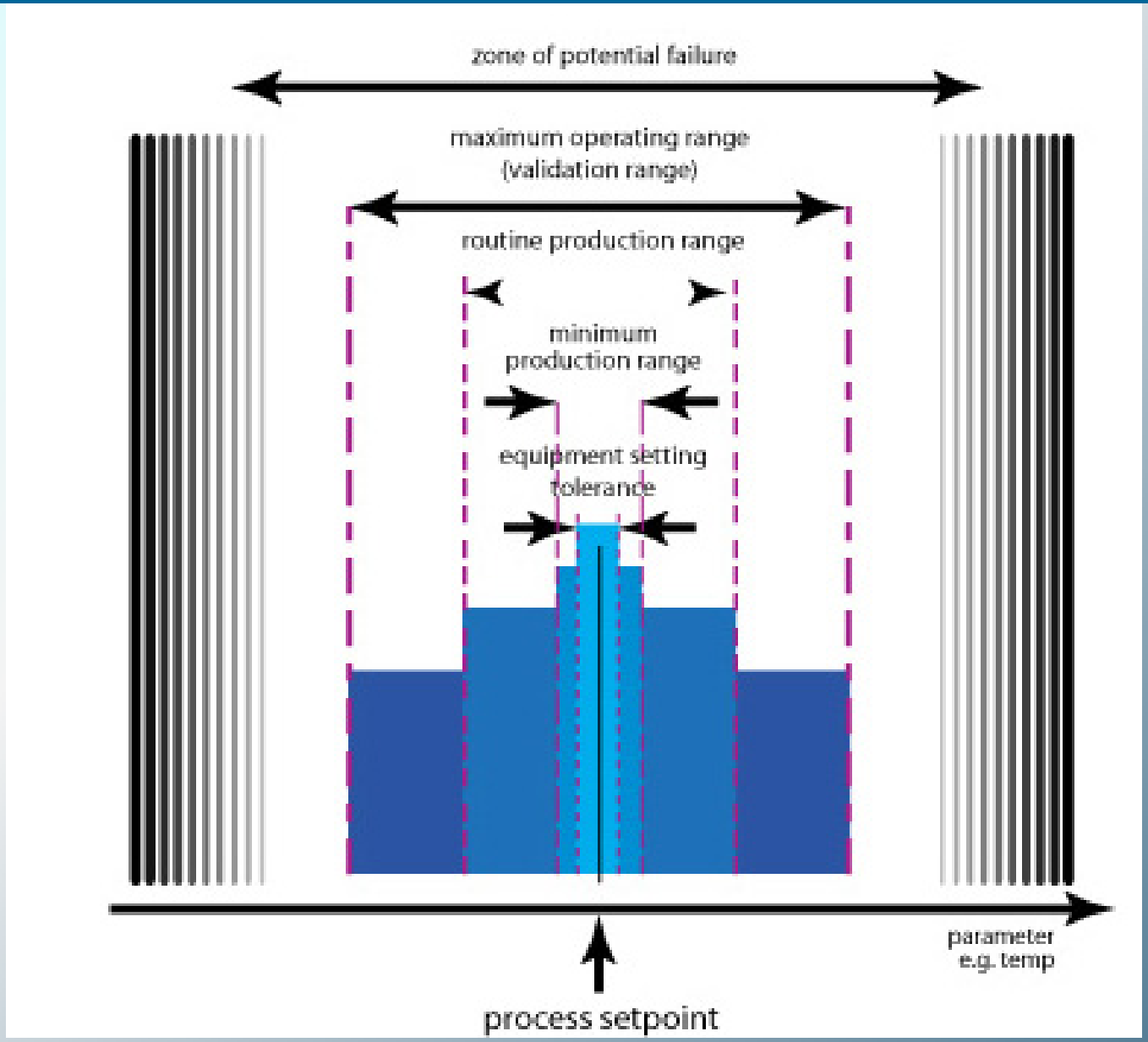
Proven acceptable ranges (continued):

- Establish the operating range to be utilized in the plant for process control.
- The proven acceptable range is documented. It may be referenced in the development report, batch records, validation reports and protocols.
- Acceptable ranges which are dependent on scale changes may be listed as to be determined (number of spray guns, FBD air volumes).

Technology Transfer or Knowledge Transfer?



Technology Transfer or Knowledge Transfer?



Technology Transfer or Knowledge Transfer?

Establish both a *good scientific* and *common sense* approach to rate each process step as having high, low or no impact on product quality.

This will aid in minimizing the subsequent validation effort (SUPAC equipment terms add clarity).

Critical area checklist:

- Weighing / addition of raw materials (vendors, personnel)
- Pre-blending of materials (volume, bulk density)
- Granulation (speed, rate of addition, time)
- Drying (LOD, time, temperature)

Technology Transfer or Knowledge Transfer?

Critical area checklist (continued):

- Particle size reduction (screen, feed rate, speed)
- Blending / lubrication (time, bulk density, assay)
- Compression (speed, feed rate, force)
- Coating (suspension prep., endpoint, air flow, temperature, spray rate)

This provides for subsequent data review for traits and atypical behavior. Data may be shown graphically to identify process variability within established specifications (process comparability).

Quality of Understanding vs. Quantity of Data = *Knowledge Space*

Technology Transfer or Knowledge Transfer?

In the context of PAT we now have the required frame work to begin to define:

- *Process Critical Control Parameter (PCCP)* – process variable that can be controlled to maintain critical product quality attributes.
- *Parametric release* – the release of product based on all process parameters being within pre-validated tolerances instead of on the results of final product testing.
- *Sensitivity Analysis* – Systematically analyzing the impact of process deviation(s) on the quality attributes of a product

Technology Transfer or Knowledge Transfer?

If we have established this frame work our next steps would be to define:

- PAT Tools
  - Process and endpoint monitoring and control tools
    - Identify and measure critical material and process attributes
    - Design a process measurement system to allow real time monitoring
    - Design process controls
    - Develop mathematical relationships
  - Continuous improvement and knowledge management tools

Technology Transfer or Knowledge Transfer?

In any case, PAT based or not we have established a means to facilitate:

- Process Understanding
  - Critical sources of variability known
  - Variability is managed
  - Product quality attributes can be predicted
- Risk Based Approach – level of process knowledge commensurate with amount of risk to product
- Integrated System Approach
- Real Time Release

Technology Transfer or Knowledge Transfer?

Key Aspects in Risk Assessment:

One aspect which must be made clear is the need defined by ICH-Q9 (Risk Management) concerning risk. Our experience is that a sponsor must work toward a system which is based on Risk Knowledge or “What If” Aspects.

This has two components

- Risk Assessment
- Risk Control

The path to achieve this goal must be to leverage product and process knowledge.

This task,knowledge management,may be seen as an enabler of all the functions and may best be dealt with in a well defined Quality System.

Technology Transfer or Knowledge Transfer?

Many firms apply PAT and use add on technologies and try to retrofit existing processes.

- The problem here is the process understanding along with the attempt to pattern acceptable results is usually somewhat anecdotal.

By application of the aspects of knowledge management new technologies which use neural networks and artificial intelligence are more effective.

- By taking the explicit knowledge gained during development experiments a data set is established which may be applied for process control in real time with responses based on the defined design space.

Technology Transfer or Knowledge Transfer?

Streamline technology transfer by minimizing process complexity. Establish the same process technology at all manufacturing sites.

- Establish a common technology agreement between the launch sites (production) and the development area.
- Integrate it into the transfer strategy.
  - Permits accelerated process introduction.
  - Phase III supplies may be sourced.
- Provides an enhancement of core capabilities.

Technology Transfer or Knowledge Transfer?

Transfer Streamlining

Combine efforts where possible such as:

- Site Qualification
- OQ data for the process
- Use final market image

- Avoid radical process changes, use the SUPAC guides to establish sameness of equipment and process.
- Develop a process using a sub batch concept, for solid dosage forms this reduces validation and supplies a defendable basis for changes in scale.
- Scale-up = increased number of sub batches.

Technology Transfer or Knowledge Transfer?

***Culture of the launch site plays heavily into the way in which we work within the structure. We must establish this upfront*.**

- This is an integral pattern of behavior and thinking.
- “This is the way we do things”.
- Within group companies this is reasonably clear.
- Other affiliations require this to be developed.
- Collaborations must have a two tier approach one is the contractual while the other is a daily working agreement.
- Agreements must be shared with all team members.

Technology Transfer or Knowledge Transfer?

While it is not required, the completion of technology transfer through validation would appear as the most expedient means to assure rapid market entry.

This appears to suggest it is good business to complete validation prior to a submission!

- This view may not be acceptable to all the players but it seems a logical strategy.
- Our hypothesis is that validation is just one step in the journey to 100% business efficiency (Peak Sales!).

Technology Transfer or Knowledge Transfer?

Where will we transfer the product?

While this seems a basic question it actually presents some of the more difficult issues. If we consider the possible scenarios as:

- An existing group company
- Contractor for custom manufacturing aspects
- Collaboration with an established company
- Facilities which are purchased for expansion (avoid purpose built facilities).

Technology Transfer or Knowledge Transfer?

Where will we transfer the product?

We must consider that the area has a supportive infrastructure and this goes beyond a GMP area and QC area!!!

A minimal list includes:

- Water, potable and purified
- Steam, pressure and capacity
- HVAC, environmental and process
- Waste, management, landfill, sewer, solvent emissions
- Permit to operate the business
- Labor pool of trained personnel
- Registration with local agencies
- Communication level, language
- Business interruption protection

Technology Transfer or Knowledge Transfer?

Establishing a technology strategy which will qualify change in the context of scale-up / transfer as well as possible post approval changes expedites product development and shortens approval time.

Effort spent in creating an IVIVC relationship early in the development cycle is well placed.

- While not always possible it will yield benefits for formulation and process optimization and the creation of meaningful specifications.
- The data will be specific to the formulation in question which may be considered a downside.

Technology Transfer or Knowledge Transfer?

An IVIVC strategy makes it part of the methods used to guide formulation development. This approach is used by development contractors.

IVIVC Strategy:

- At the product concept phase use a target in vivo profile and base in vitro specifications on an assumed IVIVC. The prototype is tested using various dissolution methods.
- The result will be a comparison of dissolution methodology with biodata allowing an IVIVC to be established.

Technology Transfer or Knowledge Transfer?

IVIVC Strategy (continued):

- During optimization of the formulation / process the IVIVC is defined and predictions from the IVIVC validated.
- During scale-up the dissolution data are used to judge the impact of process changes,as well establishing final specifications for dissolution.
- The database may be utilized during further scale-up and site transfer as well as supporting post approval changes.

Technology Transfer or Knowledge Transfer?

Alternative methods may be used to determine differences resulting from process modifications which build on establishment of meaningful specs.

- The f 2 test while part of SUPAC may be effectively used to measure differences in dissolution profiles resulting process / formulation changes.
- Comparability protocols may also be based upon these data during later stage changes and subsequent justification to regulatory agencies.

Technology Transfer or Knowledge Transfer?

The Desired State: A Mutual Goal of Industry and Regulators, Janet Woodcock, M.D. ISPE Annual Meeting November 7,2005

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

Technology Transfer or Knowledge Transfer?

Pharmaceutical Manufacturing in the 21st Century – An FDA Perspective, Moheb Nasr,Ph.D. ISPE Annual Meet November 2006

"The desired state will be realized upon the implementation of QbD to product & process Design/development,and establishing robust QS."

Technology Transfer or Knowledge Transfer?

FDA has taken action to realize these goals. The list below identifies the steps and provides a chronology of the current trend toward QbD.

- CGMP for the 21st Century
- ICH New Vision and Quality Strategy
- Quality by Design (QbD)
  - Pharmaceutical Development (Q8)
  - Quality Risk Management (Q9)
- Pharmaceutical Quality Systems
  - Pharmaceutical Quality Systems (Q10)

Technology Transfer or Knowledge Transfer?

What does FDA see as the benefits of QbD?

- Quality by Design provides increased assurance of product quality
- Design Space captures process understanding for operational implementation
  - Design space is an important part of the product Quality Control Strategy
  - A full presentation of design space includes discussion of CQAs, input parameters, and linkage between them
  - Design Space information should be included in submission
- Quality Risk Management is critical in development of the product Quality Control Strategy

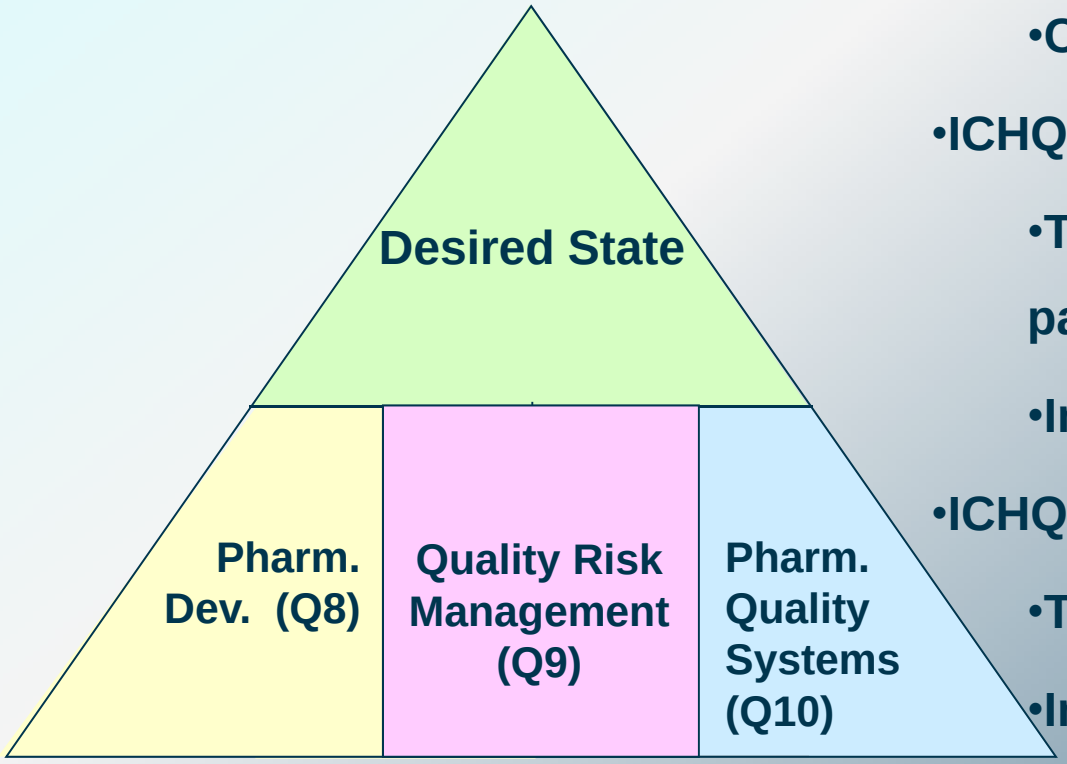
Technology Transfer or Knowledge Transfer?

What does this mean for Industry as benefits of QbD?

- **Good for business**
  - –Greater supply chain reliability and predictability
  - –Innovation and improvement encouraged and facilitated
- **Good for the patient**
  - –Improved product reliability and reproducibility
  - –Should provide opportunities for more flexible regulatory approaches

Technology Transfer or Knowledge Transfer?

Where do we want to be?



- ICHQ8 Pharmaceutical Development
  - This is what we do.
  - Create the knowledge space
- ICHQ9 Risk Management
  - This keeps our focus on the patient.
  - Includes tools “cause and effect”
- ICHQ10 The Enablers
  - The maintenance of our efforts.
  - Includes change control, knowledge management

Technology Transfer or Knowledge Transfer?

- Q10 Definition of Control

  - A planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product and drug product and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control.

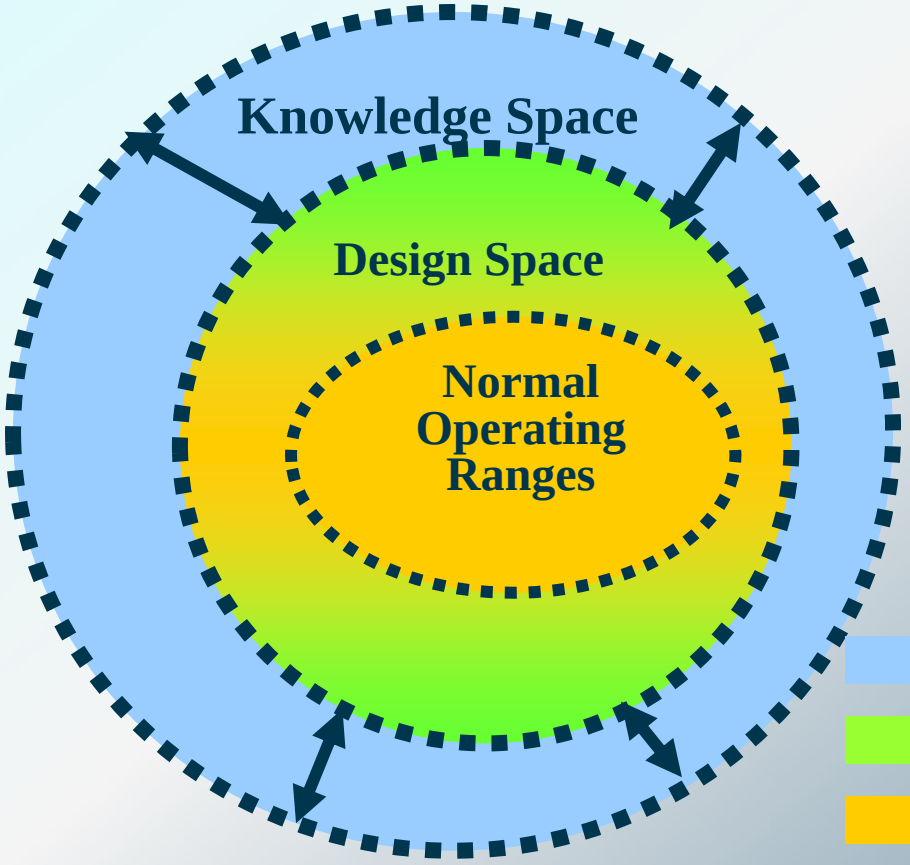
Technology Transfer or Knowledge Transfer?

- Q8 Design Space Definition

  - The multidimensional combination of interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by applicant and is subject to regulatory assessment.

So let me ask you what bit do you think is missing and where is the majority of the debate within industry?

Technology Transfer or Knowledge Transfer?



Knowledge Space Criticality Analysis

Design Space based on Knowledge

Control Strategy:
Maintaining process in the Design Space

Technology Transfer or Knowledge Transfer?

What is Knowledge Space or more correctly what do we understand as being critical?

- Scientific elements to be considered and explored for potential product attributes and process parameters.
- Includes prior knowledge across multi-disciplines and therapeutic areas that may impact product attributes or process parameters.
- It is unknown where in this region a product can be realized

Technology Transfer or Knowledge Transfer?

What is design space or more correctly where do we normally run the process we wish to control based on on our knowledge?

- A region where acceptable product can be produced.
- Arrived at by iterative application of risk assessment and experimental design to knowledge space

Technology Transfer or Knowledge Transfer?

What is control strategy or more correctly how does this maintain our established normal operating ranges?

- The control strategy will ensure the product is manufactured within the Design Space to meet all Critical Quality Attributes (CQA).
- The control strategy for a CQA is the selection and combination of different types of controls.
- These are applied to the manufacturing process & associated systems to assure the right product quality and that the risk of manufacturing failure is acceptably low.

Technology Transfer or Knowledge Transfer?

Considerations for Critical Aspects as They Relate to Process Parameters (PP) and Critical Quality Attributes.

- Any relevant designation of criticality should be aligned relative to safety and efficacy for the patient
- Criticality must be viewed as delineating different risks for critical quality attributes (CQA) than for process parameters (PP)
- Delineation of criticality for process parameters may occur along a "continuum" relative to levels of risk.
  - Risk Prioritization relative to Severity, Frequency & Detectability
    - Useful for conveying design space and control strategy justifications
    - Promotes transparency and flexibility.
    - Relative numbers – industry can have flexibility in conveyance as long as the logic is clear

Technology Transfer or Knowledge Transfer?

Considerations for Critical Aspects as They Relate to Process Parameters (PP) and Critical Quality Attributes.

- The designation of critical (either for internal or regulatory assignment) is intimately linked to the control strategy which includes appropriately established design space.
  - Criticality is independent of control?

    vs.

  - Control of a critical variable can render it non-critical?
- Risk assessment may render a variable (process parameter) critical, an appropriate and comprehensive control strategy can be used to mitigate/reduce risk and/or render the probability/impact of failure unlikely but does not change criticality.

Technology Transfer or Knowledge Transfer?

Considerations for Critical Aspects as They Relate to Process Parameters (PP) and Critical Quality Attributes (continued).

- CQA's need to be defined apriori
  - The hierarchy of the control strategy defines specific levels/limits (specifications) for quality attributes (QA)
  - QA's are derived from a target product profile
  - Risk assessment delineates criticality of process parameters (PP) based on impact to QA's
- Critical and non-critical delineation should be separated from and assigned after risk assessment prioritization.
- Assigning criticality is a reflection and function of the process used to define it.
- You may have a Control Strategy but no Design Space.

Technology Transfer or Knowledge Transfer?

CONTROL STRATEGY includes:
- Normal Operating Ranges
- Engineering Control model
- Formal investigation when outside NOR

Technology Transfer or Knowledge Transfer?

Extended Operating Range (to limit of DS). If an excursion occurs outside NOR, investigate to ensure DS boundary is not Crossed.

