Understanding Coating Processes

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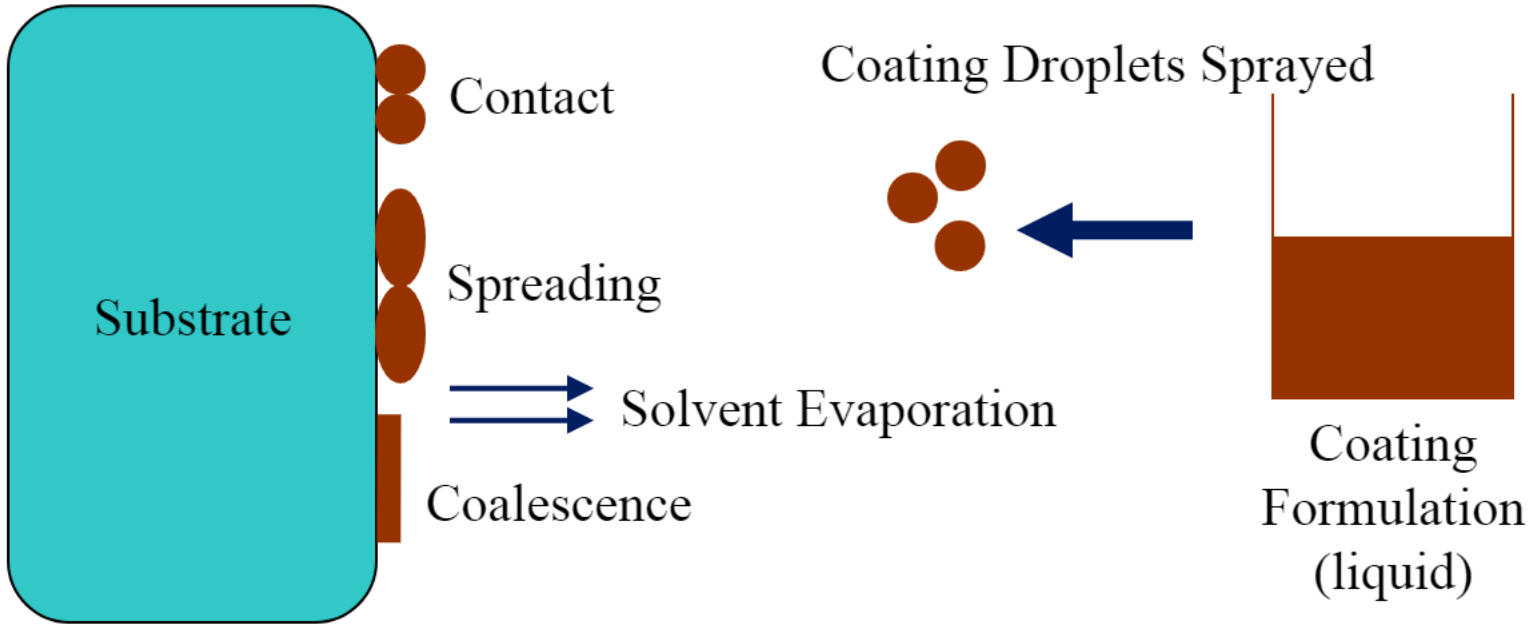
Reasons for Coating

- Alter release characteristics
- Improve aesthetic appearance
- Provide unique appearance for branding
- Protection from decomposition (water, O_2)
- Mask taste or odor
- Prevent inadvertent contact with active
- Facilitate swallowing