Process & analytical equipment controls normally operate within this range

Design Space boundary

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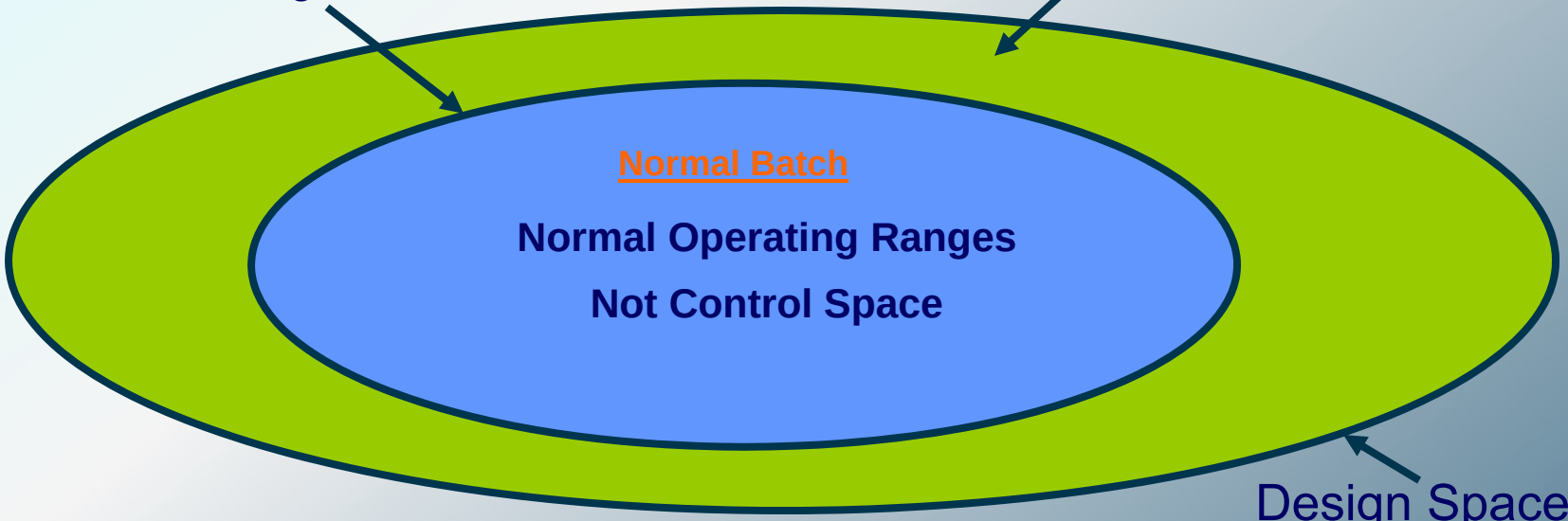

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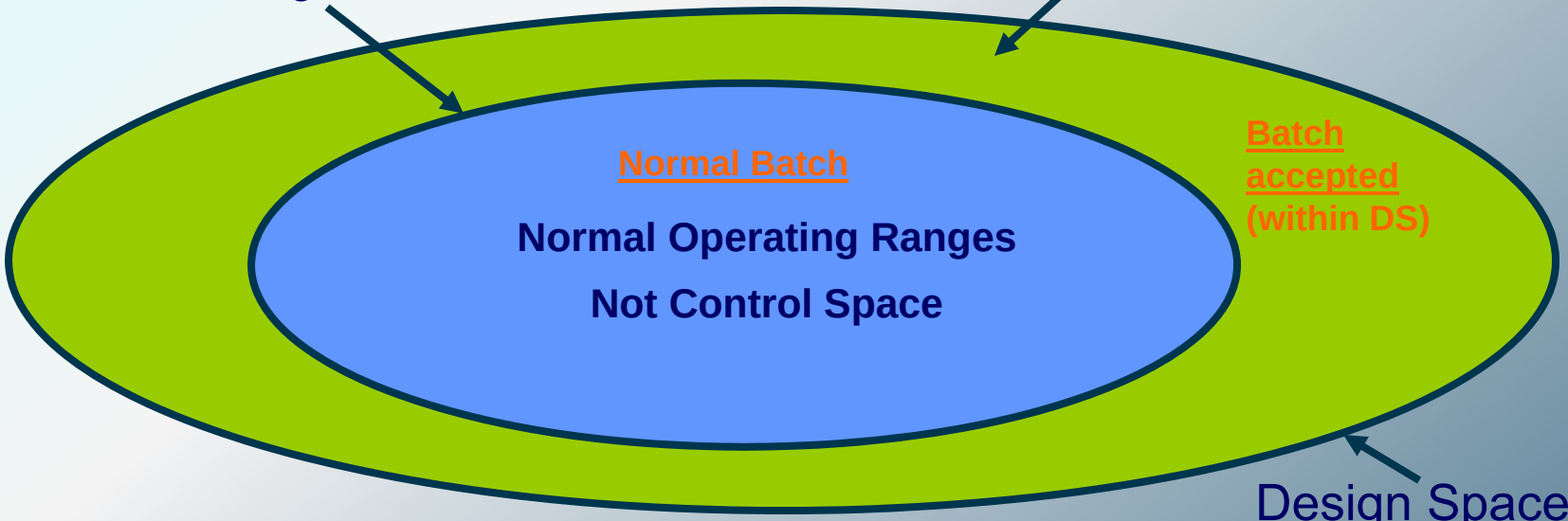

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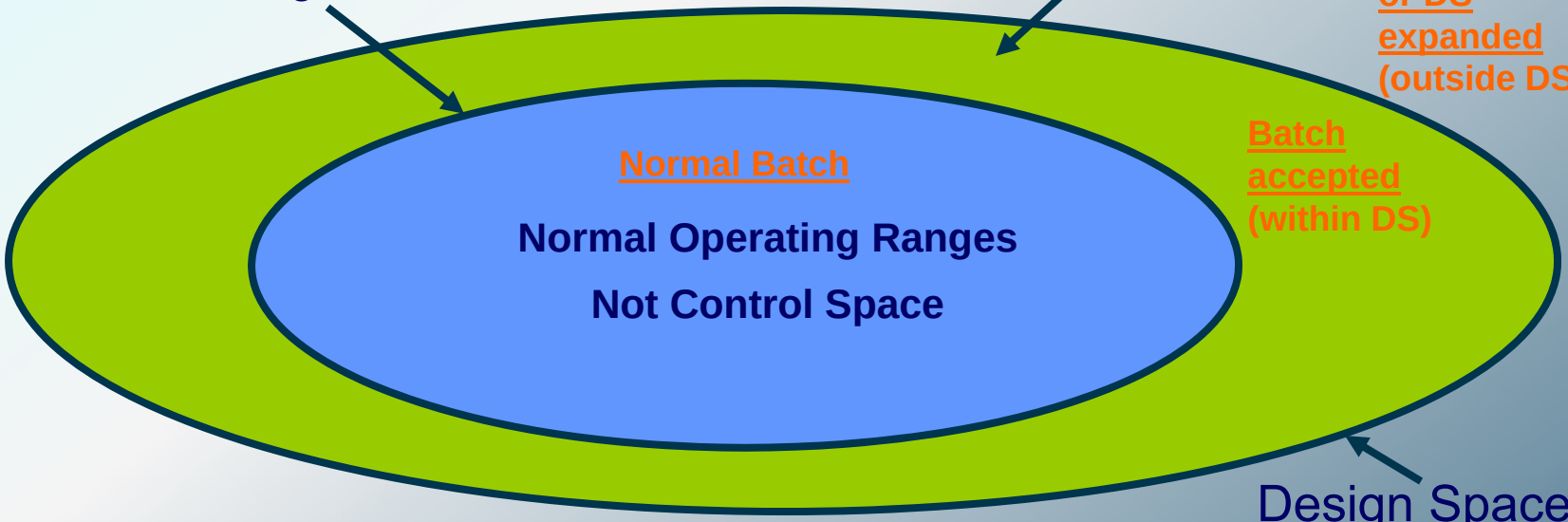

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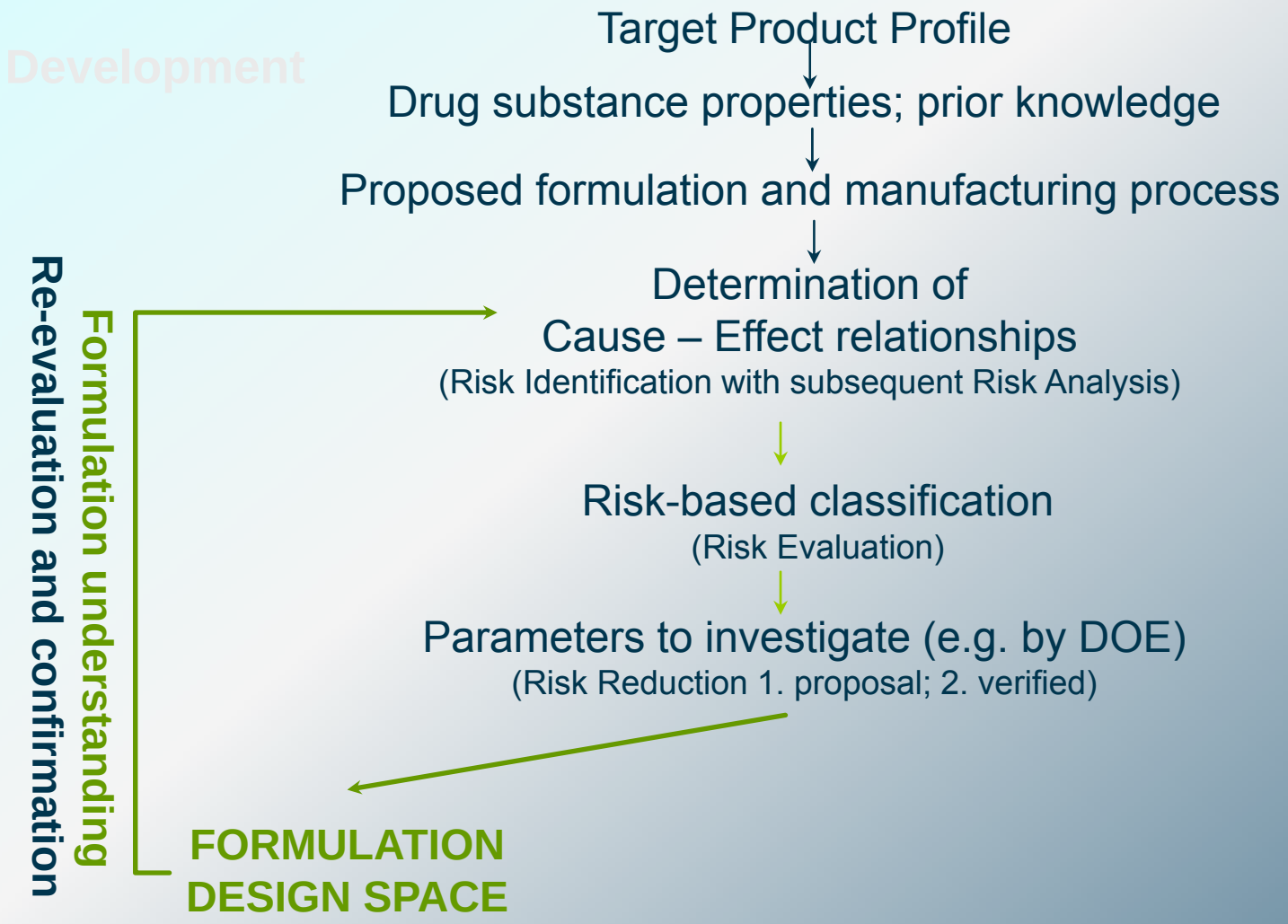

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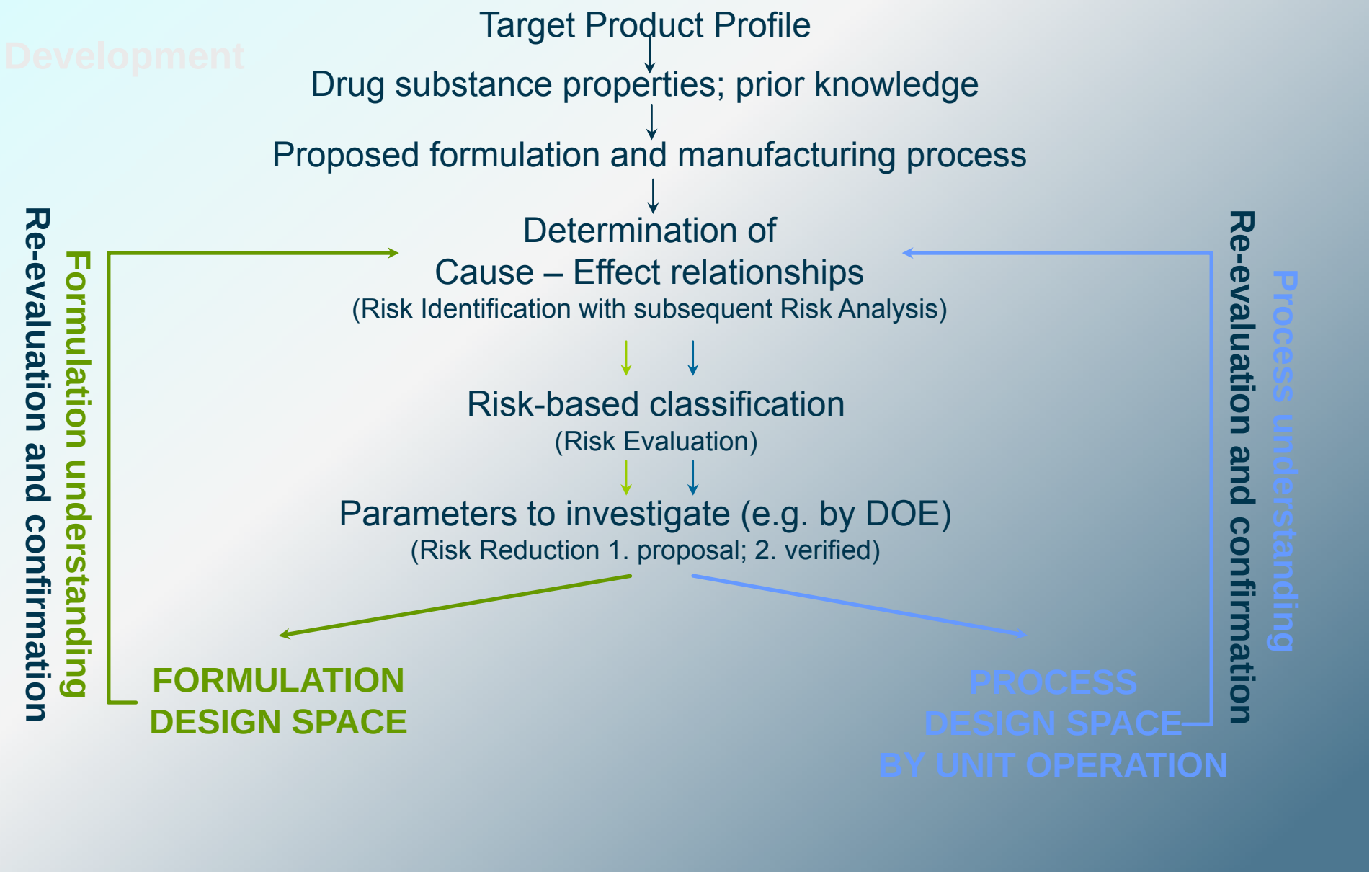

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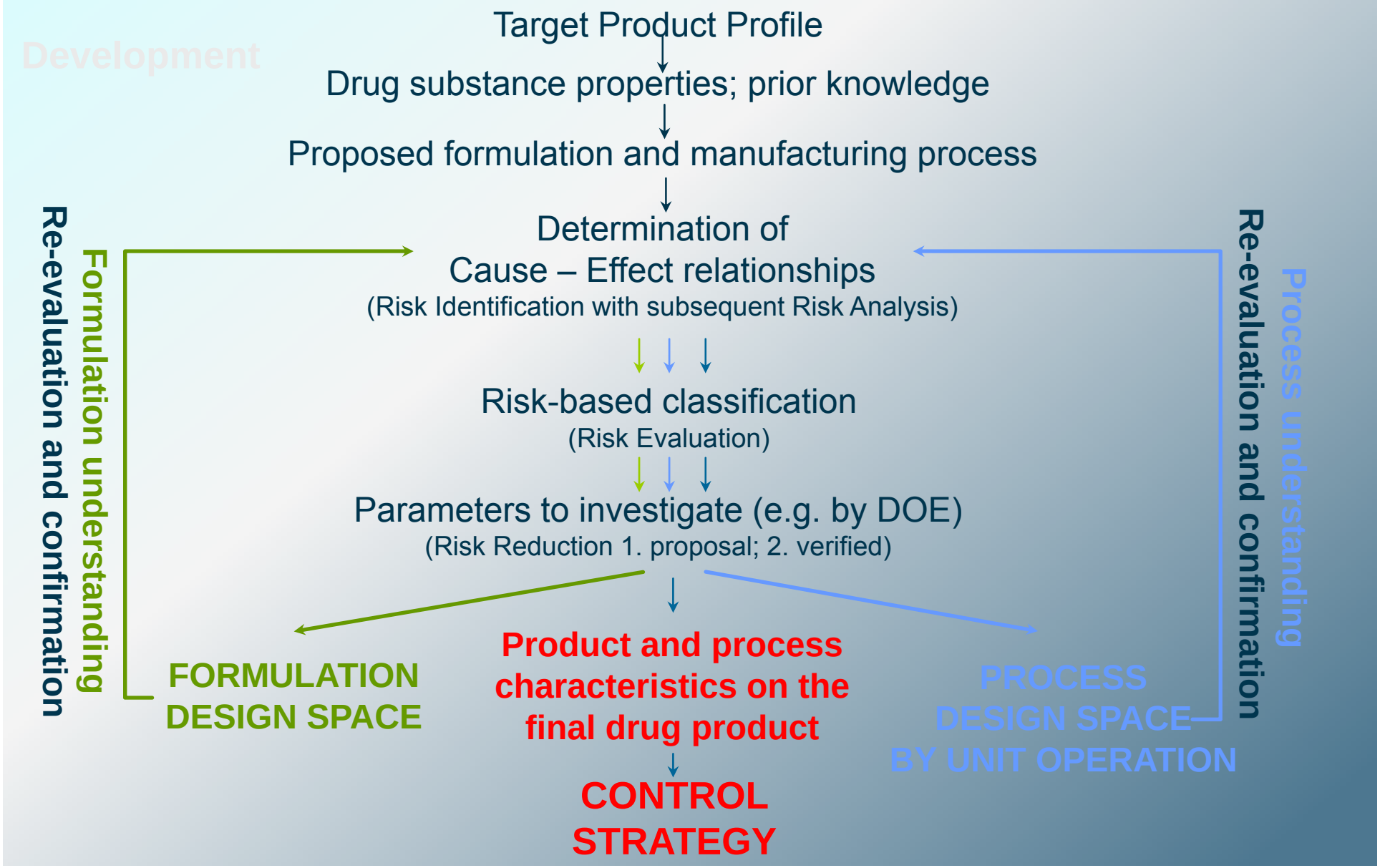

An Industry Perspective Implementation of PAT

This work could lead to proposed design space, control strategy and regulatory flexibility with these proposals not compromising safety and efficacy. For example, knowledge could be gained regarding:

- **what process parameters are critical using the firm's definition**
- **what other process parameters are important**
- **what relationships may exist**
- **impact of scale**
- **pharmacokinetic profile such that manufacturing site and post approval bioequivalence studies are obviated.**
- **stability performance to support primary package changes**

Technology Transfer or Knowledge Transfer?

SUPAC is a key regulatory guidance to be used when we are attempting to assure "same" process and justify this to health authorities.

Dosage Forms Covered by SUPAC

- **IR-Immediate Release Solid Oral Dosage Forms**

  Tablets,capsules,soft gelatin capsules

- **MR-Modified Release Solid Oral Dosage Forms**

  Delayed Release (such as enteric)

  Extended Release (such as time release)

- **SS-Topical Semi-Solid Dosage Forms**

  Creams,ointments,suspensions,emulsions,gels

Technology Transfer or Knowledge Transfer?

- **All current SUPACs have associated equipment guidance addenda.These define the aspects of ”same design and operating principle” as required within the parent SUPAC guidance.**

- **These must be used with the guidance documents when considering equipment changes.**

Technology Transfer or Knowledge Transfer?

- **What is covered?**
  - **Components/ composition**
  - **manufacturing sites**
  - **packaging sites**
  - **analytical testing sites**
  - **scale-up/scale down**
  - **manufacturing equipment**
  - **manufacturing process**

Note:drug product only!!!

- **What is not covered?**
  - **Drug substance**
  - **multiple changes submitted at one time or in a short period of time**
  - **multiple changes require contact with FDA/CDER**

Technology Transfer or Knowledge Transfer?

- **What are the levels of change?**

➢ **Level 1**

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

➢ **Level 2**

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

➢ **Level 3**

- Likely to have impact,filed PA,stability and testing as above in addition a biostudy or IVIV correlation.

Technology Transfer or Knowledge Transfer?

- How do these aspects relate to production and technical operations?
- The following items, while not a complete list,may hold the major value for using SUPAC.
  - Manufacturing Site Change
  - Batch Size Change
  - Manufacturing Process Change
  - Manufacturing Equipment Change
  - Analytical Testing Site Change
  - Packaging Site Change

Technology Transfer or Knowledge Transfer?

Manufacturing Site Change

- **Level 1**

  Same facility,filed as an AR,normal testing

- **Level 2**

  Same campus,different building,filed as CBE,accelerated stability,dissolution profile testing

- **Level 3**

  Different campus,international transfers for example,CBE for IR and PA for MR,testing as above with biostudy or IVIV correlation for MR only

Technology Transfer or Knowledge Transfer?

Batch Size Change

- **Level 1**

  Scale-up to ten times the biobatch,filed AR,long term stability and normal testing as per NDA.

- **Level 2**

  Scale-up beyond ten times the biobatch,filed as a CBE,all the above plus accelerated stability and dissolution profile testing.

Technology Transfer or Knowledge Transfer?

Manufacturing Process Change

- **Level 1**

  Within the existing process ranges supported by the current NDA,filed AR,normal testing.

- **Level 2**

  Outside the existing ranges,filed CBE,long term stability and dissolution profile testing.

- **Level 3**

  Different process,filed PA,all the above plus accelerated testing and biostudy or IVIV correlation.

Technology Transfer or Knowledge Transfer?

Manufacturing Process Change

- **Older Products**

  These will require careful review to identify critical process parameters,adequate specifications,clear manufacturing directions and a critical review of the product history.

  Although SUPAC offers an opportunity to improve our procedures the cost of dealing with incomplete data must be considered a risk.

  At the least they must be validated within recent process history!!

Technology Transfer or Knowledge Transfer?

Manufacturing Process Change

- **New Products**

  These offer the best opportunity for change since past history is clear in development reports and validation.

  Review may be simplified to examination of the related development documentation.

Technology Transfer or Knowledge Transfer?

Manufacturing Equipment Change

- **Level 1**

  Change to an automated or mechanical material handling system,or equipment of the same design and operating principle,filed AR,long term stability and normal testing.

- **Level 2**

  Change to a different design and operating principle,filed PA,all the above plus accelerated stability and dissolution profile.

Technology Transfer or Knowledge Transfer?

What is same design and operating principle?

The equipment addenda define equipment into “class” “sub class” and “example”.

The class defines equipment that have the same operating principles,while sub class defines variation in design.

Equipment changes within a class are defined as the same (level 1),changes to another class are different (level 2).

Technology Transfer or Knowledge Transfer?

What is same design and operating principle?

- **Example:**

  The class of diffusion mixers contains several sub classes.The mixing action within the class is the same while the sub class defines physical attributes. Therefore V blenders are in one sub class while bin tumblers are in another. They both have the same mixing action but differ in physical design.

  They are considered the same in this case!

Technology Transfer or Knowledge Transfer?

Analytical Testing Site Change

- Covers drug product testing ONLY!
- The site must have a recent cGMP certification.
- One batch released from the site must be on long term stability.
- Must use only testing procedures filed in the NDA.
- These changes normally require a 30 day wait for FDA review prior to implementation.
- Offers advantages for third party utilization to deal with large/rapid changes in testing volume.

Technology Transfer or Knowledge Transfer?

Packaging Site Change

- The site must have a recent cGMP certification for the specific packaging procedure under consideration.
- Filed as a CBE with the associated 30 day review period.
- First batch must be placed on long term stability.
- Offers advantages for third party utilization in order to deal with rapid growth in product demand.It offers an alternative to capitalization for more equipment

Technology Transfer or Knowledge Transfer?

Will SUPAC have associated cost savings?

- The value of SUPAC is reduced regulatory burden and this equates to time savings.
- The cost of assembling good data packages will not be reduced since all changes require associated validation and documentation.
- SUPAC is regulatory relief and NOT validation relief.
- Rapid implementation of changes and subsequent entry into the market will yield the benefits!

Technology Transfer or Knowledge Transfer?

How do we pull all this together to get the job done?

The "ISPE Good Practice Guide for Technology Transfer"offers a comprehensive source for industry.

Features:

- Defines key terms.
- Provides a consistent interpretation.
- Allows flexibility for innovative approaches.
- Covers various scenarios:
  - Part of product development.
  - Post approval transfer.
  - Site to site to leverage manufacturing capacity.
- Covers analytical methods, APIs, and Dosage Forms
- Accounts for US, Europe and Asia transfer scenarios.

Technology Transfer or Knowledge Transfer?

Key Regulatory Factors

- Acceptance Criteria and specifications for products and processes.
- Adequate facilities and staff.
- Protocols, SOPs, agreed to by both parties.
- Data = documented evidence.

Key Business Factors

- All methods,processes,development history.
- All results and rationale are documented.
- Complete history is available avoids duplication.
- After process is completed data are compiled.
  - Critical process parameters
  - Composition tables and rationale
- Cost reduction and capacity increase.

Technology Transfer or Knowledge Transfer?

Analytical Method Transfer

The following are tested:

- Pharmaceutical Products
- Inert Ingredients
- Cleaning

Procedures are Used for the:

- Release of Product
- Stability Testing for Expiration Date
- In Process Controls
- Active Pharmaceutical Ingredient
- Excipients

Technology Transfer or Knowledge Transfer?

Transfer Protocol Contents

- Outlines materials, methods, and equipment.
- Experimental Design.
- Acceptance Criteria.
- Reference Samples (sample selection is key here).
- System Suitability for the selected application.

Careful establishment of acceptance criteria needs to be balanced with respect to the method as well as the results expected.

Deviation must be documented along with the rationale associated with the outcomes and final disposition.

Technology Transfer or Knowledge Transfer?

Experimental Design

- Assay, 2 analysts, 3 lots in triplicate to yield approximately 18 results for comparison of mean and variability.
- Content Uniformity, if this is the same as the assay method no additional transfer is required. Use 1 sample lot for acceptance as ± 3% from the reference lab.
- Impurity Testing, something which is neither added as an API or inert material. Sample handling is key with regard to storage packaging and age. If none are present then a spiked sample must be used.

Technology Transfer or Knowledge Transfer?

Experimental Design (continued)

- Dissolution,used to measure the profile of drug release the application of the F2 test for 12 samples per lot is the basis of comparison.

- ID Test, if this is based on the retention time in an HPLC method which is part of the method no additional transfer is required, sample preparation is key here. If this is based on a chemical reaction or physical property no transfer is required.

Technology Transfer or Knowledge Transfer?

Active Pharmaceutical Ingredient (API)

The following are tested:

- Active Pharmaceutical Ingredient
- Starting Materials
- Cleaning

Procedures are Used for the:

- Release of API
- Stability Testing for Retest Date
- In Process Controls
- Reprocessing Steps

Technology Transfer or Knowledge Transfer?

Transfer Protocol Contents and Factors

- Analytical Methods while available may not be validated this is true for new chemical entities (NCEs).
- Fundamental Chemical Pathway.
- Raw materials, starting material, reagents, and catalysts.
- Process technology for all intermediates and final product must be outlined.
- Key material that will be tested for identity, appearance, impurities, and physical characteristics.
- Providing a list of approved suppliers for these aspects permits this to become a more manageable issue during transfer.

Technology Transfer or Knowledge Transfer?

Consider this as following three possible options

- From R&D to commercial this requires the highest level of information.
- From site to site not quite as involved as from R&D.
- The material is purchased as a commodity this has the lowest level of detail.
- Commodity purchases usually use a DMF reference.

Technology Transfer or Knowledge Transfer?

Experimental Design

- Registered Starting Material
  - Major structural elements of the API.
  - Stages which take place before the registered API starting material are not subject to cGMP.
  - Less formal protocol content is required here.
- Regulatory Implications and Considerations
  - Starting materials are raw material.
  - Intermediates or another API are significant structural elements.
  - Reagents effect structural transformations but become exhausted during the process.
  - Catalysts similar to reagents but remain chemically unchanged.

Technology Transfer or Knowledge Transfer?

Experimental Design (continued)

- Chemical Testing
  - Focus on things which may change during storage.
  - LOD, residual solvent, impurities, assay, and pH.
  - Methods must be stability indicating.
- Physical
  - These monitor aspects which may effect bioavailability.
  - Polymorphic form
  - Cohesivity
  - Particle size distribution

Technology Transfer or Knowledge Transfer?

- **Experimental Design (continued)**
  - Microbiological
    - Determine if the AI can support micro growth.
    - Is the process susceptible to contamination.
    - If this is possible then a bioburden test must be conducted.
  - Stability Profile
    - All chemical, physical, and micro requirements.
    - Use ICH guide Q1A.
    - We must keep in mind there may be key regional requirements (environmental).

Technology Transfer or Knowledge Transfer?

Health Safety and Environmental

- MSDS
- Handling and containment, monitoring as well as engineering controls for the site establish OELs.
- Personal protection.
- Sample collection and testing for OELs.
- Local laws while not applicable for APIs must be checked for raw materials in regions of the EU “Notification of New Substance”.
- There are many regions where chemical inventories mandate allowing import or export and will present a major hurdle to transfer.
- Waste minimization and identification of effluent streams.

Technology Transfer or Knowledge Transfer?

Process Information

- Manufacturing description.
- Flow charts and scale-up history.
- Material that is recycled, solvent recovery aspects.
- In process controls, point checks or continuous.
- Functionality check in the final dosage form.

Cleaning Properties

- This should be part of the product development cycle and needs to be a part of the package.
- Key aspects are solubility, cleaning methods, swabbing recommendations, and acceptable limits.

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer

This covers the scenarios where:

- Scale-up to commercialization (R&D to market).
- Post approval transfer (pilot plant to market).
- Acquisition from an external source (contractor to internal assets).

The Key Time Factor is Stability

- The studies are usually conducted with product made at the launch or manufacturing site.
- Amount of data needed and timing for filing the change are dependent on the classification of the drug substance and the complexity of the dosage form.

Technology Transfer or Knowledge Transfer?

The Key Time Factor is Stability (continued)

- Complex forms or high risk products need 3 months at filing from 3 batches (MR, Transdermal, MDI).
- Moderate level forms need 3 months from one batch submitted during the review cycle depends on the content of the original filing (IR, solutions, suspensions).
- Other dosage forms or minor level require simply a commitment for long term and accelerated stability at filing.
- Alternatively the validation batches may be used to confirm the site is under control.
- The CofA is filed for the batches they are then placed on regular stability and the data are supplied as an annual review.

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer

There are two aspects here components and process.

Components

- Drug substance, this conforms to the testing which was outlined under the API transfer. The functionality must be confirmed in the dosage form under consideration.

Excipients

- These may be compendial, non-compendial, or a novel material. These require a detailed level of information when filing.
- Multiple suppliers are qualified to accommodate site specific needs when transferring the product.
- Conventional wisdom suggests that validation batches be conducted using the established source.

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer (continued)

Process

- **R&D to Manufacture**
  - Establish a chronology of the process and parameters for the product (PIB→Capsules→Lab Scale→Pilot Scale→Full Scale).
  - Once the process has been established, key in process specifications may be used and SPC may be applied as a transfer strategy.
- **Site to Site**
  - Transfer of an approved product from one manufacturing site to another.

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer Key Aspects

- Technology match between sites (use SUPAC).
- Facility is suitable for the product under consideration (penicillin's, cephalosporin's).
- Equipment is IQ/OQ.
- IPC have been established and limits put in place.
- Quality Risk Analysis has been completed.
- Raw material sources have been identified.
- Bulk transfer between process steps.
- Process description is laid out in detail.

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer Key Engineering Aspects

- Layout design corresponding to the specific needs of the selected dosage form.
- Design qualification provides background to purchase and install required utility system.
- Commissioning document for all equipment and systems
- IQ for all related cGMP systems.
- Process flow for each type of product/dosage form (raw material movement, in process testing locations).

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer Key Documents

- Master manufacturing records.
- Raw material and finished product storage requirements.
- Process validation report (this assumes it has been validated prior to transfer).
- CMC components.
- Analytical methods.
- Cleaning procedures and validation reports

Technology Transfer or Knowledge Transfer?

Dosage Form Transfer Packaging Aspects

- For new products from R&D a significant level of detail is available which covers the level of protection, safety, compatibility and performance.
- These are refined based on the nature of the dosage form.
- For mature products these data will need to be expanded if all the needed source documents do not exist.
- In most cases for mature products a simple transfer of the package component specs and equipment description is adequate.

Technology Transfer or Knowledge Transfer?

So Where Are We?

- Technology = Knowledge = Continuous Improvement
- Use Incremental Knowledge to Grow.
- Minimize tacit knowledge - Maximize explicit knowledge.
- Watch your competitors, monitor the market and learn.
- Streamline, reduce complexity and combine efforts.
- So whose culture is this anyway?
- Know *a lot* about where you are going.
- Use a chart to list proven acceptable ranges.
- Make validation part of the business strategy.
- Leverage your ability to change (IVIVC).
- Pick up those frequent flyer miles!
- Use regulatory relief to your best advantage.
- Look for PAT aspects you may already have in place!

Technology Transfer or Knowledge Transfer?

So Where Are We?

- The development aspects needed to support a submission using a business as usual approach are very similar to those which are key to QbD submissions.
- Systematic scientific updates provide a means to leverage key CMC aspects of our submission.
- Answering questions along the way prevents the “fishing expedition” and delay.
- Clear path to where we see the product in its lifecycle allow proactive rather than reactive post approval submissions strategies.
- We have the majority of the data available but need to configure it to defend our product,facility, and process.

Technology Transfer or Knowledge Transfer?

So Where Are We?

- The systems to achieve this are simple and may be applied to existing business models.
- In any case with product knowledge we are positioned for success and to deal with QbD NDAs and question based ANDAs in the future.
- New technologies exist which remove the sticky knowledge elements for process control.
- *Know what you do not know.*

References

- M. Subramanian, S. R. Rosenthal, Journal of Management Studies, 6, 773(2) (1998)
- O. Gasmann, M. Zedtwitz, R&D Management, 3, 147 (1998)
- W.B. Werther, E. Berman, Organizational Dynamics, 3, 20 (1994)
- A. Rangaswamy, Journal of Marketing Research, 1, 177(8) (1997)
- R. Kieffer, L. Torbeck, Pharmaceutical Technology, 6, 66 (1998)
- J. Butler, The Pharmaceutical Journal, 1, 31 (1999)
- Guide to Inspection of Solid Dosage Forms Pre/Post Approval Issues for Development and Validation, Issued January, 1994
- R.Somma, “Using Technology Transfer to Maximize Business Efficiency” Pharm. Eng. 27,5 (2007)

References (contd)

- P. J. von Dochren, R. St. John Forbes and C. D. Shively, Pharm Tech, 6, 139 (1982)
- K. D. Popp, Drug Dev. And Ind. Pharm., 13, 2339 (1987)
- K. Chapman, R&D to Manufacturing, ERIPT Meeting, 1983
- R. Somma, Technology Transfer, The International Experience, EPTM Meeting, 1990
- R. Somma, The Research-Production Interface, AAPS Annual Meeting, 1999
- "Pharmaceutical Process Scale-Up" M.Levin, Marcel Dekker, Inc., 2002, New York
- "Pharmaceutical Process Validation" R.A. Nash, A.H. Wachter, Marcel Dekker, Inc., 2003, New York
- R.Somma, "Development Knowledge Can Increase Manufacturing Capability and Facilitate Quality by Design" J.Pharm. Innov. 2, 87-92 (2007)

References (contd)

- ICH Q8, Pharmaceutical Development, Draft 1, No.3, October 25,2005.
- QbD Principles to be Implemented in Future FDA Guidance, DIA Dispatch, Oct. 28,2005.
- ISPE Good Practice Guide, Technology Transfer,ISPE, Tampa,FL, 2003
- R.Somma, "PQLI Conference Summation" ISPE PQLI Conference, Arlington,Va, June 7,2007
- C.Potter, "ObD Now", ISPE PQLI Conference, Arlington,Va, June 7,2007
- J.Spavins, "Design Space Summation" ISPE PQLI Conference, Arlington,Va, June 7,2007

References (contd)

- T.Shultz, “Critical vs. Non-Critical Summation”ISPE PQLI Conference, Arlington,Va, June 7,2007
- B.Davis, “Control Strategy Summation” ISPE PQLI Conference, Arlington,Va, June 7,2007
- G.Migliaccio, Manufacturing Science, June, 2002
- A.H.Kibbe, Process and Analytical Validation Working Group, June,2002
- A.S. Hussain, The Subcommittee on Process Analytical Technologies (PAT): Opening Remarks, June, 2002
- G.K.Raju, Laying The Foundation for a “CAMP” Response, March, 2003
- T. Sami, “Novartis Using PAT with aid of IVIVC”, Validation Times, p.3, Vol.5, No.6, 2003

Technology Transfer or Knowledge Transfer?

Contact Information

Russ Somma,Ph.D.

SommaTech, LLC

3 Executive Drive

Somerset,NJ 08873

732-748-1990 ext. 203

rsomma@sommatechconsulting.com

www.sommatechconsulting.com

Any Questions?

Metin.Celik@pt-int.com

War Stories Failures and Solutions
Things That Keep You Up at Night

Russ Somma, Ph.D.

SommaTech, LLC

Aug 30, 2012

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War Stories Failures and Solutions

Outline

- What keeps you awake?
- What is prior knowledge and how best to apply it effectively?
- Where will your problems come from or how to you expect the unexpected?
- What are the main factors contributing to our failures:
  - API
  - Formulation
  - Process,
  - Facility
  - Combinations of all these

War Stories Failures and Solutions

Objectives

- To review aspects based on the course content from API to Technology Transfer and how problems may begin to surface.
- To extract aspects which have caused projects to fail based on the inability to recognize key factors.
- To present questions which will highlight commonly encountered issues.
- To use several case studies as a baseline for possible solutions and expected outcomes.
- To interact and suggest strategies for mitigation of actual problems faced and potential pathways.

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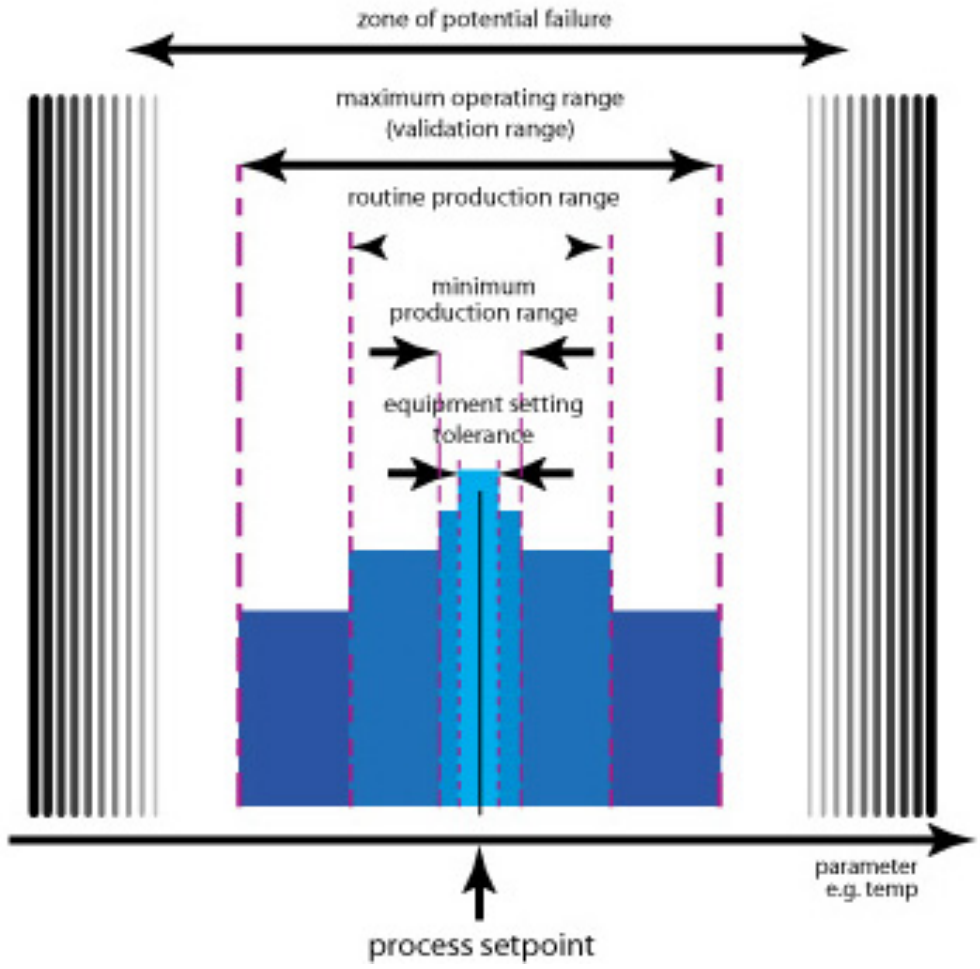
War Stories Failures and Solutions

Let’s start with process parameters, a common problem.



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Process Parameters

- Process Set Point
  - Set value for a parameter
- Equipment Setting
  - Normal control variation or the engineering capability of the system
- Minimum Process Range
  - Pragmatic approach is to set this at twice the equipment setting
- Normal Production Range
  - Set point +/- normal variation for the process in question
- Maximum Production Range
  - Limits within the product quality will not be effected
- Zone of Failure
  - Process limits where the quality of the product can not be assured

So the question is "Where do you run the validation?"

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Based on the type of tablet manufacturing process the nature of what is critical varies.

Direct Compression

What is critical here?

- Weighing
- Sieving
- Mixing
- Capsule filling
- Tablet compression

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War Stories Failures and Solutions

Based on the type of tablet manufacturing process the nature of what is critical varies.

Direct Compression

What is critical here?

- Weighing No is this true in all cases? Exceptions?
- Milling Yes when you reduce particle size No when it is a process aid. Exceptions?
- Sieving No when it is fixed. How is this established?
- Mixing Yes when it is to distribute the API No for lubrication only? What about API levels high / low?
- Capsule filling Yes
- Tablet compression Yes

Is this a technology which you would select for your products?

If not then what is the logical next option?

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Something which has become common place see if this sounds familiar.

- We all have heard that multi-use facilities enable companies to leverage their capital investment across a number of development projects.
- Recent growth in highly potent drugs, however, complicates the issue, since many of these classes of drugs exhibit significant adverse events, including cytotoxic, fetotoxic and sensitizing effects.
- This makes it more critical than ever to safeguard both personnel and patients from inadvertent exposure.
- If capital were no object, or if the drugs in question were destined to be blockbusters, the strategy would be clearer: simply manufacture each potent compound in a dedicated facility.
- In most cases, however, manufacturing the product in a multi-use facility is the more economically desirable approach.

How have you handled this question?

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So if you have looked into what is critical and characterized your materials are you safe?

Think again!

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You need to know what you do not know.

A phrase which should strike fear into any formulator is,

“Not clinically significant.”

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You should have many tools in your toolbox.

Some of these reside in areas into which you must drill down.

Depending on the manner your firm is structured this may require searching.

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The development of acceptable limits and parameters should extend to defining:

- The aspects of ADME for the compound (adsorption, distribution, metabolism and excretion)
- Assuring the target in-vivo profile which is created using simulations and predictions meets the clinical expectations.
- The biopharmaceutical classification (BCS) and associated data for the compound have been defined.
- Based on the BCS data and the nature of the product functionality what are the risks to determination of bioequivalence and/or the establishment of an IVIVC.
- Based on the need for process and site flexibility is the establishment of an IVIVC critical.

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What risks do you have control over during formulation and process development based on the points we have established?

- The output for the PAR will be based on tests which we apply (CU, dissolution, assay).
- These results can be measured and evaluated.
- The nature of the compound while clear from a physicochemical standpoint (solubility) is not as transparent from a drug absorption aspect.
- In this regard we must understand that there are points which we can not effect but we must design our process around.
  - Low GI permeability
  - First pass metabolism
  - These are sources of variability to the desired PK profile.