Overview of the Coating Process



Substrate Variables

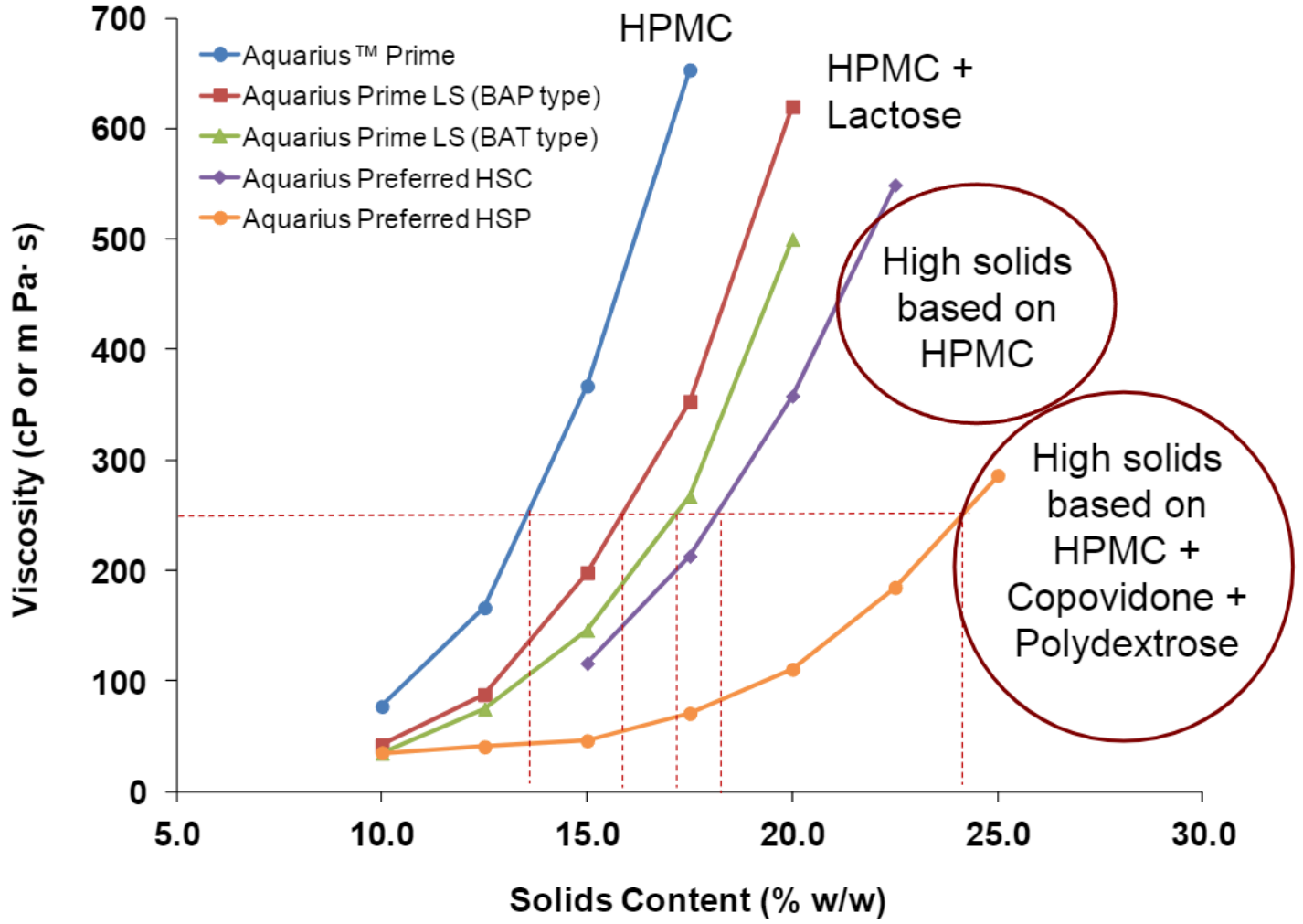
Processing Variables

Coating Variables

Coating Formulation

- Polymer(s)
  - Water soluble polymers
  - Water insoluble polymers
  - Polymers with pH-dependent solubility
    - Enteric systems (delayed release)
    - Reverse enteric systems (taste masking)
- Solvent (dissolve or disperse polymer in)
- Plasticizer
- Anti-tacking agents, pigments, surfactants

High-Solids Coating Systems



Courtesy of Dr. Stu Porter, Ashland

Advantages of High Solids Coating Systems (solutions)

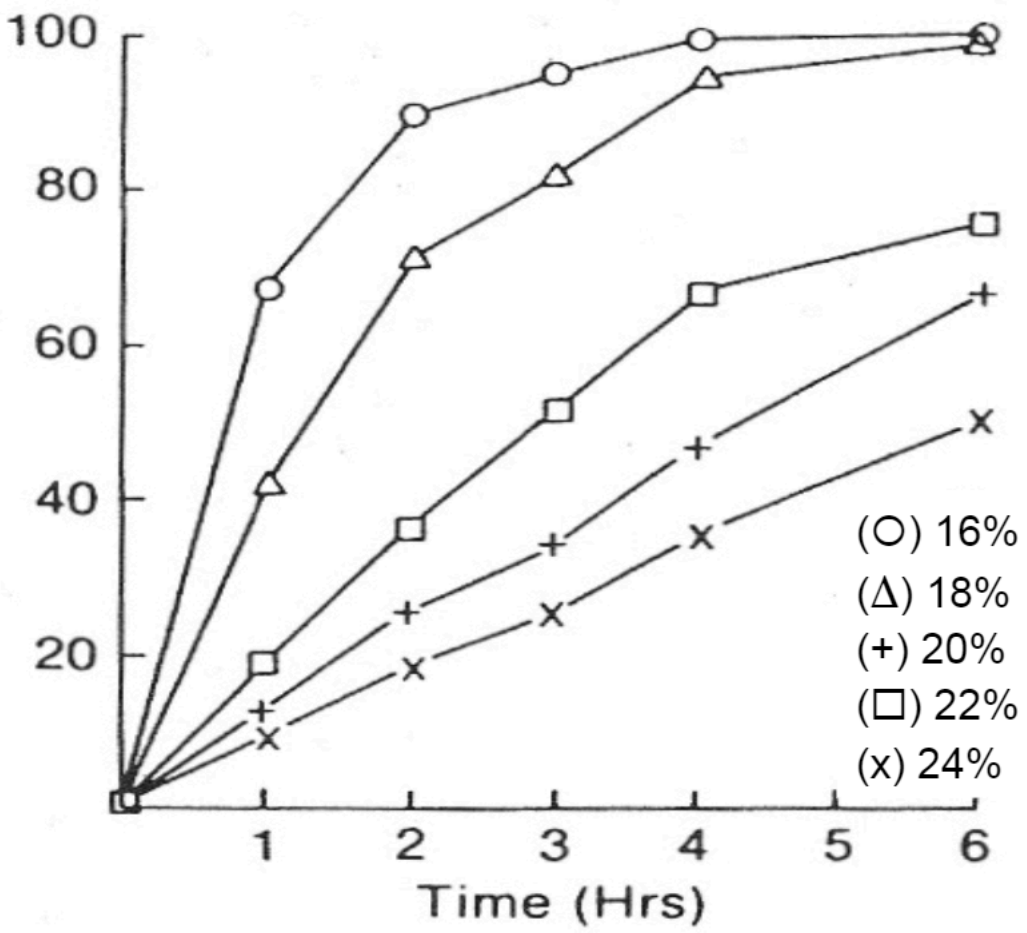
- Significant reduction in processing time
- Improve product stability
  - Reduced exposure to high processing temperatures and humidities
  - Minimize moisture penetration into cores
- Allow the use of lower processing temps
  - Beneficial for thermolabile drugs