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How do we gauge this risk aspect in our knowledge store for the product and process?

•We may define our drug substance by using the BCS categories.

- Class I = high solubility, highly permeability
- Class II = low solubility, high permeability
- Class III = high solubility, low permeability
- Class IV = low solubility, low permeability

•These may be further refined by applying additional data to our drug product.

- Absorption number , permeability of the drug substance
- Dose number, the solubility aspect of the drug substance
- Dissolution number, the release from the drug product

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How do we use this to anticipate PK problems?

Generally the following may be used as a guide:

- Class I products are usually no problem.
  - Assuming we have not created a problem in our process or formulation (secondary growth, blending)
- Class II products will usually be no problem
  - Assuming we already have comparability in various dissolution media (pH 1, 4.5 , 6.8).
  - We have not changed the release mechanism from the tablet due to composition and mixing.
- Class III these may be problematic and will require PK studies which are adequately powered (n >12)
- Class IV there is no certainty in PK outcomes here one may apply a large n>25 but the use of a small scale pilot study seems advisable.

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The manner in which we answer these questions and mange our risk greatly effect our formulation, process and business plan.

Let’s consider some examples of a few realistic balancing acts.

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Case Study 1:

Background:

Develop a fixed combination product which will match innovator profiles and form the basis for submission based on bioequivalence strategy.

Objectives:

- Keep tablet size small.
- Protect the two drug substance components from degradation.
- Use available conventional technology.
- Match dissolution profiles for both innovators.

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Case Study 1:

Outcome:

- Tablet size was kept within reasonable range for patient acceptance.
- The in-vitro data provided a reasonable match for both materials under consideration.
- The combination was shown to be stable over 12 weeks at accelerated conditions.
- Move forward with a study to confirm the in-vitro results.

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Case Study 1:

PK Study Results:

- The plasma data showed an increase in the input for the fixed product.
- One of the components showed a marked shift in availability when compared to reference.
- This required a wider approach using various media (pH) and conditions to resolve and enhance the predictive nature of the in-vitro testing.

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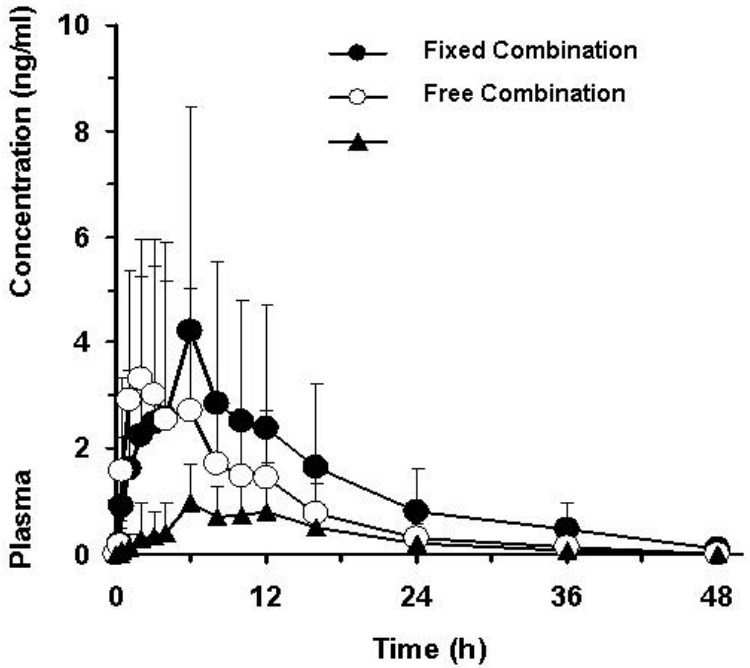

Lesson learned here is that a more critical eye toward some early studies.

The knowledge store may have provided some insight.

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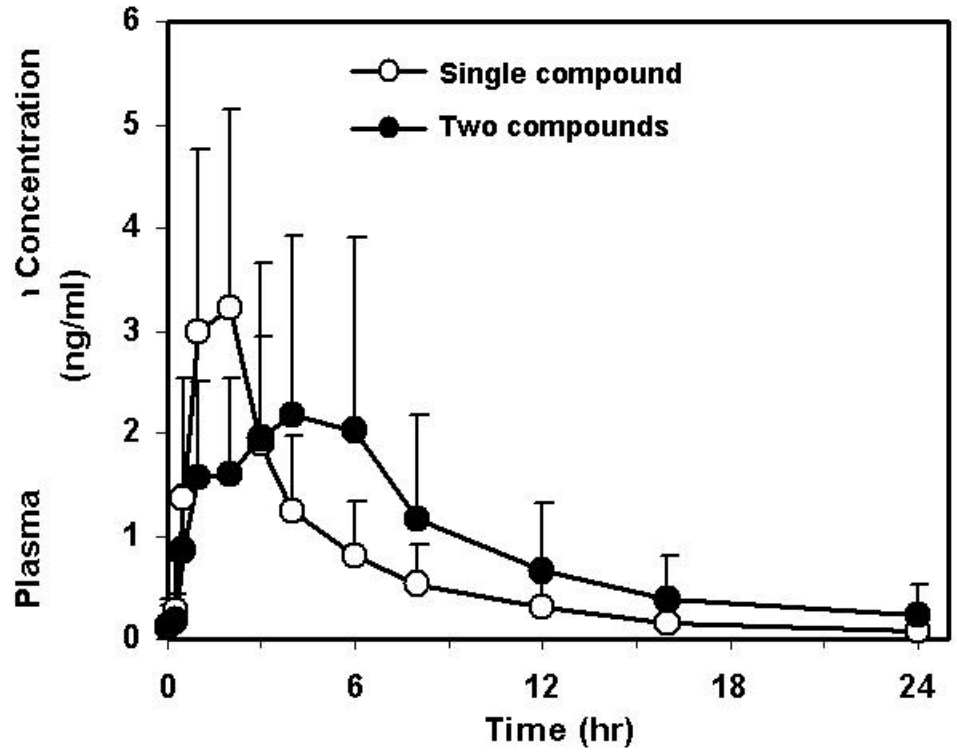

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Case Study 2:

Background:

Develop a modified release product which will match clinical requirements and address an unmet medical need.

Objectives:

- Provide up to 12 hours of activity.
- Maintain dosage form size.
- Use available conventional technology.
- Match current in-vivo profile as established by clinical practice.
- Leverage process and site changes.

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Case Study 2:

Outcome:

- A “fast and slow” study was selected as the best approach to establish a range.
- Clinical materials were prepared based on simulations and the anticipated need for release rate specifications.
- These specifications were balanced against process capability and envisioned variability.
- Move forward with a study to confirm the in-vitro results.

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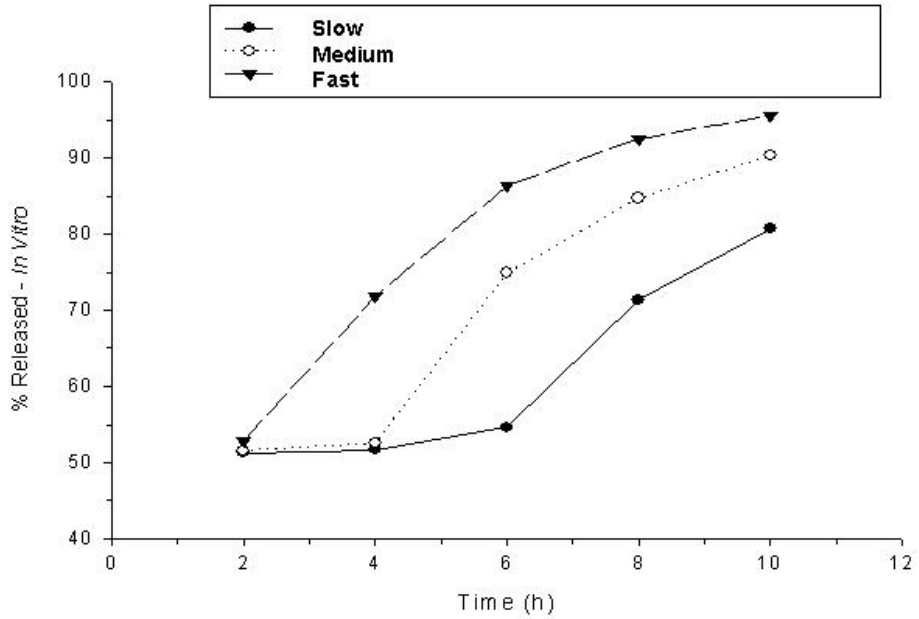

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Case Study 2:

PK Study Results:

- The study was conducted comparing the fast and slow samples to the target as well as a reference.
- This provided the establishment of a BE baseline for the extremes studied in this product.

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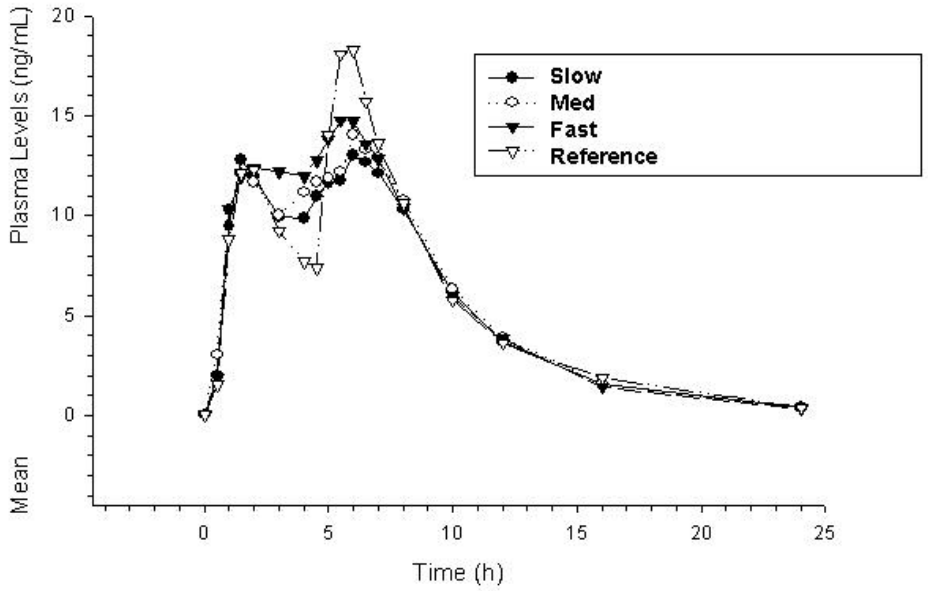

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References

- J.Aurora, V.Pathak, The Fate of Drugs & Drug Development: An Overview

  http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=225
- P.Veng-Pederson, J.V.S. Gobburu, et.al. Biopharm. and Drug Disposition 21,1, (2000)
- R.G.Buice, "Bioequivalence & In Vivo-In Vitro Correlations Study Design and Data Interpretation based on BCS", 2005
- M.C.R. Johnson, Pharmaceutica Acta Helvetiae, 47,p.546 (1972)
- J.Barra, R.Somma, Drug Development and Industrial Pharmacy, 22 (11) p.1105 (1996)

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Contact Information

Russ Somma, Ph.D.
SommaTech, LLC
3 Executive Drive
Somerset, NJ 08873
732-748-1990 x203
rsomma@sommatechconsulting.com

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Opportunities in Formulation Development of Poorly Water-Soluble Compounds

Sudha Vippagunta

August 30th 2012

Novartis Pharmaceutical Corporation

Current Trends

- Estimated 40-60% of new chemical compounds are poorly water-soluble compounds.

- Majority of new small molecule compounds that go into clinical trials with low aqueous solubility belong to therapeutic **area of Oncology**.

- For Oncology, the required doses are usually high.

Challenges with development of poorly water-soluble compounds

- High Doses to achieve MTD; exposure plateauing at high doses
- Significant positive or negative food effect
- Combinations with other compounds to multiple target sites.
- Limited excipients and allowable limits which could be used in humans
- Patient Compliance: Multiple regimens and large individual dosage units

Current Technologies Available

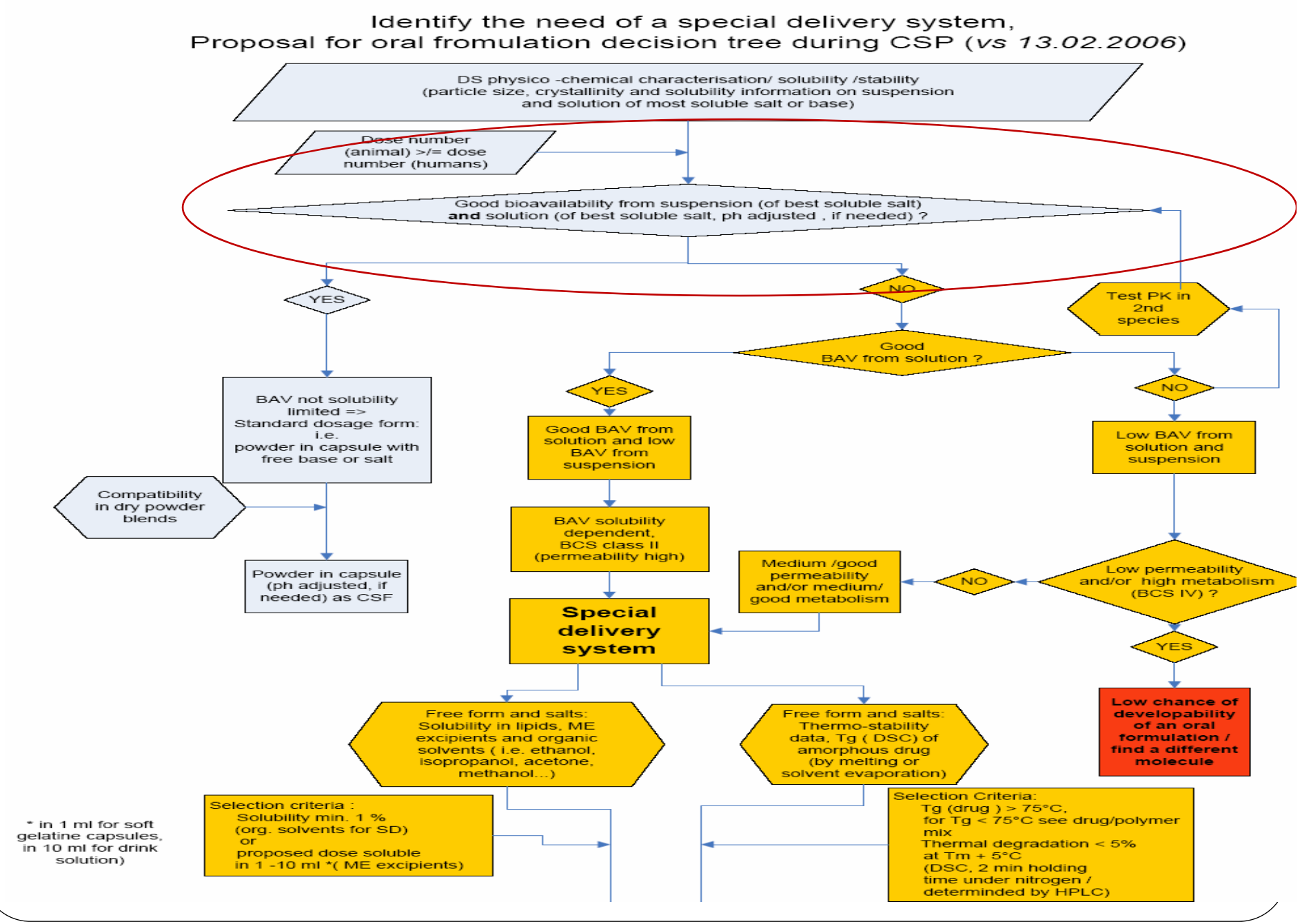
- Salts, Co-Crystals, Complexes
- Micronization
- Precipitation Inhibitors
- Microemulsions
- Crystalline and Amorphous Solid dispersions
- Nanosuspensions
- Lipid based Formulations

Criteria for Selection of a Suitable Technology

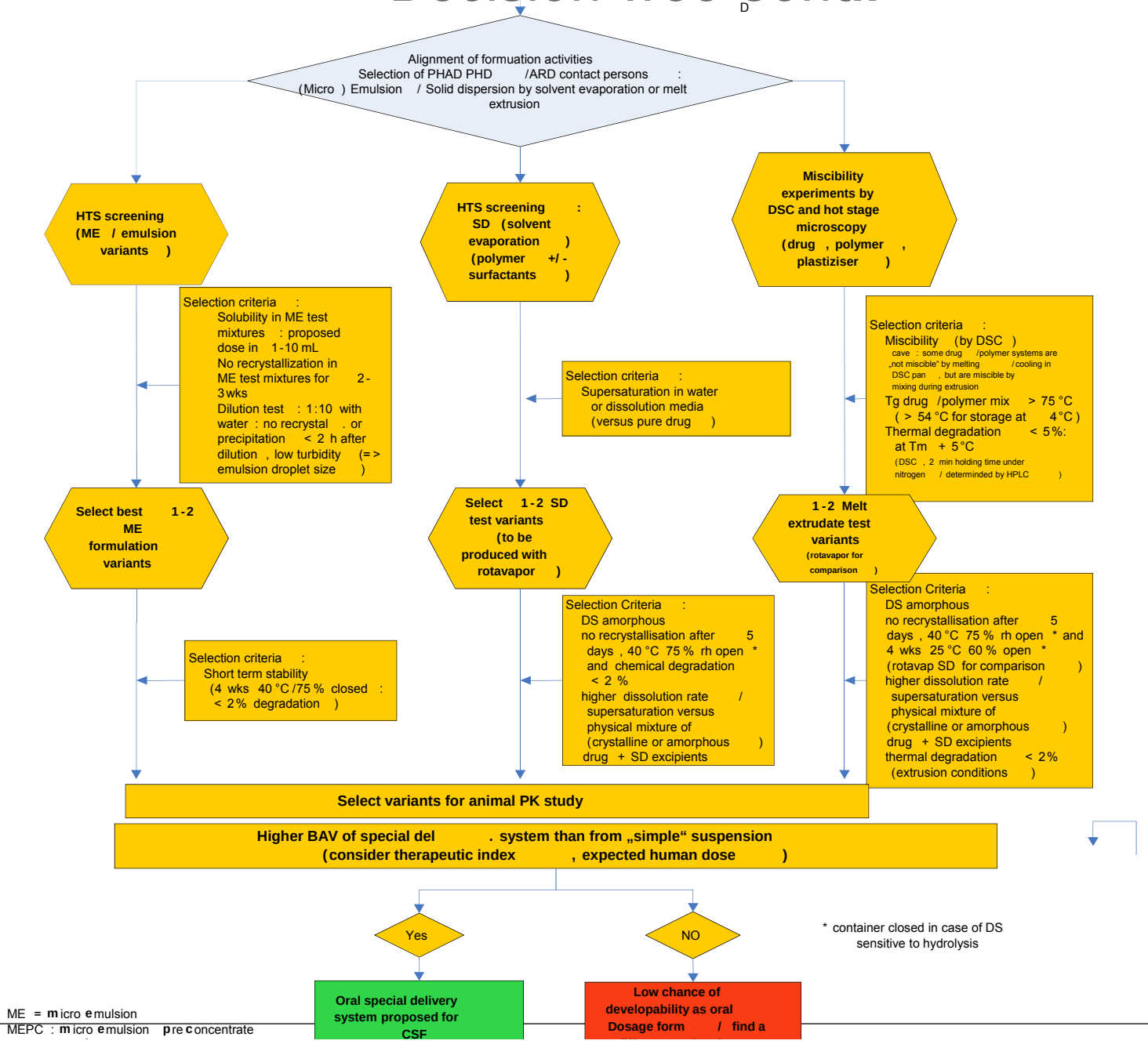
Key considerations:

- Thorough understanding of Drug Substance properties
- Dose : Highest dose to be administered for MTD (maximum tolerated dose) study
- Scale-up potential for the selected technology
- Availability of advanced analytical characterization techniques

Decision Tree



Decision Tree Cont..



ME = **m**icro **e**mulsion
MEPC : **m**icro **e**mulsion **p**re **c**oncentrate

Precipitation Inhibition: Case Study1

How do Precipitation Inhibitors Work?

- By keeping the compound in the super saturated state.
- What is Supersaturation?
  - A state where drugs are in solution at a concentration above their saturation solubility
  - Thermodynamically unstable
- Two essential steps needed to exploit supersaturation as a strategy to improve intestinal absorption of poorly water-soluble drugs:
  - Generation and maintenance of the metastable supersaturated state

‘Spring and Parachute Approach’

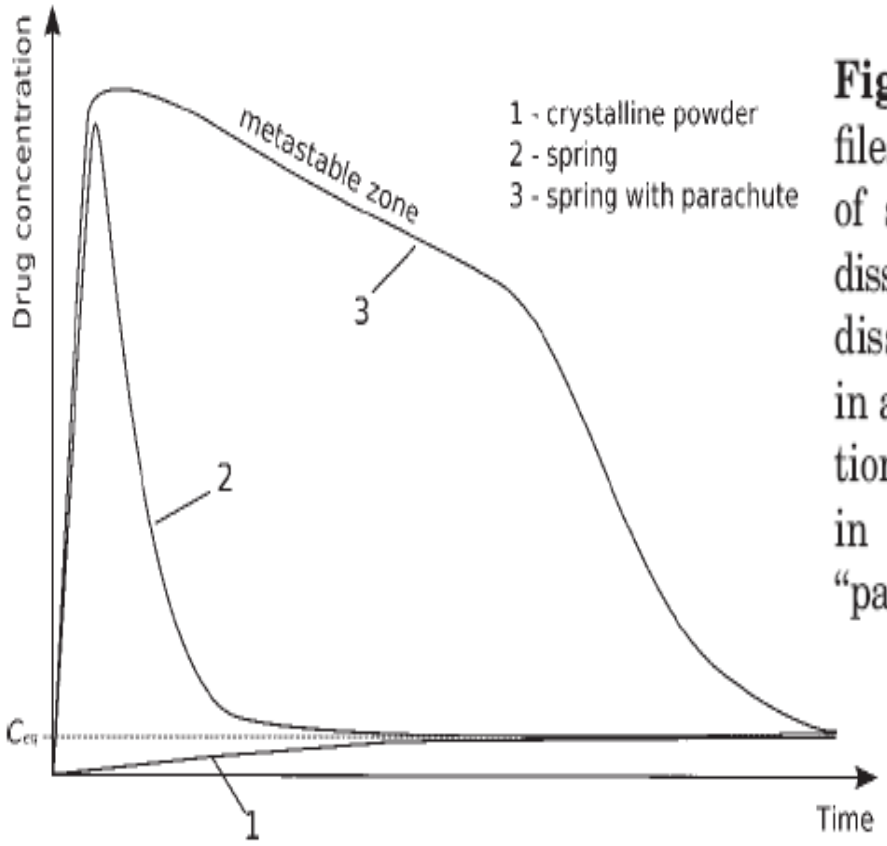


Figure 1. Schematic drug concentration–time profiles illustrating the spring and parachute approach of supersaturating drug delivery systems. Profile 1: dissolution of the most stable crystalline phase; profile 2: dissolution of a higher energy “spring” form of the drug in absence of precipitation inhibitors; profile 3: dissolution of a higher energy ‘spring’ form of the drug in presence of precipitation inhibitors that act as a “parachute.” C_{eq} represents the equilibrium solubility.

Brouwers J *et al.* J. Pharm. Sci. 2009 2549-2571

Compound A properties

- Low and high Clinical doses to be developed
- Properties of Compound A
  - Weak base
  - Solubility: > 1 mg/ml at pH ≤2 and < 0.02 mg/ml at pH >4.5
  - Crystallinity: very high
  - BCS class II
  - Chemically stable in solid form
  - Suspension formulation exposure in animal models similar to solution formulation at low to medium doses
  - Conventional dosage form may not provide adequate exposure at high doses in clinical trials.

Precipitation Screening Results

- The results of the screening

Polymer concentration	Start pH	Final pH	0 min ppt	Comments on ppt
1% PEG 4000	1.9	6.8	no	yes after 3 min
0.1% SLS	1.9	6.8	no	yes after 18 hrs; no after 5 hrs
0.02% SLS	1.9	6.8	no	yes after 3 min
0.5% PVP K30	1.9	6.8	no	yes after 30 min
0.5% TPGS	1.9	6.8	no	yes after 20 min
0.001% HPC EXF	1.9	6.8	no	yes after 1.5 hr
0.001% HPMC 3cps	1.9	6.8	no	yes after 18 hrs; no after 6 hr
0.0005% HPMC 3cps	1.9	6.8	no	yes, few after 30 min
Controls				
0.25 mg/ml compound A	2	6.78	no	yes after 5min

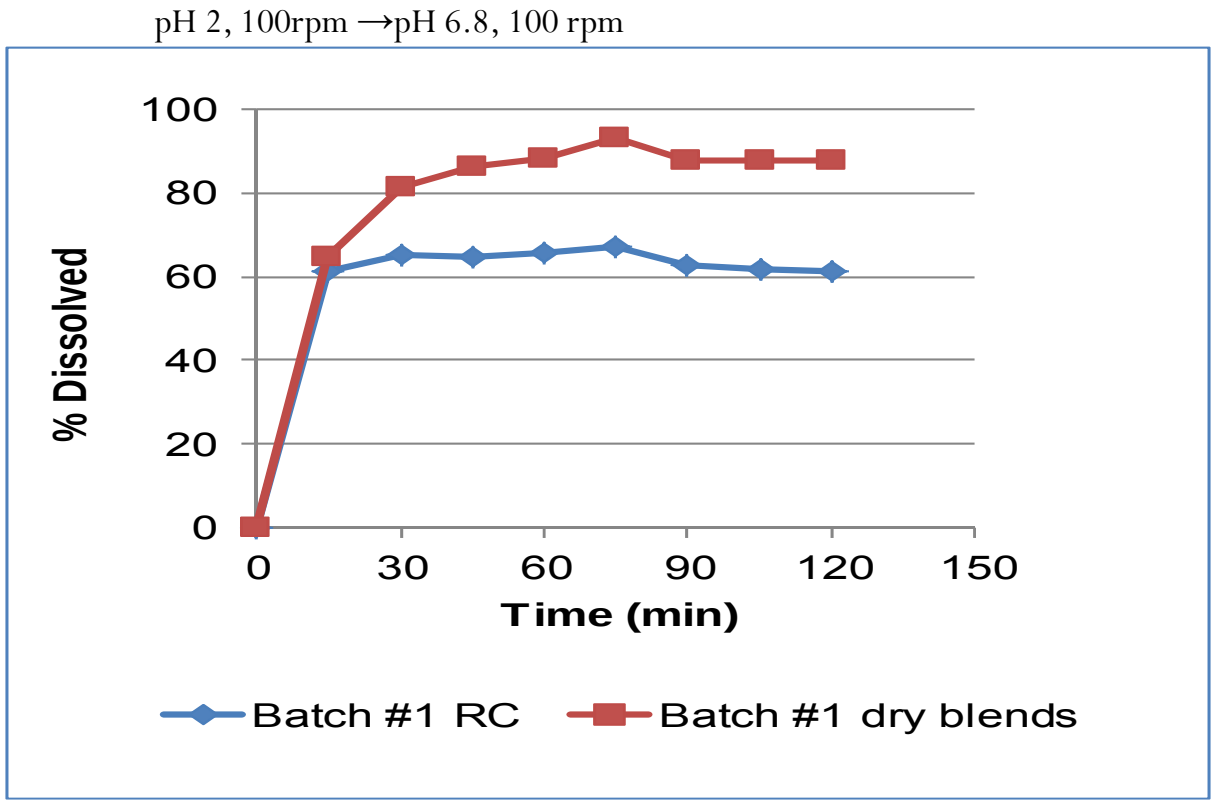
- Calculation of HPMC 3cps concentration in relative fluids

  Assumption: 200mg Compound A / capsule

% HPMC/cap	50 ml	100 ml	250 ml	900 ml
2%	0.016	0.008	0.0032	0.00089
4%	0.032	0.016	0.0064	0.0018
10%	0.08	0.04	0.016	0.0044

- **Conclusion: 2% HPMC 3cps should be able to keep compound A in solution in 900 ml medium at pH 6.8**

Dissolution Results of Compound A Roller Compacted formulation with HPMC 3cps



HPMC 3cps prevented compound A ppt at pH 6.8.

Crystalline & Amorphous Solid Dispersions – Case study 2

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug.

The carrier or matrix could be a water-soluble polymer, pH dependent polymers or even small molecules.

Why Solid Dispersions?

- Improves Solubility and Dissolution
- Improvement in Oral Bioavailability
- Improvement in processing and tabletting properties

Types of Solid Dispersions

Depending upon the state of the drug in the solid matrix, solid dispersions can be divided into:

- Crystalline solid dispersions – Eutectic and Monotectic
- Amorphous solid dispersions
- Solid Solutions

Crystalline Solid Dispersions (Eutectic and Monotectic)

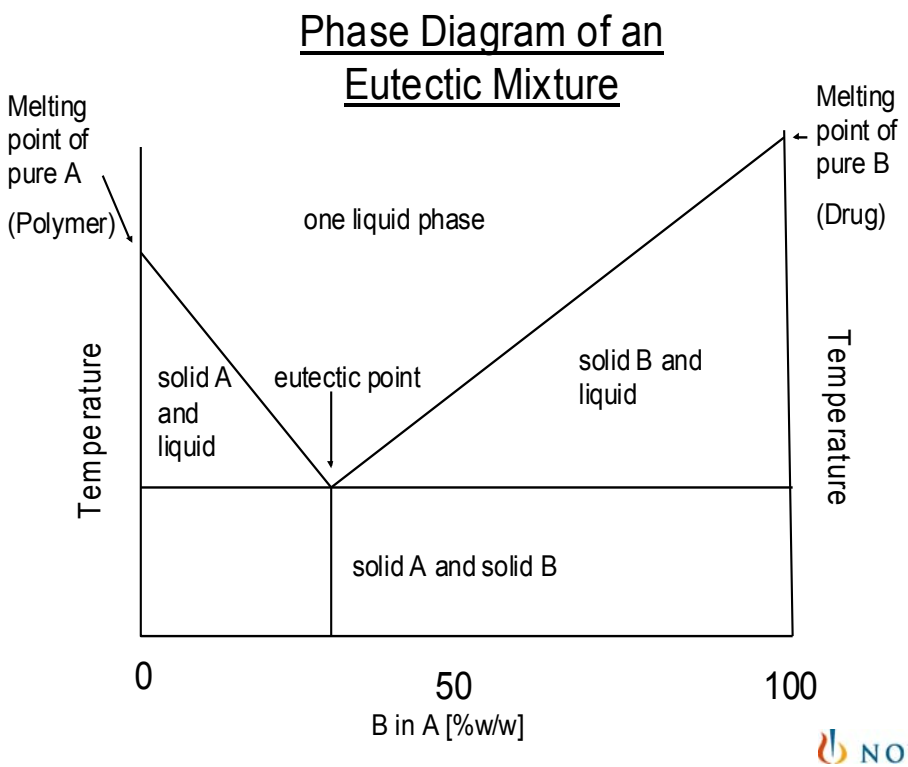
What are Eutectic and Monotectic solid dispersions

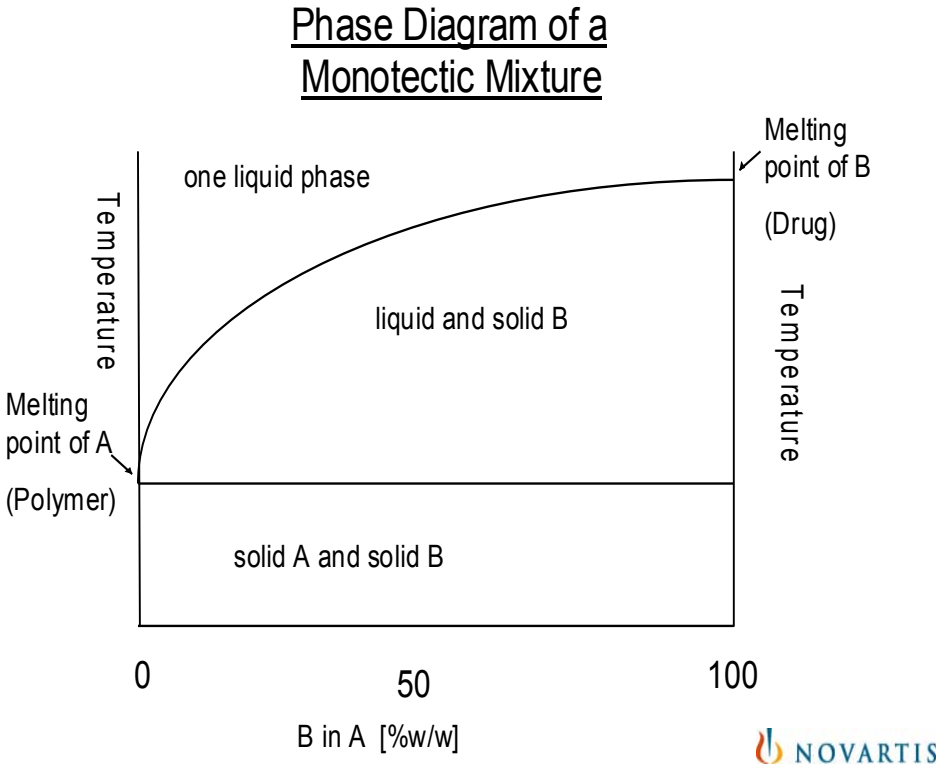
- **Eutectic solid dispersions may be defined as systems where the melting point of the mixture of drug and carrier will be below the melting point of drug and carrier alone.**

- **Monotectic solid dispersions may be defined as systems where the melting point of the mixture of drug and carrier cannot be below the melting point of the component with lower melting temperature.**

Phase Diagrams

Eutectic solid dispersions offer several advantages over monotectic solid dispersions such as : (a) reduction of particle size of both the drug and polymer to ultrafine crystals at and below eutectic composition (b) higher solubility of the drug in the carrier, and (c) lower processing temperatures.





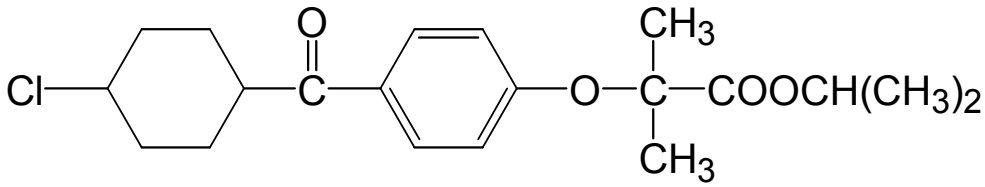
Advantages of Eutectic and Monotectic Solid Dispersions

Increased rate of dissolution resulting in increased absorption of poorly water-soluble drugs:

- **Reduction of particle size of both drug and carrier to ultrafine or colloidal crystals ; could be the size of nanoparticles.**
- **Crystalline solid dispersions are thermodynamically stable compared to amorphous solid dispersions.**
- **An increase in drug solubility due to solubilization effect by the carrier**
- **Absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug.**
- **Excellent wettability and dispersibility of a drug in a water-soluble matrix**

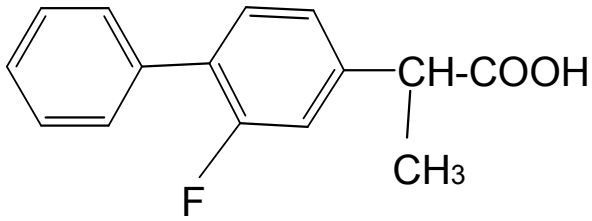
Model Drugs

Fenofibrate



MW: 361; m.p. 79 °C; ΔHf (kJ/mole): 34
Solubility in water: 0.1 ug/ml

Flurbiprofen



MW: 244.3; m.p. 115 °C; ΔHf (kJ/mole): 28
Intrinsic Solubility: 12.2µg/ml; Solubility in water: 95.2µg/ml

Model carrier

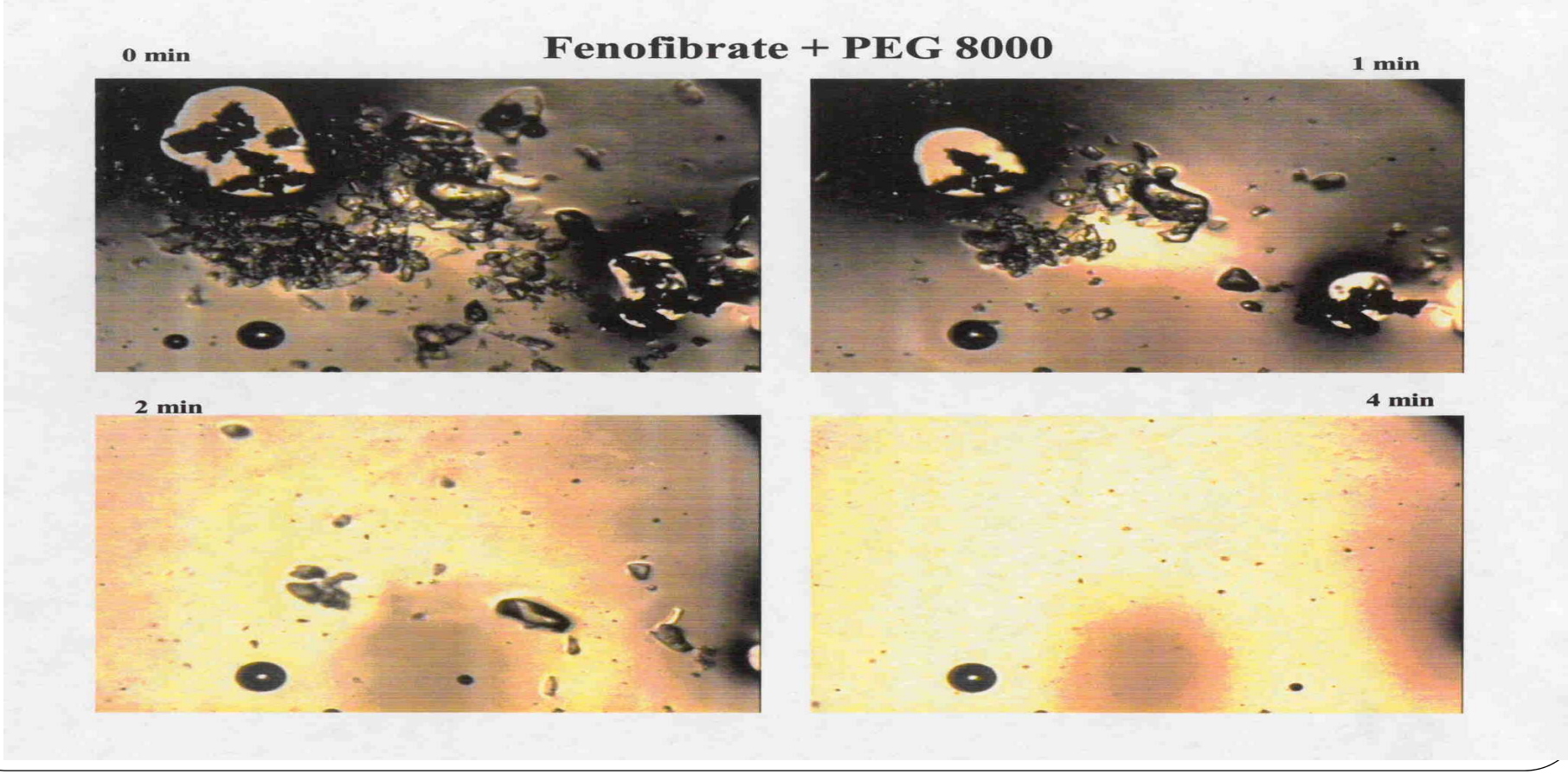
PEG 3350

$H\text{-}(OCH_2CH_2)_n\text{-}OH$

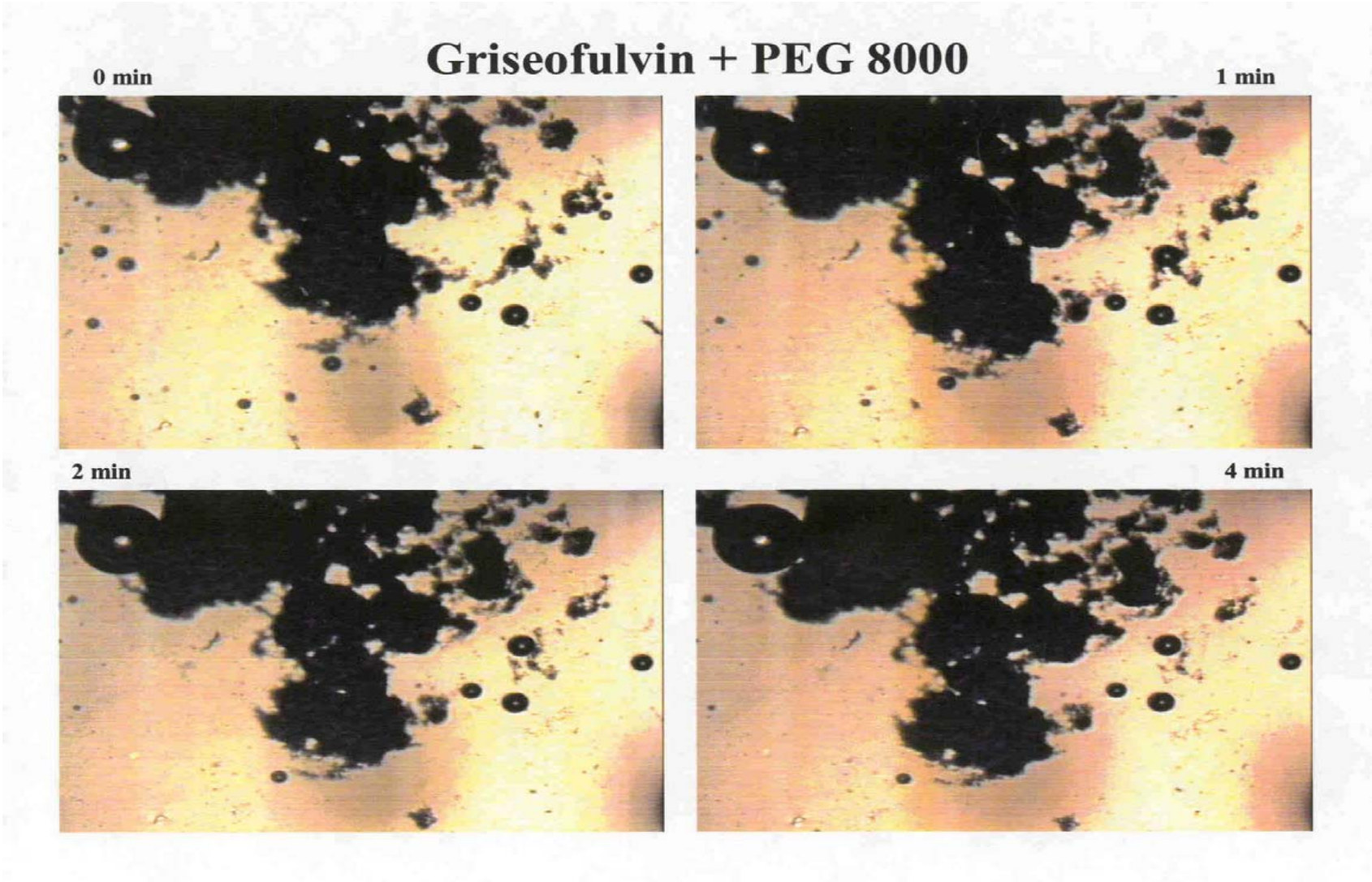
MW: 3000-3700 ; m.p. 56 °C; ΔHf (kJ/mole): 578.4

Quick screening method to identify eutectic or monotectic solid dispersions, using hot stage microscopy

(a) Fenofibrate dissolves at melting temperature of PEG8000 (eutectic system)



(b) Griseofulvin does not dissolve at melting temperature of PEG8000 (monotectic system)



Modeling of theoretical drug-carrier phase diagram to identify eutectic or monotectic solid dispersions and to determine eutectic composition

$$^{1}\ \Delta H_{fi}(1-T/T_{fi}) = -RT(\ln\phi_i + \phi_j(1-V_i/V_j)) - \Delta W_{ij}\phi^2_j$$