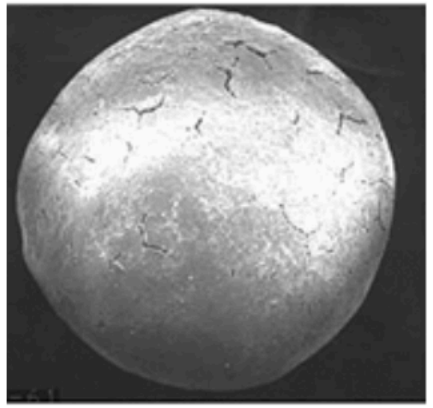
Plasticizers

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

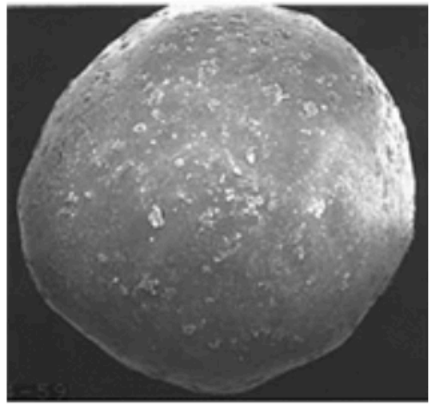
Plasticizer Concentration Influences Drug Release