ΔH_{fi} = Heat of fusion of component i

T = Temperature on the liquidus curve

T_{fi} = Melting temperature of component i

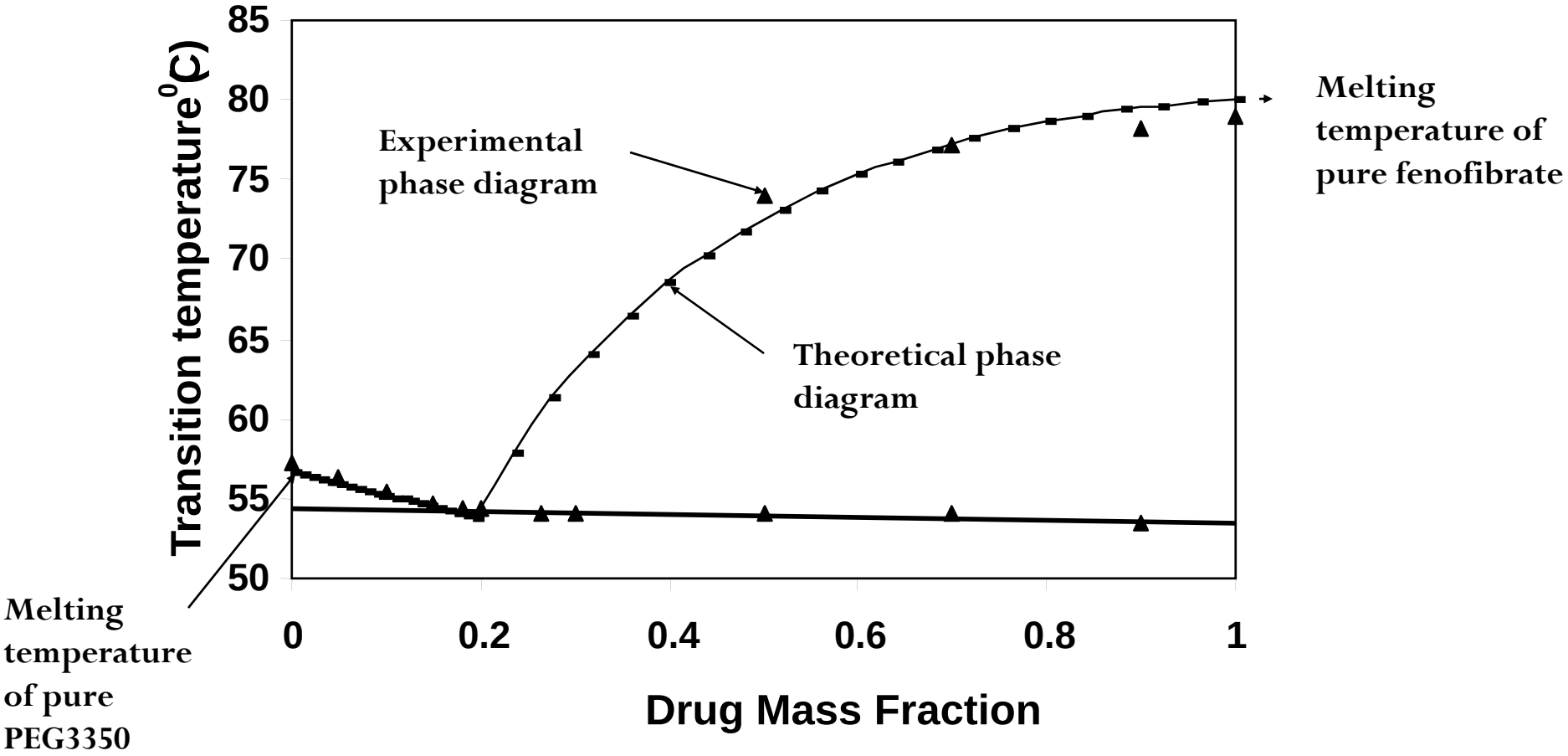
ϕ_{ij} = Volume fraction of each component i and j

V_{ij} = Mole volume of each component i and j

ΔW_{ij} = Total interaction energy per macromolecular volume element

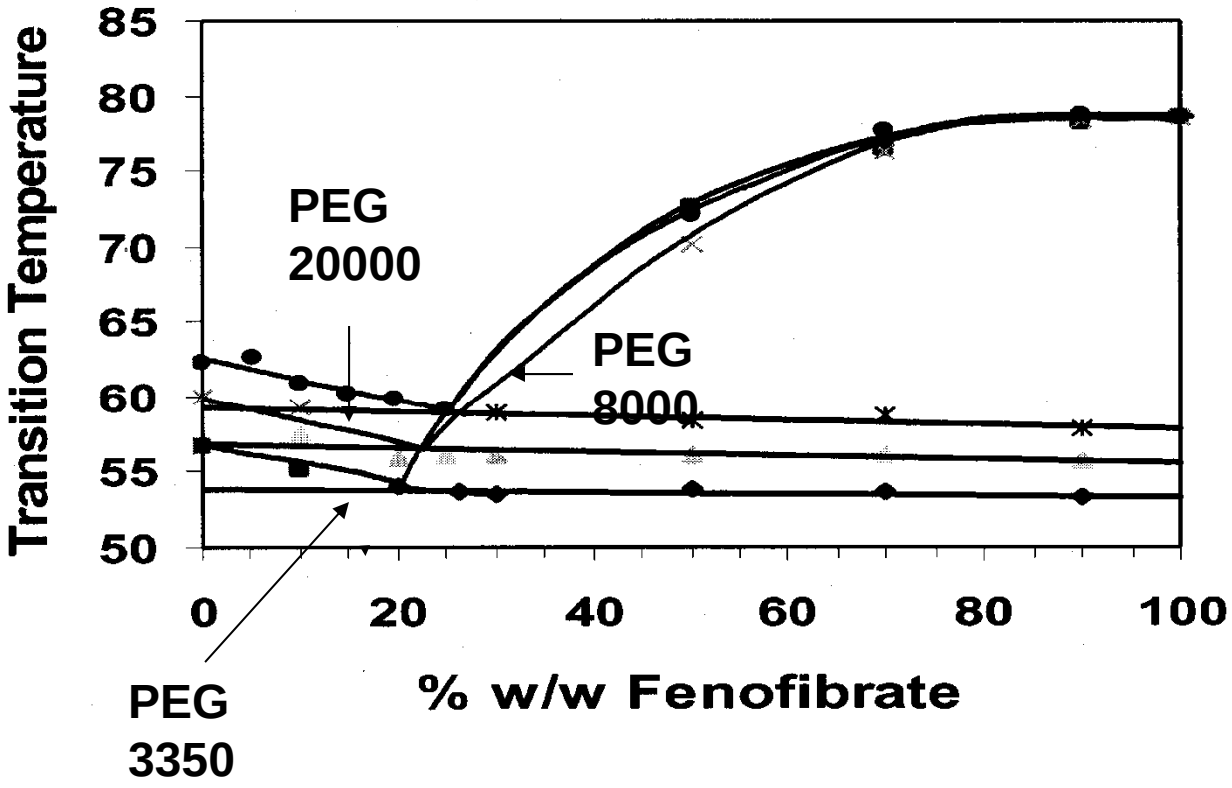
Experimental and Theoretical Phase Diagram of Fenofibrate + PEG 3350 ΔWij=0)

Eutectic composition: 21% w/w Fenofibrate



Theoretical model could predict the eutectic phase diagram of fenofibrate-PEG3350 system, when the interaction energy (ΔW) between fenofibrate and PEG3350 was zero. This result suggests the absence of specific interactions between fenofibrate and polymer.

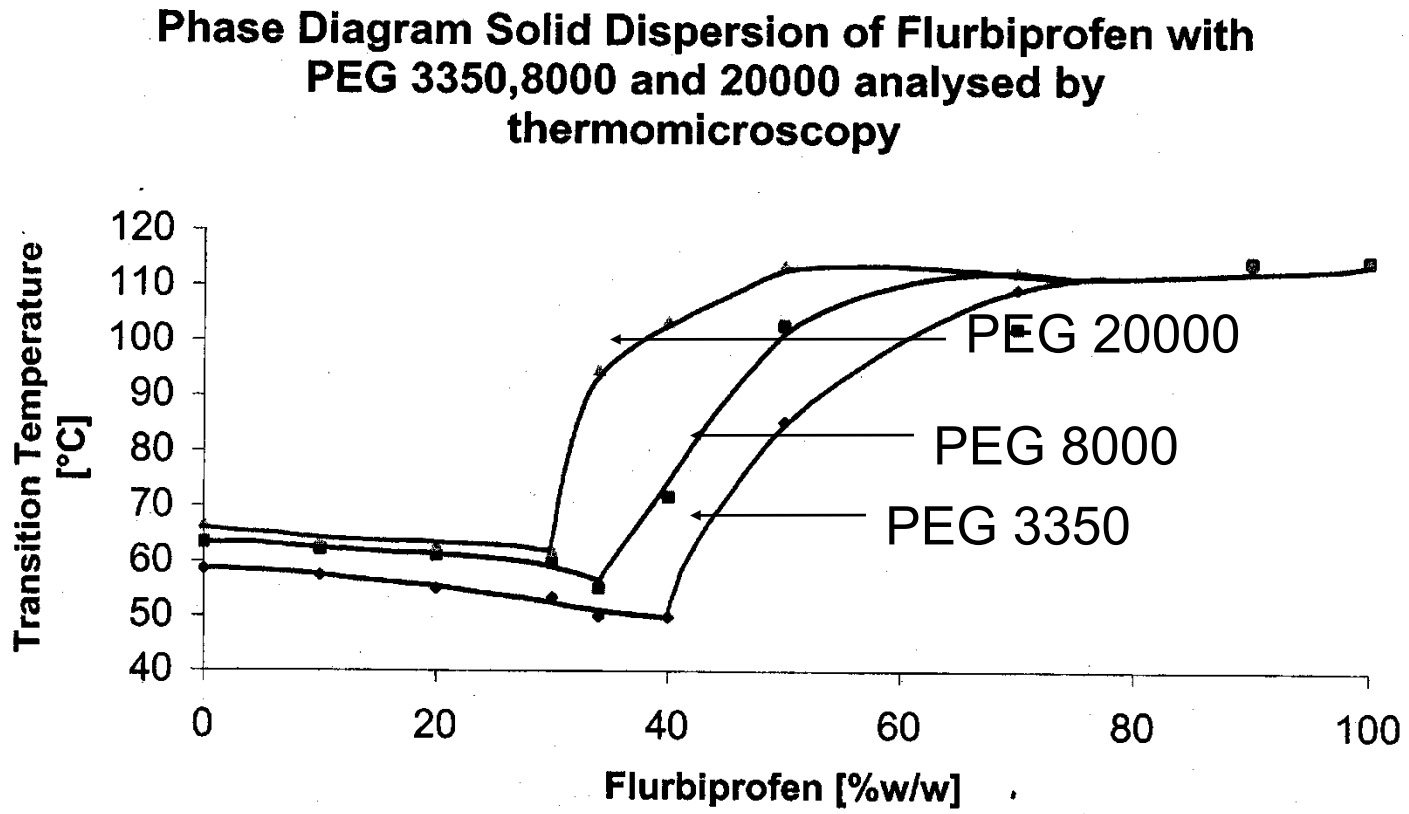
Phase Diagrams of Fenofibrate and PEG 3350, 8000, 20,000 Solid Dispersions



The eutectic composition did not change significantly with increase in PEG molecular weight. Drugs such as fenofibrate, which do not form specific intermolecular interactions with carrier, change in molecular weight of carrier does not affect the eutectic composition.

Effect of specific intermolecular interactions between drug and carrier on eutectic composition

Model Drug: Flurbiprofen **Model Carriers: PEG 3350, 8000, 20,000**



The eutectic composition of flurbiprofen-PEG system changed with molecular weight of PEG in the order : PEG3350>PEG8000>PEG20,000.

Any New Opportunities for Crystalline Solid dispersions ???

Nanocrystalline Solid dispersions:

Nanocrystalline solid dispersions (NCSDs) of drug were prepared by antisolvent precipitation followed by spray drying, using hydrophilic polymers.

It has been shown that the crystallization takes place in a two-step process: a portion of the polymer crystallizes first (Step 1), followed by crystallization of drug and remaining polymer (Step 2) (Qian et al., Pharm. Res. 2007).

The size of drug crystallites in the drug-polymer solid dispersions is independent of polymer topology, but is caused kinetically by a combined effect of nucleation rate and crystal growth rate.

Amorphous Solid Dispersions

Case Study with Compound B: Objective

The objective of this study was to evaluate feasibility of preparing a physically and chemically stable amorphous solid dispersion of Compound B, a poorly water-soluble compound, using melt-extruder

Critical DS and Carrier Properties Considered

- T_m, Melting point
- T_g, Glass transition temperature
- δ, Solubility parameter (Related to miscibility and processibility)
- S_c, Configurational entropy (Related to stability)
- Φ, Flexibility (Related to re-crystallization)
- $1/\tau$, Molecular mobility (Related to re-crystallization)

Solubility Parameter, δ

- Miscibility
- Like dissolves like
- Thermodynamics of Miscibility

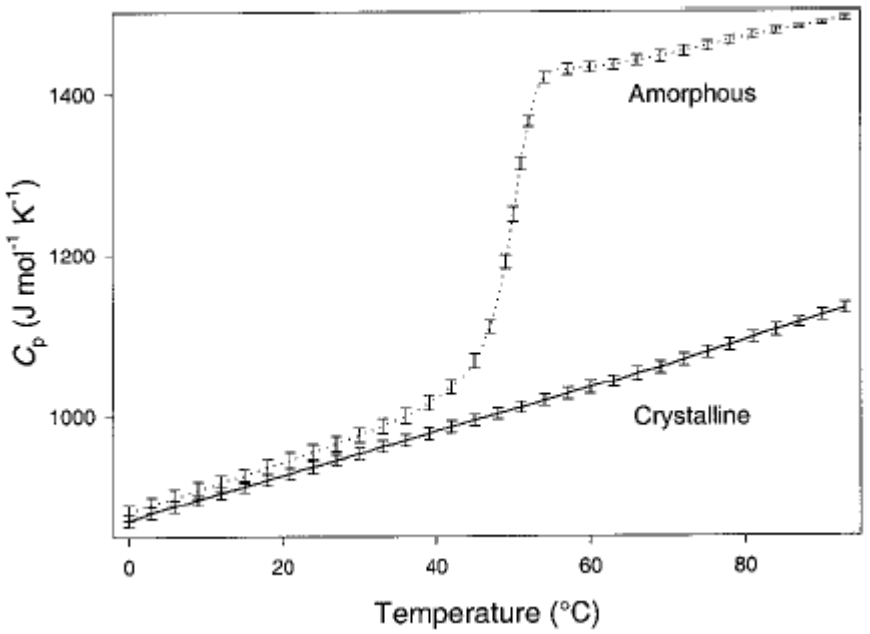
$$\delta = (\Delta E_{coh} / V)^{1/2}$$

where, ΔE_{coh}: cohesive energy; V: molar volume

Configurational Entropy & Molecular Mobility

Configurational Entropy (S_c)

$$S_c(T) = S^a(T) - S^x(T)$$
$$= \Delta S_m + \int_{T_m}^{T} \frac{C_{p\,\mathrm{conf}}}{T}\, dT$$



Molecular Mobility ($1/\tau$)

Predicts the relaxation time, which in turn predicts stability

Higher S_c α Higher MM α (1/re-crystallization)

Zhou et al., 2002

Compound B DS Properties

- Molecular Weight: >500
- Log P: >5
- MP: >250 °C (decomposition upon melt)
- Tg: >150 °C
- Solubility: <0.1 ug/ml

Challenges

- Crystalline Drug Substance
  - Insoluble
  - High melting point (>250 ˚C) and decomposition upon melt
- Attempts to Form Amorphous Drug Substance
  - Melt Extrusion: decomposed
  - Solvent Evaporation: partially crystalline

Strategies Applied to Formulate Amorphous Solid Dispersion

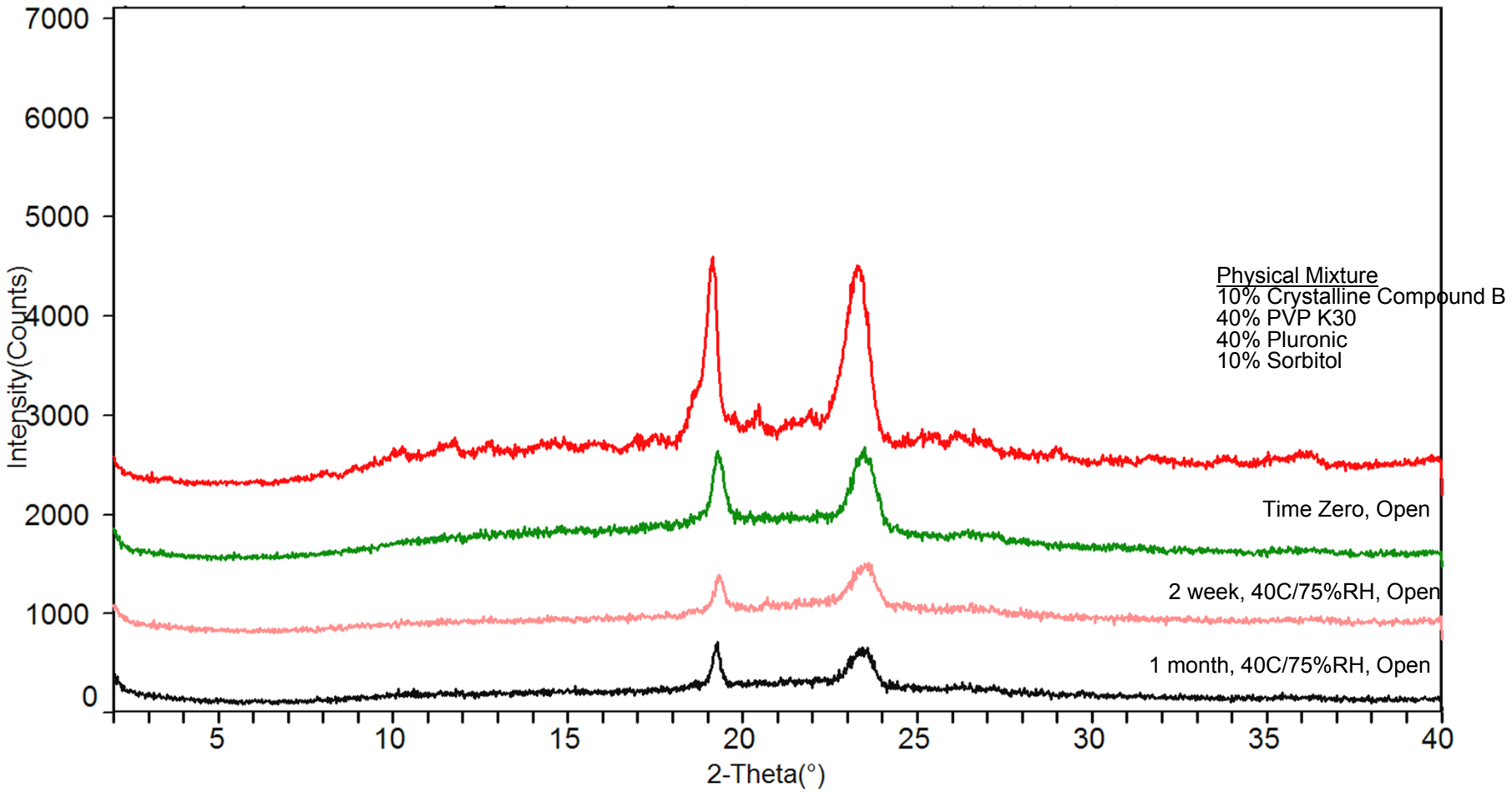
- Lower the processing temperature:
  - using low Tg polymers ⇒ PVP K30, PVP K17, PVP/VA
  - start with solvent evaporated drug substance
- **Solubilizing agents ⇒ Pluronic F68, Vitamin E, Ryoto sugar**
- H- Bond Donor ⇒ PVA, Polydextrose, Maltitol
- Complexing Agent ⇒ Captisol
- Different Plasticizers ⇒ Sorbitol, PG

Potential Formulations Identified

Potential Formulation	Time Zero		2 Week, 40°C/75% RH, Open	
	Assay (%)	Karl Fischer (%)	Assay (%)	Karl Fischer (%)
10% Crystalline Compound B 40% PVP K30 40% Pluronic F68 10% Sorbitol	105.69 (.33)	8.2	107.34 (1.31)	24.2
15% Amorphous Compound B 65% PVP K30 10% Pluronic F68 10% Sorbital	98.76 (.23)	7.2	93.30 (1.08)	18.8