6% Aquacoat ECD coated onto theophylline beads





16% DBS

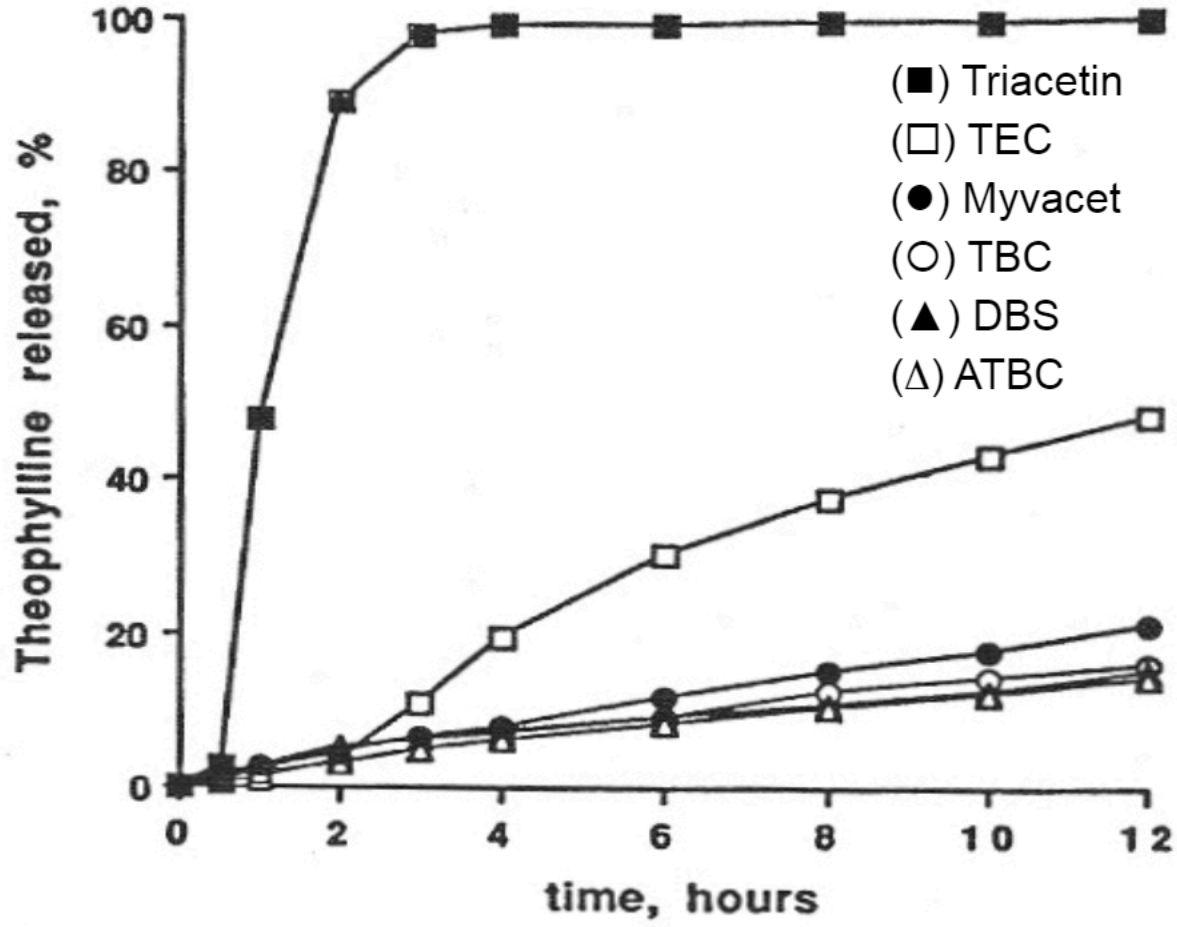


24% DBS

Carlin, Li, and Felton, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2016

Plasticizer Type Influences Drug Release

Aquacoat ECD coated on theophylline beads



Siepmann et al., Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2016

Criteria for Plasticizers

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

Predict Polymer-Plasticizer Miscibility

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

	Solubility Parameter (δ) $(J/cm^3)^{1/2}$	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)

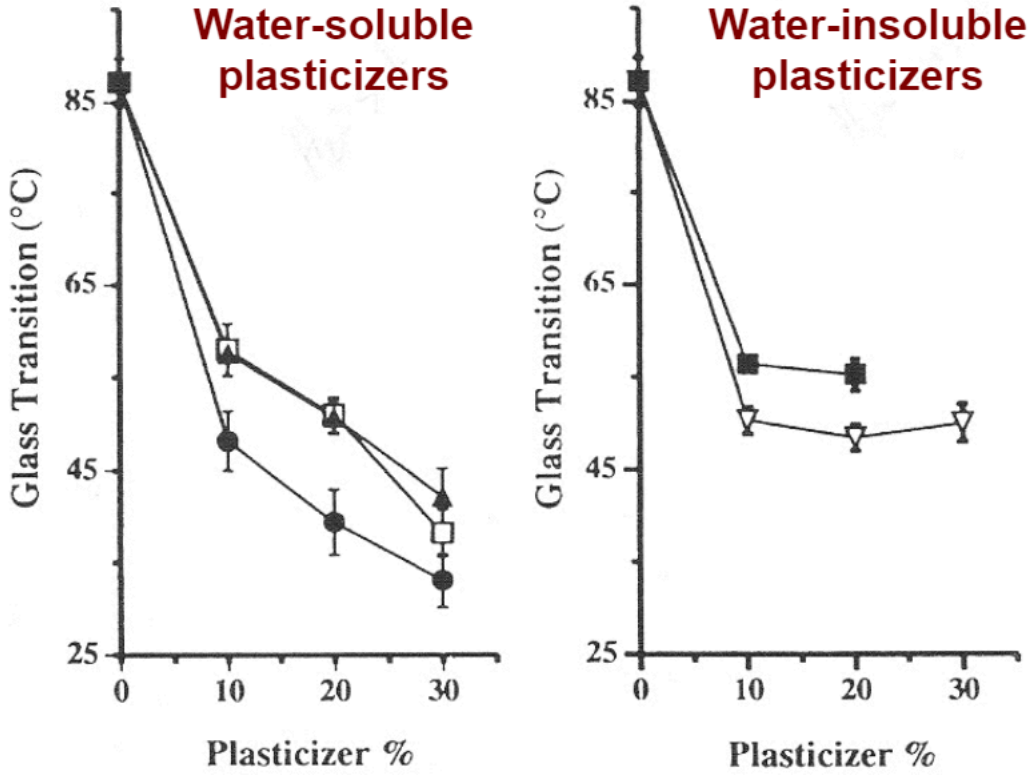
[1]Calculated by Van Krevelen method
[2]CRC Handbook of solubility parameters

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
- Decrease in Tg related to either
  - Less restriction in mobility of polymer chains
  - Decrease in crystallinity of the polymer

Tg to Evaluate the Effectiveness of Plasticizers



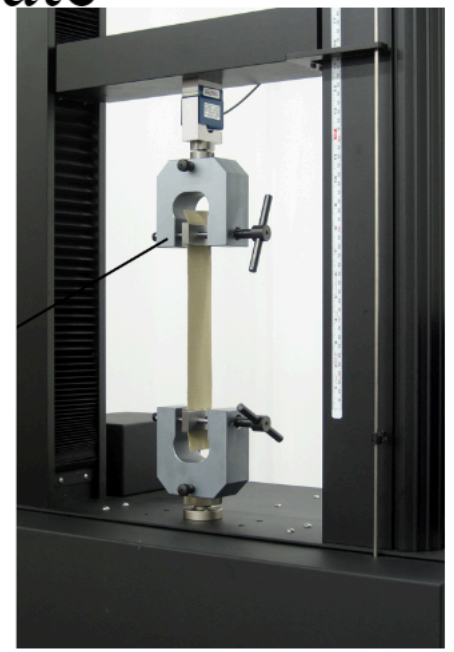
Effect of different levels of plasticizers on the Tg of Eudragit L100-55 films (60 days at 23C/50%RH followed by 30 days at 23C/0%RH)

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

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

Tensile Testing of Free Films

- Films strips stretched at specified rate
- Record force and displacement
- Convert to stress/strain