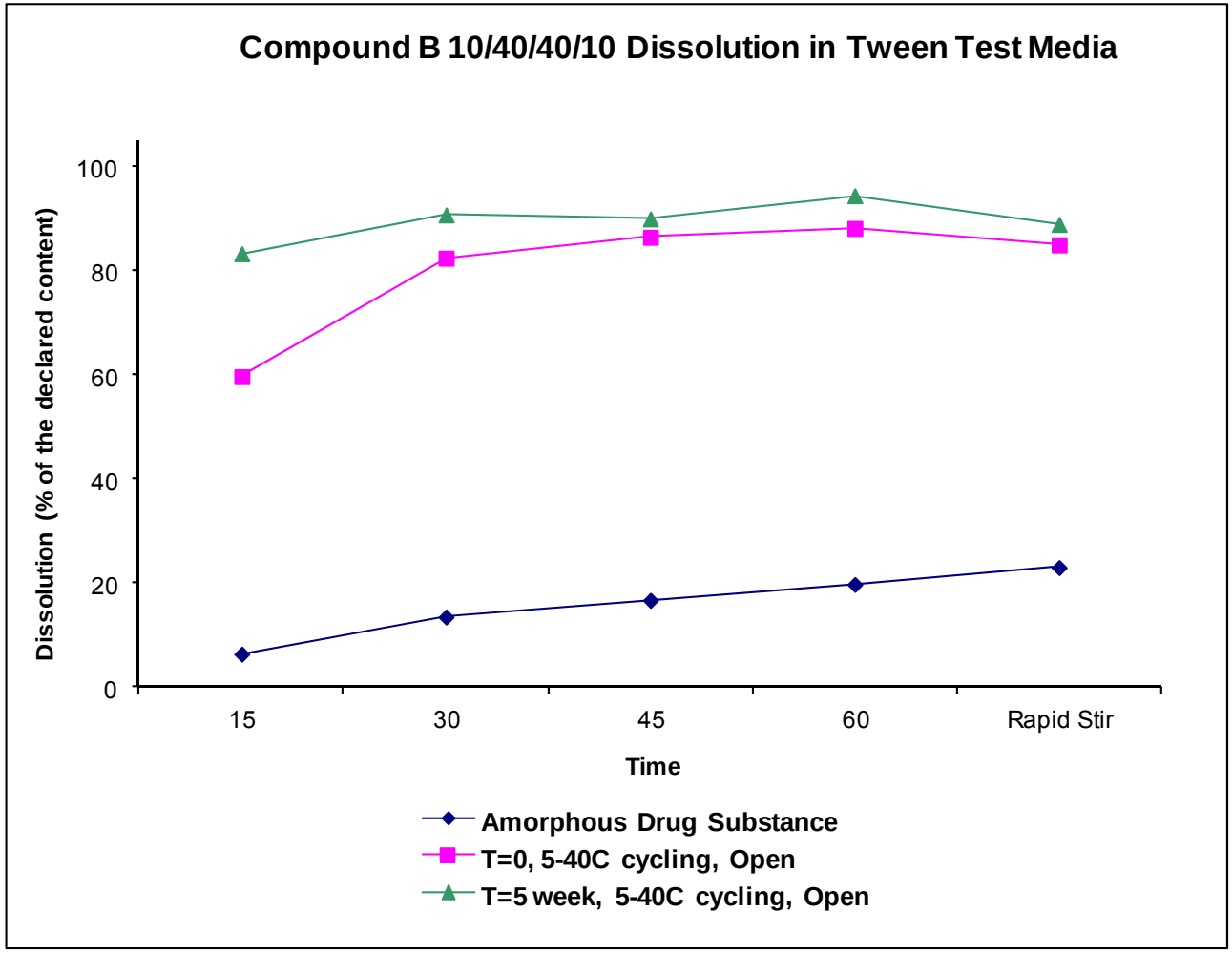
PXRD 10/40/40/10 Solid Dispersion (Crystalline Compound B/PVP K30/Pluronic/Sorbitol)

40 °C / 75% Relative Humidity, Open



Dissolution

10/40/40/10 (Crystalline Compound B/PVP K30/Pluronic/Sorbitol):



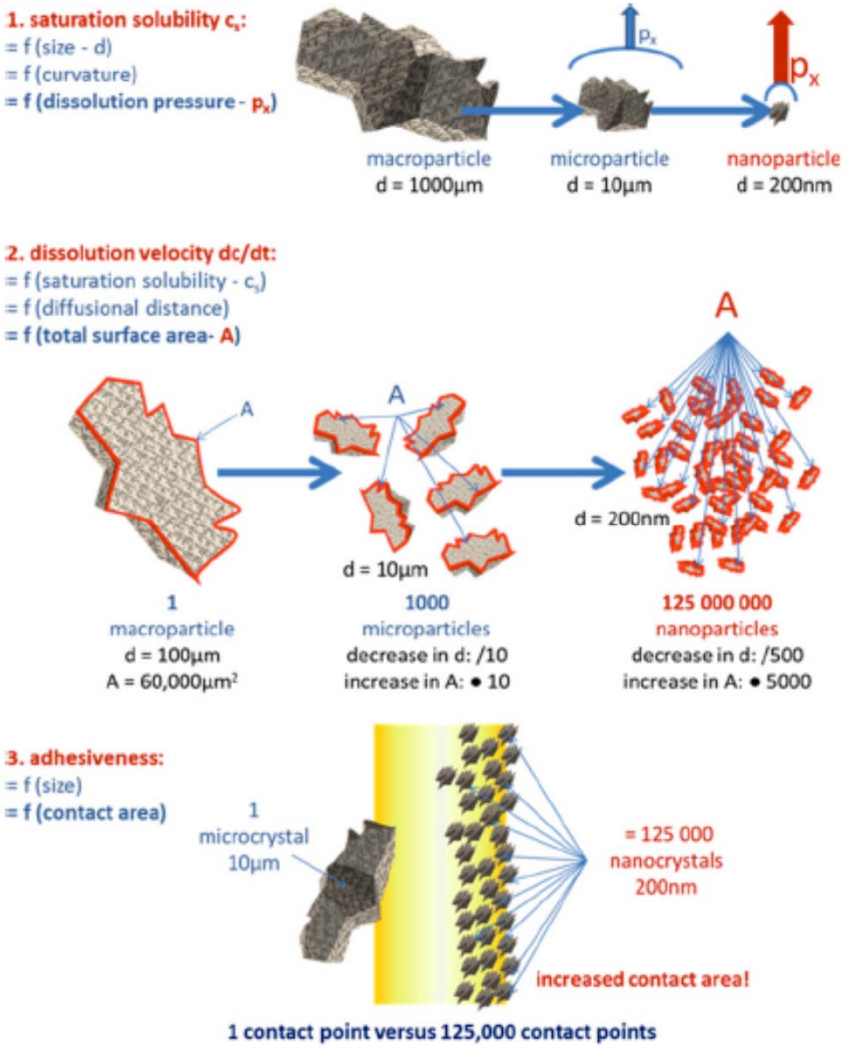
Conclusions

- **Amorphous solid dispersions for Compound B which is highly water insoluble, thermally unstable, and with a high melting temperature were prepared utilizing melt extrusion technology.**

- **Pluronic F68 and sorbitol potentially help in breaking the crystal lattice of Compound B allowing for the conversion to an amorphous drug substance.**

Nanosuspension

Benefits of Nanoparticle dosage form

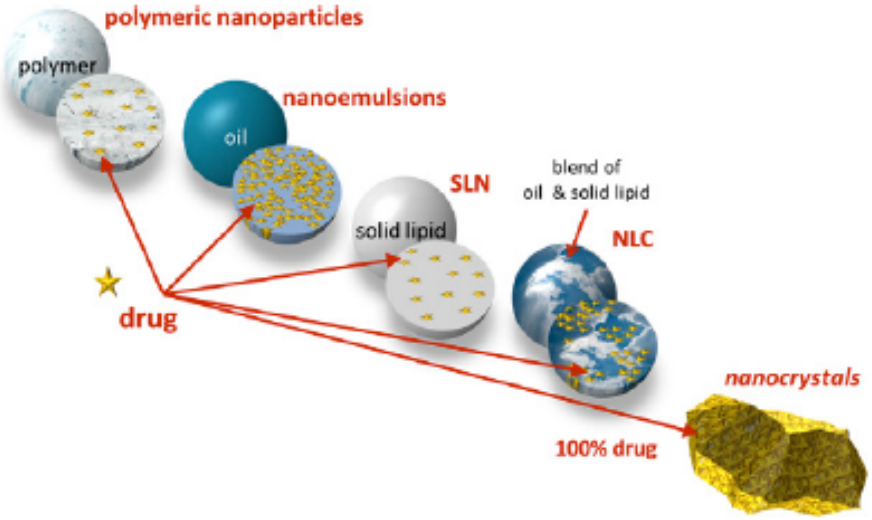


Rainer H. Müller et. al, EJPB

- ❑ Main application to BCS Class 2 molecules.
- ❑ Nanoparticulate dosage form has wide area of applications – **oral**, parenteral, transdermal, inhalation etc, by –
  - ✓ Improving the bioavailability
  - ✓ Decreasing the food effect
  - ✓ Decreasing intra subject variability
  - ✓ Reducing the dose
  - ✓ Reducing the Dose-Response variability.

Techniques for producingNanoparticles

- **Nanosuspensions** - Submicron colloidal dispersion systems.
  - Bottom-up approach (Dow Pharma ; BASF)
  - **Top down approach** (Elan's NanoCrystal ; Sky-ePharma's Dissocubes technology)
    - ✓ Wet Milling
    - ✓ High Pressure Homogenization
    - ✓ Supercritical Fluid Process

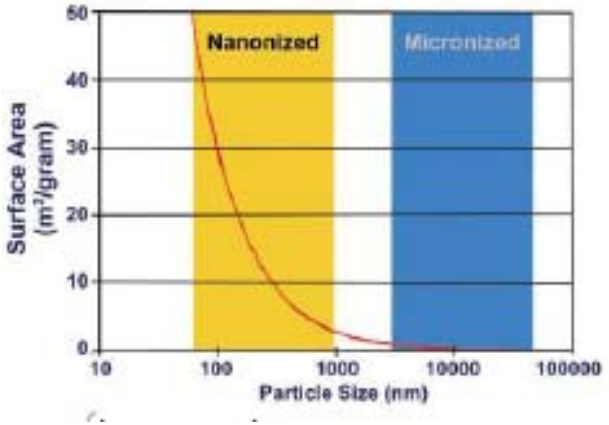


Wet media milling

❑ **Wet Media milling** - comprises mechanical attrition of drug particles using milling media such as yttrium stabilized zirconium oxide beads of definite size range (e.g. 0.1-0.5 mm ceramic beads)

❑ **Benefits** –

- ✓ Drug crystallinity remain intact during processing.
- ✓ No organic solvent.
- ✓ Unimodal size distribution.
- ✓ Simple and cost effective

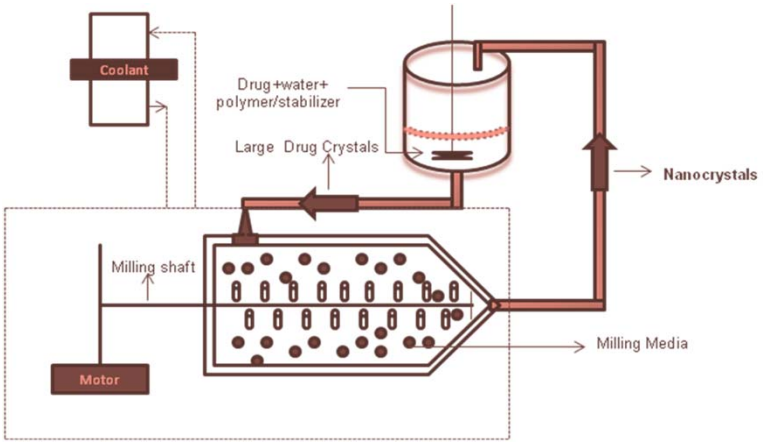


❑ **Theoretical aspects** –

✓ **Dissolution rate** - Noyes-Whitney equation: $dx/dt = A.D/h\ (Cs\text{-}X_d/V)$

✓ **Solubility** - Freundlich-Ostwald equation: $S = S_\infty \exp(2\gamma M/r\rho RT)$ – Related to particle curvature applicable to PS < 100 nm.

Nanosuspension – Formulation design and testing



Formulation effect

- **Effect of Solubilizer:** Vitamin E TPGS, SLS, Pluronic F68, F127, DOSS
- **Effect of stabilizers / suspending agents:** PVP K-30, HPMC 3cps, HPC EXF

Drug substance properties

- **Size and size distribution:**
- **Particle charge(zeta potential):**
- **Morphology by SEM, TEM, AFM**
- **Crystalline status: By X-ray, DSC**
- **Surface coverage and morphology: SEM,TEM,AFM**
- **Assay, Deg.**
- **Dissolution.**

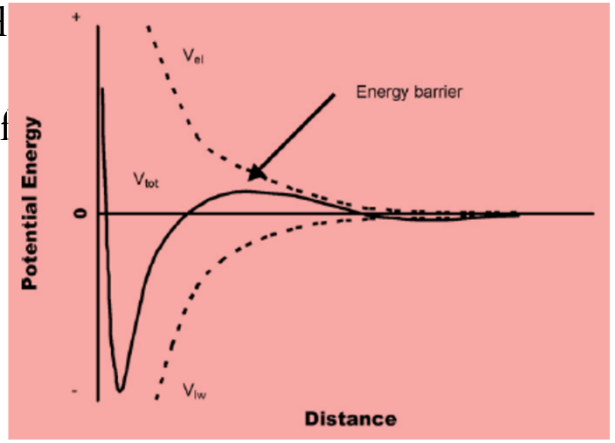
Bulk suspension properties

- **Rheology**
- **Sedimentation rate**

Nanomilling - Stability

❑**Stability –**

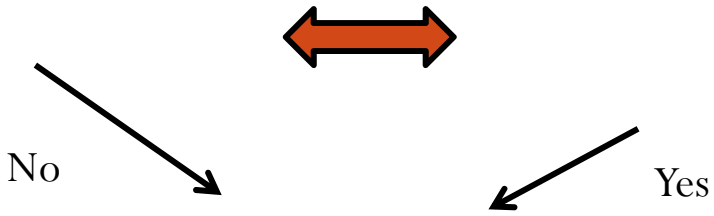
✓ During the milling process due to the change of Gibbs free energy thermodynamically unstable nanosuspensions formed which is responsible for Ostwald ripening and agglomeration phenomenon or crystal growth during process or during shelf life **due to high particle mobility.**



✓ Proper selection of stabilizers are required for tailoring the particle surface.

Steric stabilization

Electrostatic stabilization



Impact crystal structure

Overall Conclusions

- Technologies are available to help develop formulations for Poorly water-soluble compounds with different physico-chemical properties.
- A systematic approach to understanding the properties of Drug substance, Biopharmaceutical properties and Clinical needs lead to a suitable formulation.

Future Needs

- Flexible dosage forms which are different than the traditional unit dosage forms.
- Continuous manufacturing could provide some solutions.

Acknowledgements

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- **Daya Verma**
- **Colleen Ruegger**

B P D C L L C

Components of Variation Statistical Selection of Factors For a Design of Experiment (DOE)

Alpaslan (Alp) Yaman, Ph.D.

Biotech, Pharma & Device Consulting, LLC

B P D C L L C

Components of Variation (COV)

- To appreciate the value of a COV, one needs to evaluate one's reason for doing a Design of Experiment (DOE) and one's understanding/philosophy for this type of experimental approach.

B P D C L L C

Design of Experiment

What is the intent or purpose of a DOE?

- What is the real advantage to a DOE?
  - Is it the time savings for being able to do more than one factor at a time?
  - Is it to understand the ranges of the selected factors?
- The real advantage of a DOE is:
  - To be able to learn about factor interactions
    - Primarily two-way and three-way interactions for most commonly designed studies.

BPDCLLC

Design of Experiment

How is a DOE typically designed?

- Factor Selection
  - The number of factors selected realistically should not be more than 5. Typically, most DOEs only have 3 or 4 factors.
  - Selection is typically based on experience or known science as being key factors (key main effects). This approach does not truly consider effects resulting from interactions.
  - Can have a strong interaction from two seemingly minor factors, this interaction can be stronger than a single “main” factor.

B P D C L L C

Design of Experiment

How should the factors be selected?

- Factor selection should be based on a planned study that analyzes many potential factors over a wider range than is studied in a DOE.
  - Designed to understand if there are any statistically significant interactions.
  - Also, which factors are truly statistically significant for the process under study.

BPDCLLC

Components of Variance (COV)

When resolving an issue, the COV approach:

- Also known as an Analysis of Variance (ANOVA)
- Use this approach to screen factors, statistically, to determine what factors should be in the DOE.
- Use this approach to determine which factors have the significant interactions that need further study.

B P D C L L C

Components of Variation (COV)

- Design allows for study to be crossed or nested thereby maximizing the ability to determine the potentially significant factor interactions.
- Used to identify a Lurking Variable. Lurking variables cannot be identified in a DOE.
- Lurking variables can confound the outcome of a DOE.

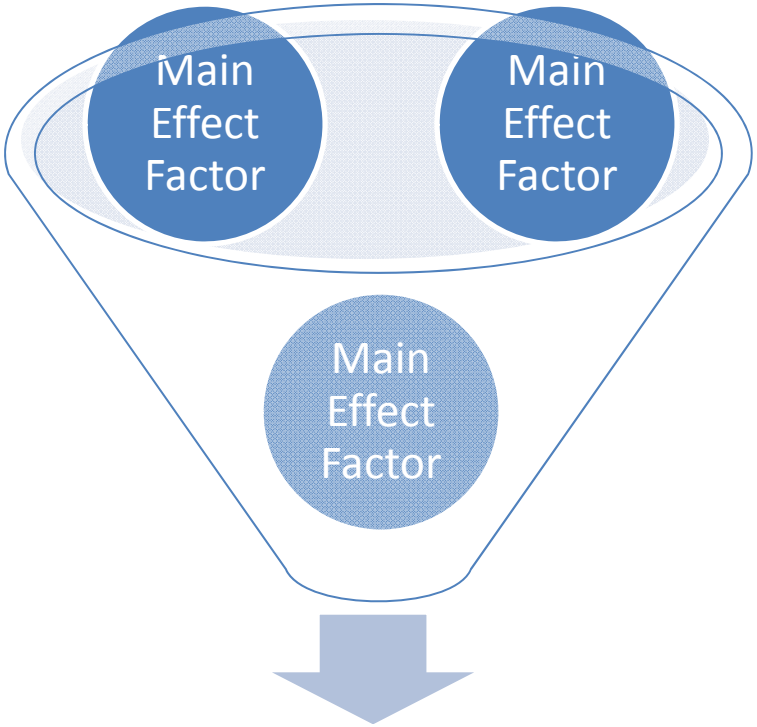
B P D C L L C

Components of Variance (COV)

- In essence, the COV is like a ‘funnel’ for the DOE. A study design is executed that has many factors inputted into the study, with wide study ranges. The statistical output of this study determines which factors will be selected for the ensuing DOE.

B P D C L L C

- COV is essentially a funnel:
- DOE should not be done without first doing a COV.



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COV Design

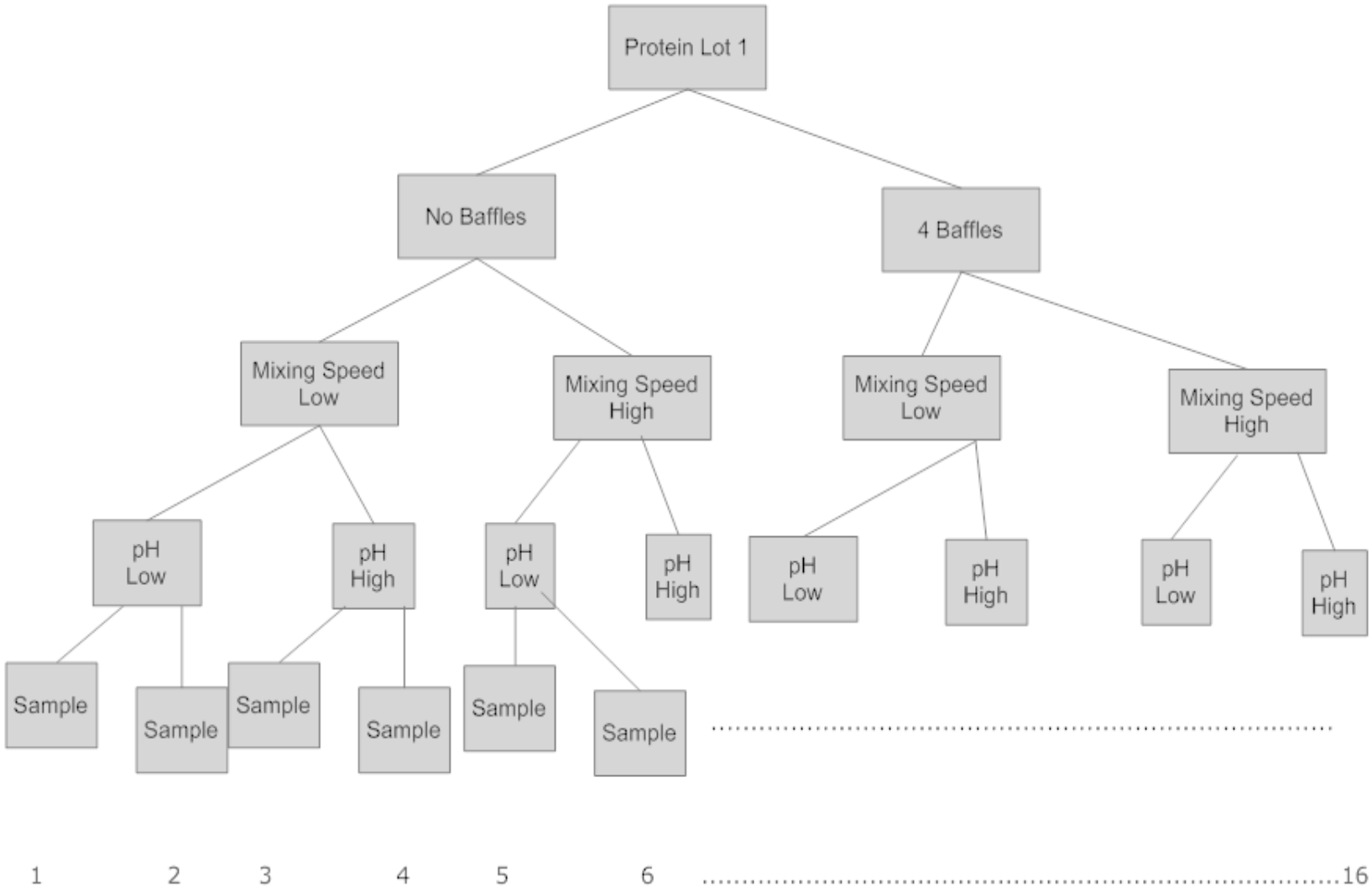
- At the onset, design the ultimate COV.
  - Include all possible sources of variability
  - Then look at the total design “tree”
  - Now decide if the entire “tree” is going to be executed or a part of it that seems more significant, for the study at hand.
    - This partitioning of the study would only be considered if the study is design is impractically large, with regards to time and cost constraints.