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

  - Measure of film strength

Strain = Increase in length (elongation) during test ÷ initial length (b/w grips)

  - Generally expressed as a percentage
  - Measure of film ductility

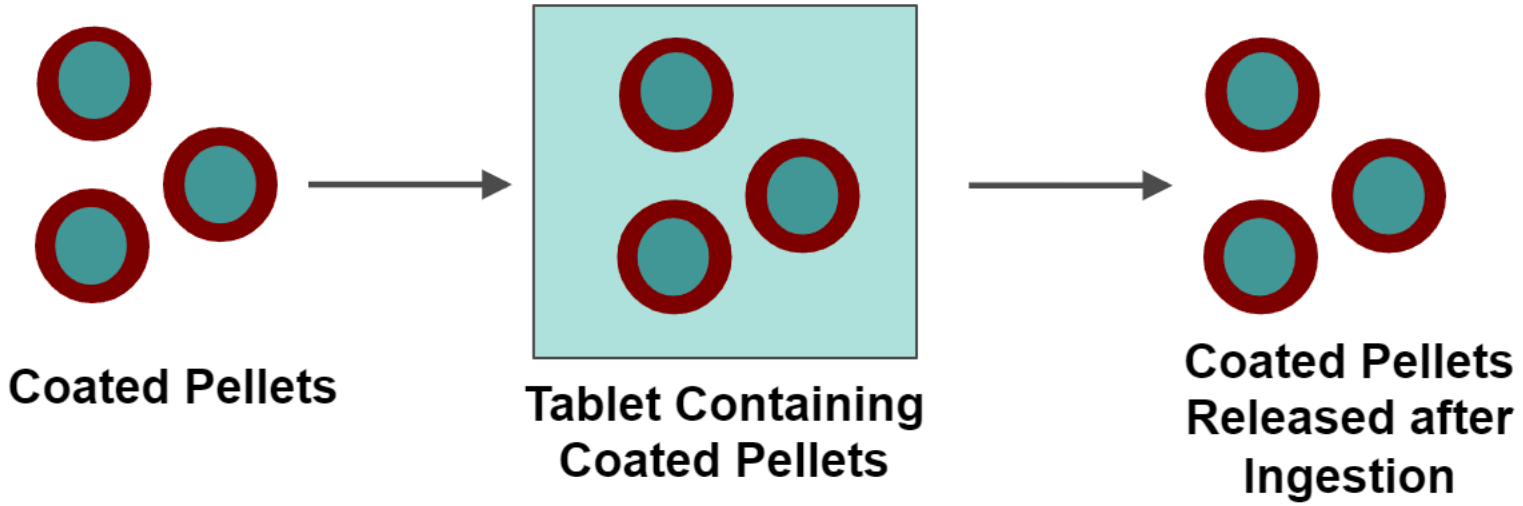
Other Parameters Obtained from Tensile Testing

- Young's Modulus
  - Slope of the linear region of the stress-strain diagram
  - 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

Variables that Influence Mechanical Strength

- Film formulation
  - Polymer(s), MW of polymer, film thickness
  - Additives to the coating formulation
    - Plasticizers (type and concentration)
    - Pigments
    - Anti-adherents
- Storage conditions
  - Temperature and humidity
- Experimental parameters
  - Rate of displacement used

Tableting of Coated Pellets



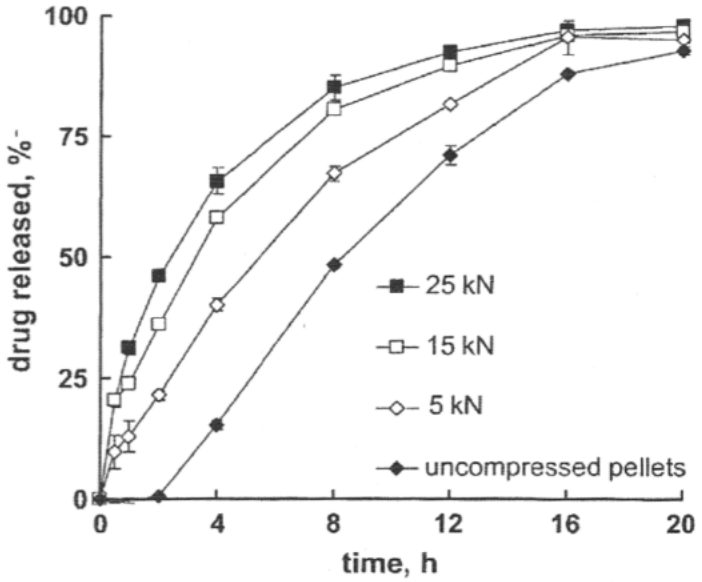
- Reduce potential for dose dumping
- Eliminate the use of gelatin capsules
- More uniform transit throughout GI tract

Considerations when Tableting Coated Pellets

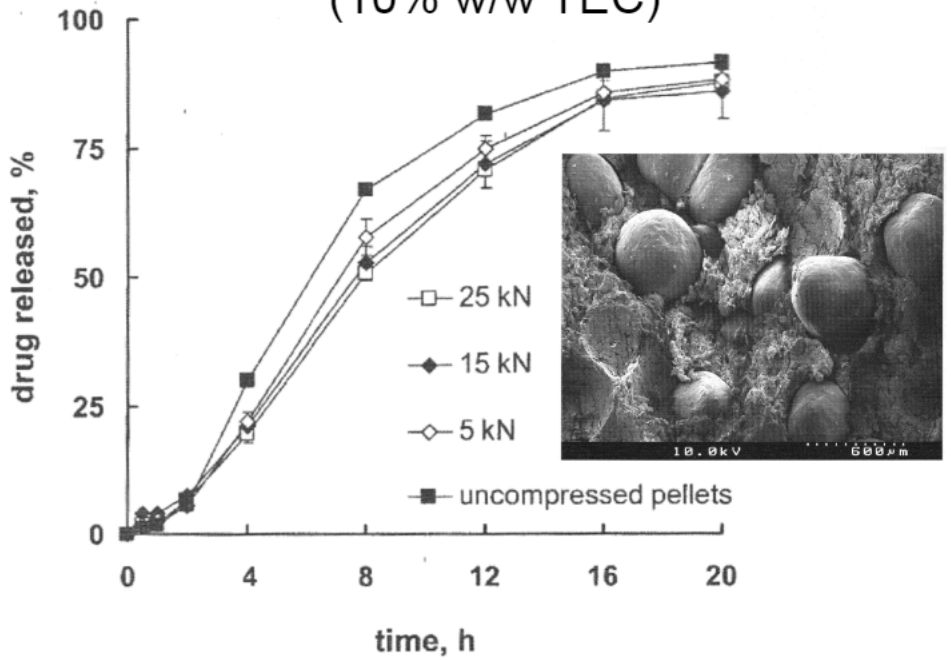
- Coating must be mechanically strong to withstand compression
  - Rupture of coating → faster release
  - Fusion of beads to form matrix → slower release
- Coating must be flexible, non brittle
- Core should have some plasticity to deform
- Tableting excipients ('Cushioning' agents)
  - Prevent rupture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

Compressional Force During Tableting Affects 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

Compression Testing

- Similar to tensile testing of free films
  - Uniform displacement rates applied to sample
  - Direction of applied stress is different
  - Record force and displacement values
    - Convert to stress and strain; graph data
- Investigate affects of substrate, storage conditions, and physical aging
- Provides qualitative adhesion information

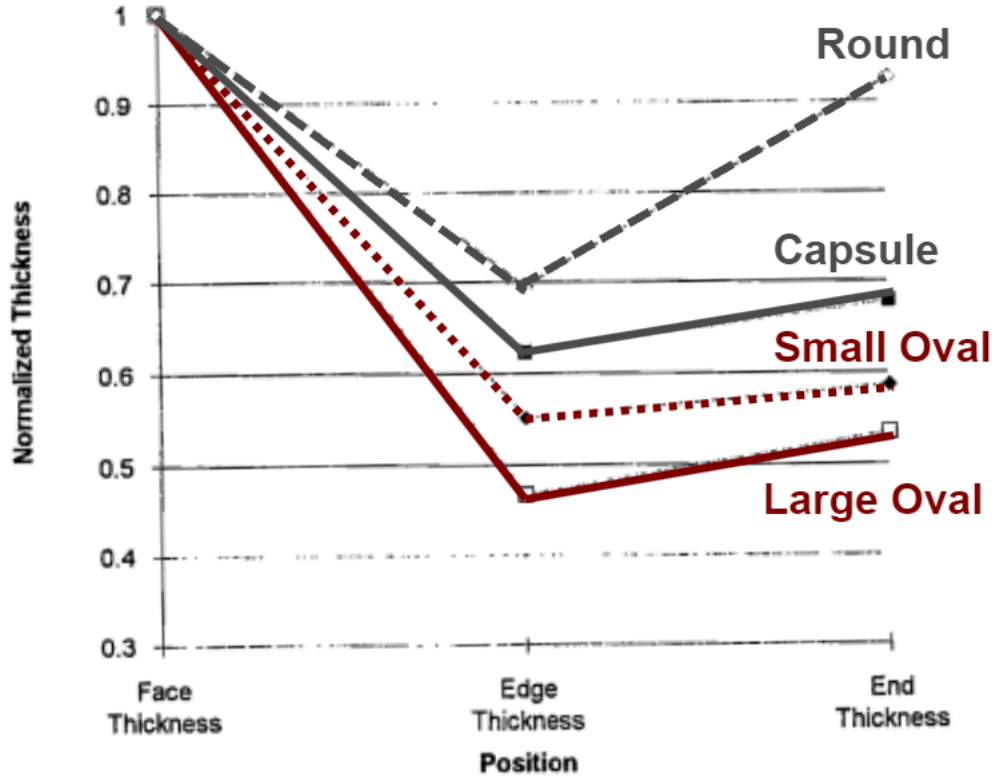
Substrate Considerations for Coating Processes