BPDCLLC

EXAMPLES OF COV STUDY DESIGNS

B P D C L L C

Components of Variance (COV: for mixing process)



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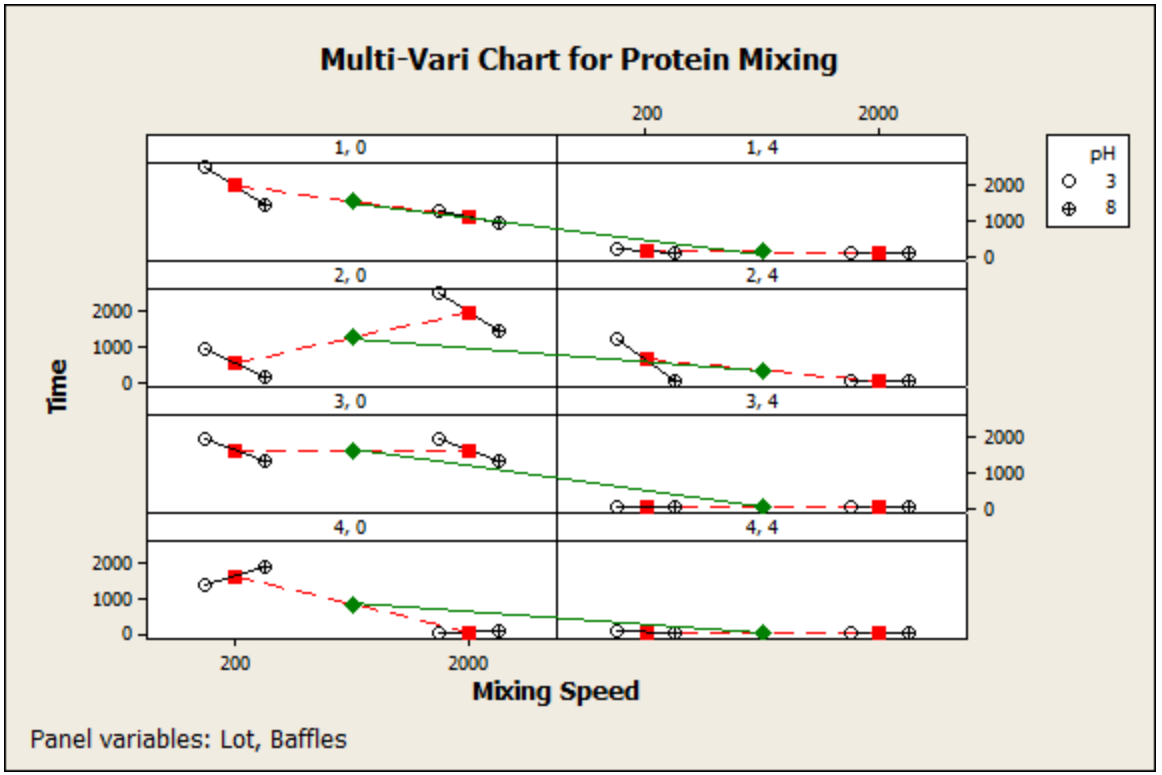
Components of Variance (COV)



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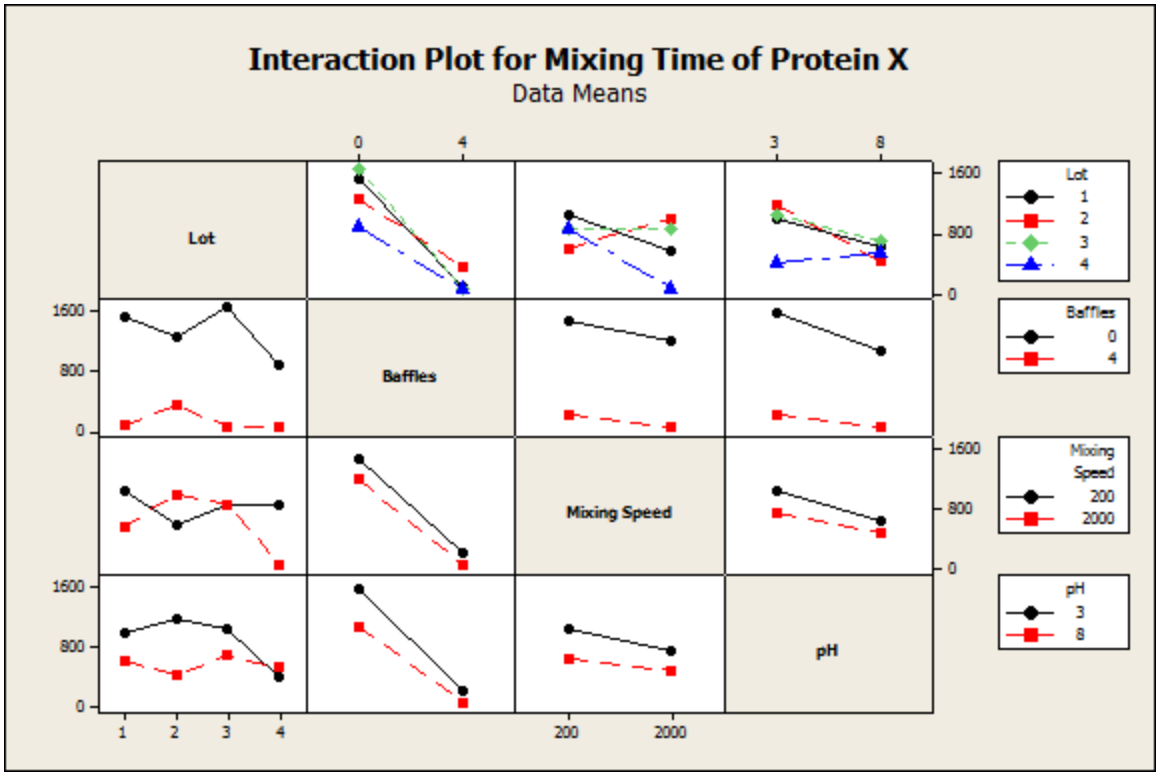
Components of Variance (COV)



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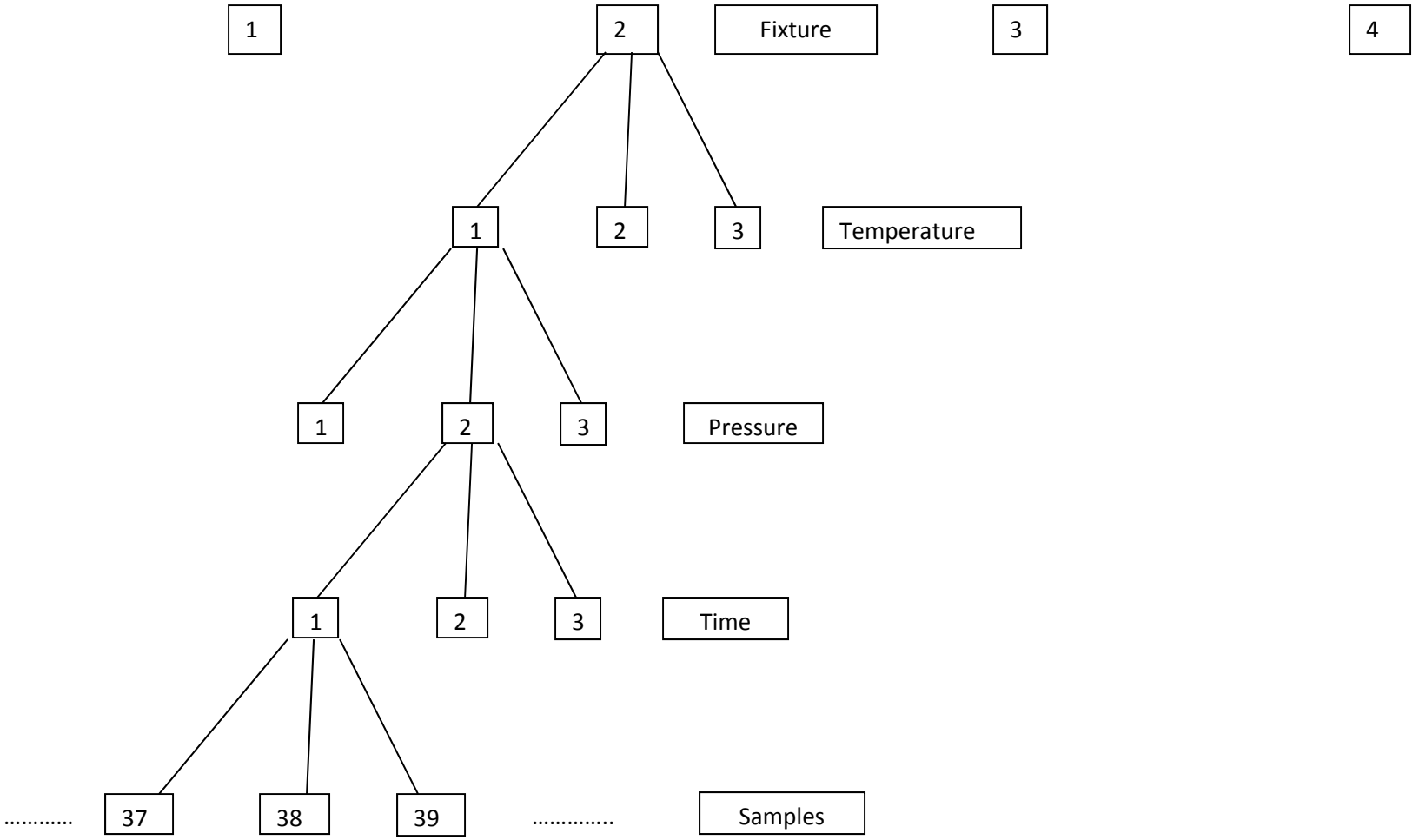
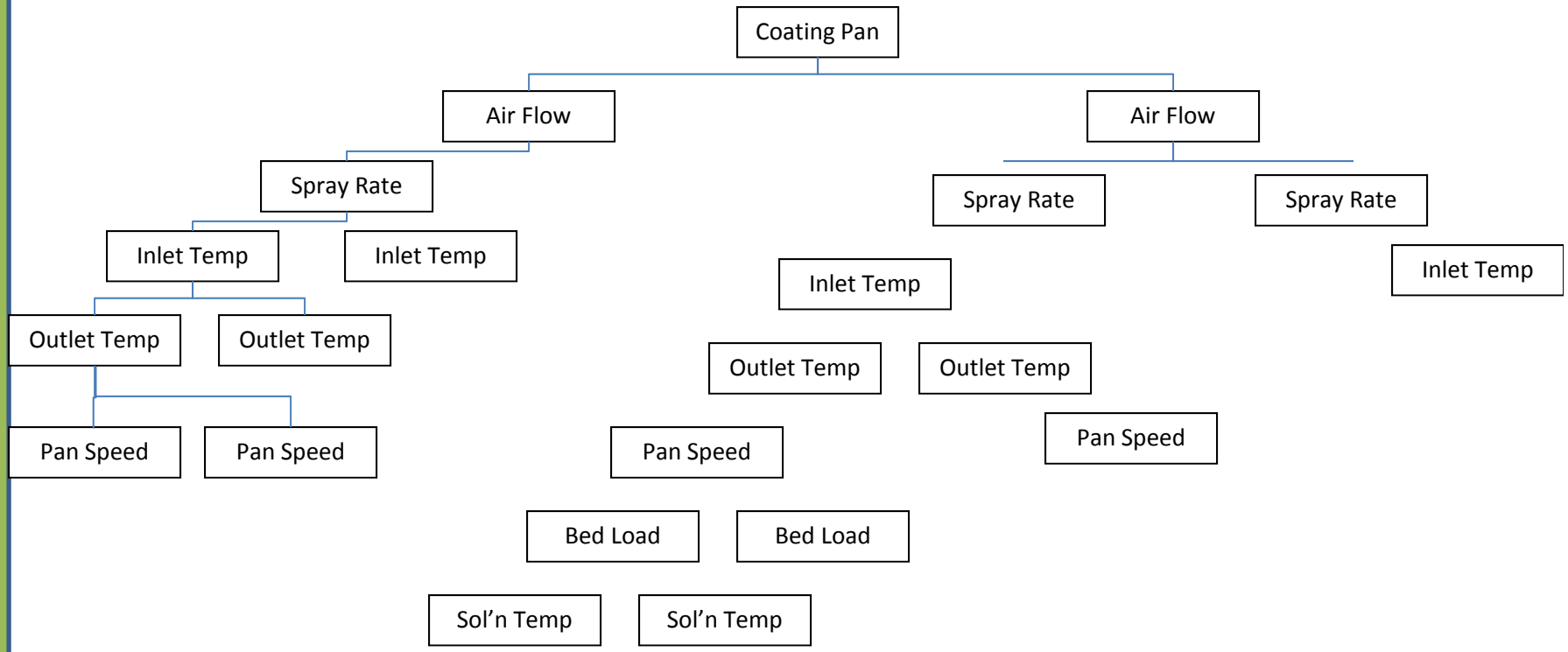
COV Tree Spray Coating a Medical Device



B P D C L L C

COV Tree for Coating Process



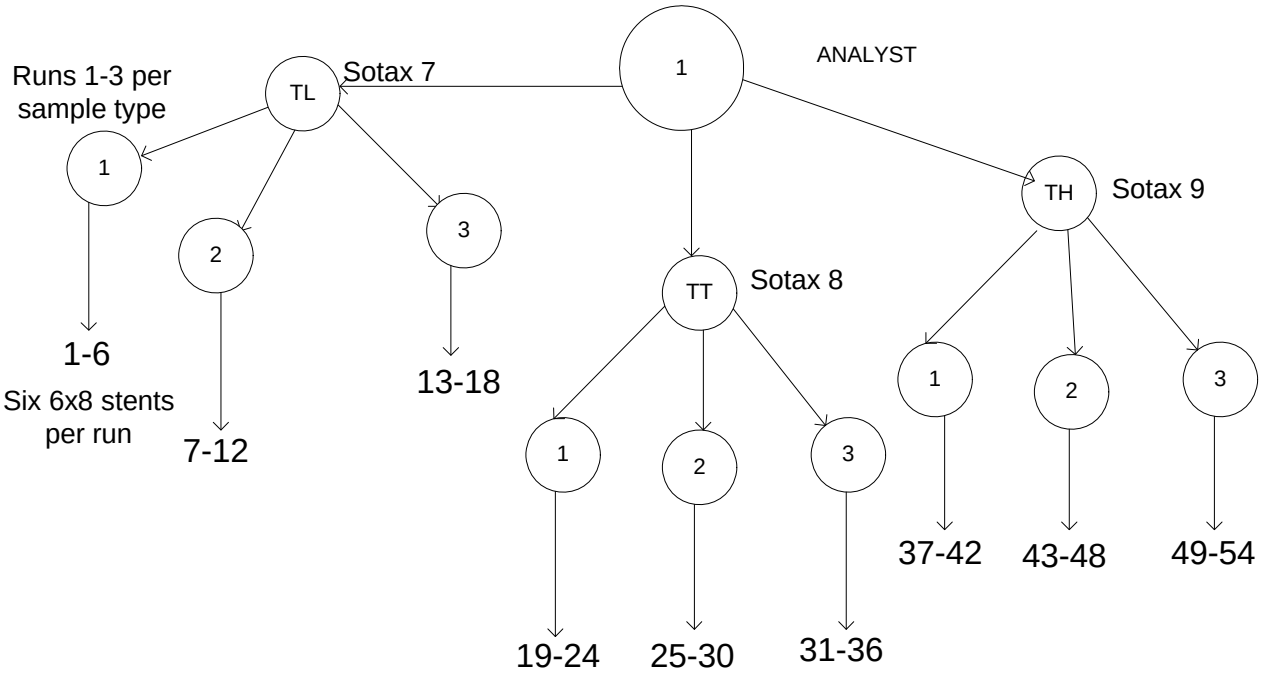
BPDCLLC

Components of Variance (COV)

- A Gage R & R is a type of COV study, it is used to determine what percentage of the overall variation present is due to the testing method used to acquire the data from the sample. It gauges the Reproducibility and Repeatability of the method and the analyst.

BPDCLLC

Components of Variance (COV)



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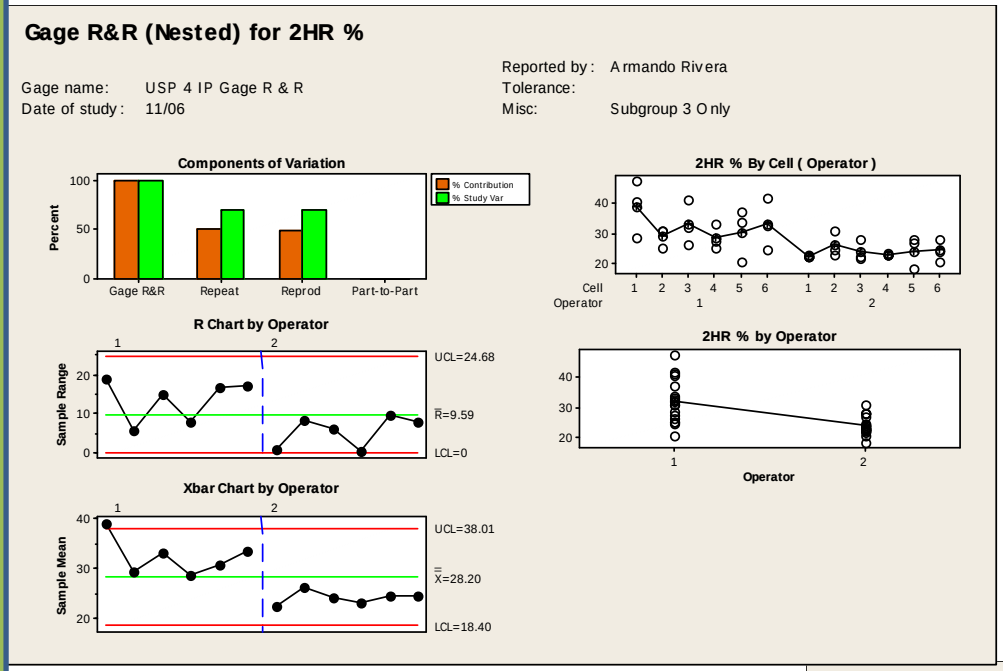
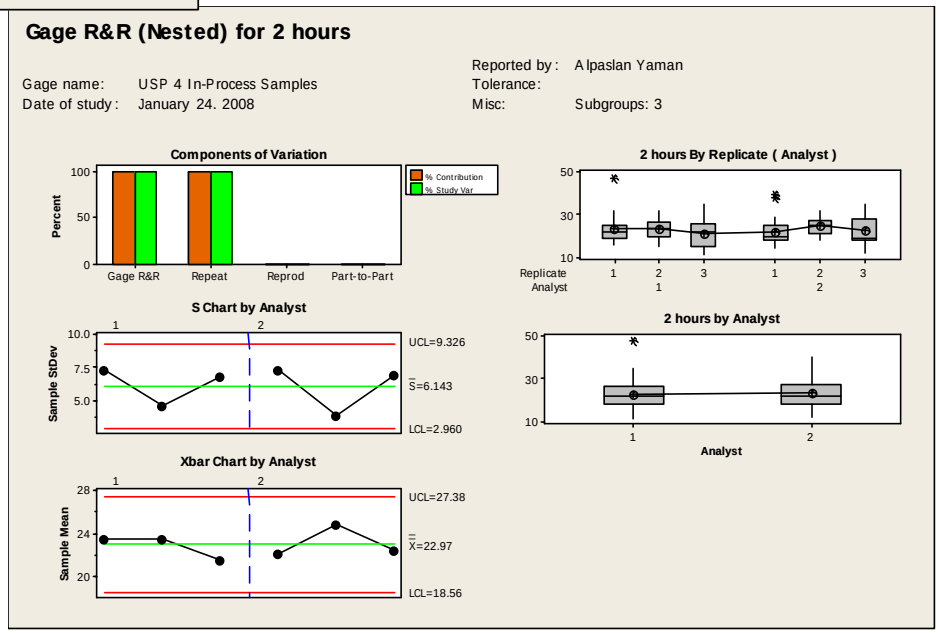


Below is the Final Gage R&R results which shows that the analyst no longer has a strong impact on the outcome of the test results. The variability associated with the analyst has been removed..

Above is the Original Gage R&R results showed that the analyst had a strong impact on the outcome of the test results. The analyst introduced variability into the results.



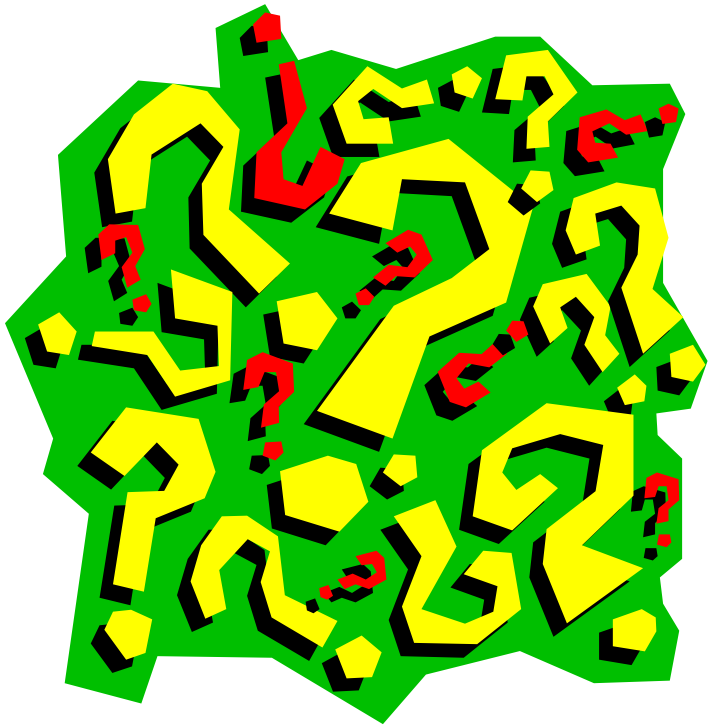
B P D C L L C

Components of Variance (COV)

- A COV can be used as a cost savings tool to determine what factors should be studied in the experimental design (DOE) to yield the most information for the expended resources.

B P D C L L C

General Discussion & Questions



B P D C L L C

Contact Information

Alpaslan (Alp) Yaman, Ph.D.

Principal Consultant

Biotech, Pharma & Device Consulting, LLC

ayaman@biopharmadvice.com

www.biopharmadvice.com

(973) 896 8047