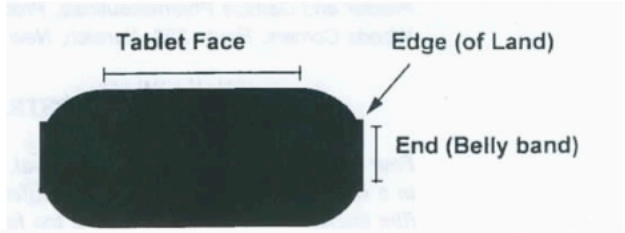
- Able to withstand processing
  - Movement within coating apparatus
    - Physical strength of the product
    - Tablet shape/size
  - Heat and solvent (water)
    - Chemical stability of API
    - Physical stability of product
- Appropriate surface for film adherence
- Minimal/no interaction with coating

Tablet Shape

- Physical strength of the tablet
  - Attrition and/or erosion during coating
- Uniformity of coating distribution
  - Movement within the coating equipment
  - Especially important when applying functional coatings and ‘active’ coatings
- Sticking or agglomeration of substrates during coating

Tablet Shape Influences Intra-Tablet Coating Uniformity





Tablet Dimensions and Shape

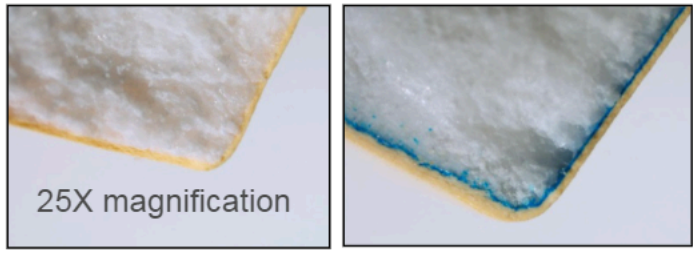
Tablet Shape	Dimensions	(mm)	Top View (l x w)	End View (w x h)
Round	Diameter	11.3		
	Height	5.2		
Capsule	Width	6.0		
	Height	6.0		
	Length	14.9		
Small Oval	Width	7.8		
	Height	5.4		
	Length	14.7		
Large Oval	Width	7.1		
	Height	5.9		
	Length	17.7		

Data normalized to account for surface area differences

Wilson and Crossman, Drug Dev Ind Pharm, 1997

Influence of Shape on Enteric Performance

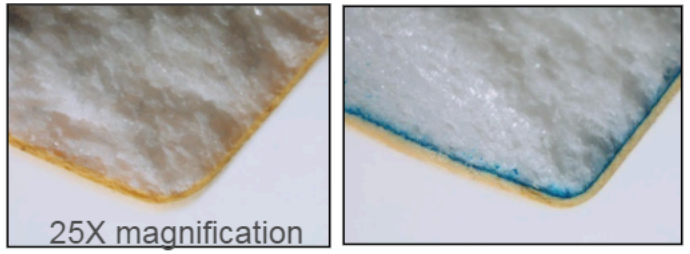
Shallow Concave



10% weight gain
No sub coat

10% weight gain
2% sub coat

Standard Concave



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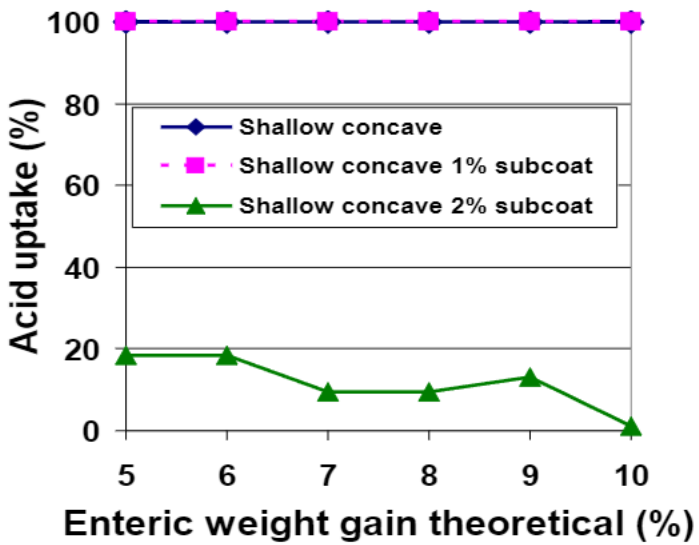
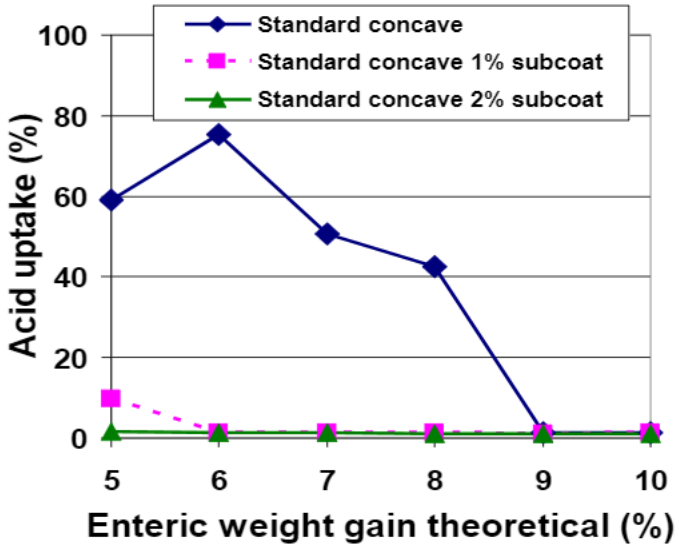


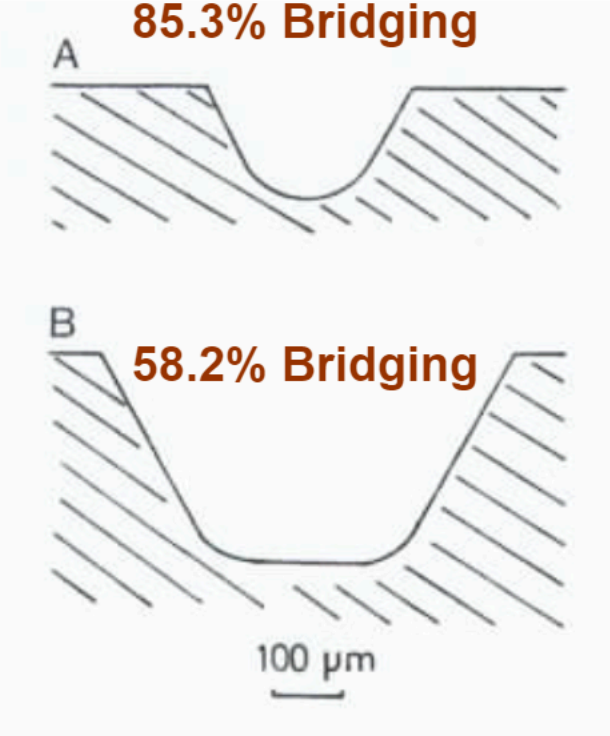


Cunningham et al, AAPS Annual Meeting, Toronto, Canada, Nov. 2002

Tablet Shape Influences Tendency for Agglomeration

- Flat edges prone to sticking/twinning
- Slight changes in tablet shape can reduce/eliminate twinning

Logo Shape and Placement Can Be Critical



Greater surface area = greater area for interfacial contact, so better adhesion

Rowe and Rose, J Pharm Pharmacol, 1981

Conventional Placement

Placement for Tablets with Soft Crowns

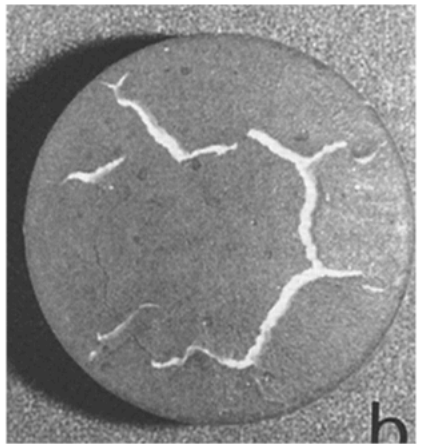
Porter, 2013 PTI Formulation and Process Development training program

Interactions between API and Polymer

- Classic example:
- Enteric coating of drugs that degrade in acidic environments
  - Enteric polymers contain acidic functional groups
- Avoid such interactions with a subcoat

Interactions with Excipients

- Excipients can change surface chemistry
  - A more hydrophobic tablet surface could result in poor adhesion
- Swelling of an excipient in the presence of water
  - Can result in cracking
- Dissolution of an excipient
  - Could result in pitting



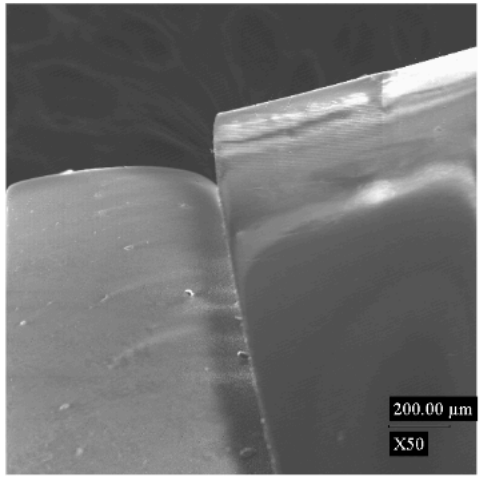
Cracking from substrate swelling[1]

Dissolution of stearic acid caused pitting[2]

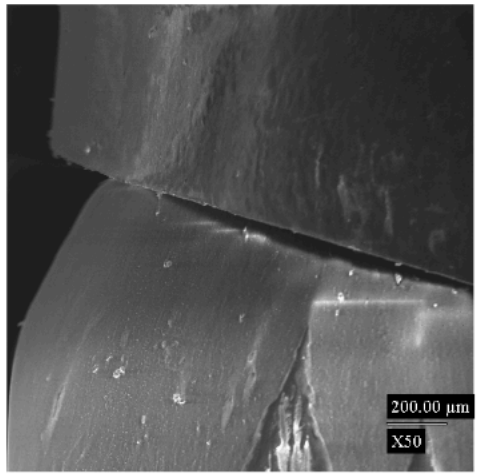
[1]Rowe, Informa, 2008; [2]Rowe and Forse, Int J Pharm, 1983

Coating Hard-Shell Capsules

- Relatively smooth surface
  - Potential for adhesion problems
- Properties of the shell material
  - Gelatin dissolves in warm water
  - HPMC swells/dissolves in water
- Residual moisture in shell
  - Potential to evaporate during coating; shell could become brittle
- Cap/body joint

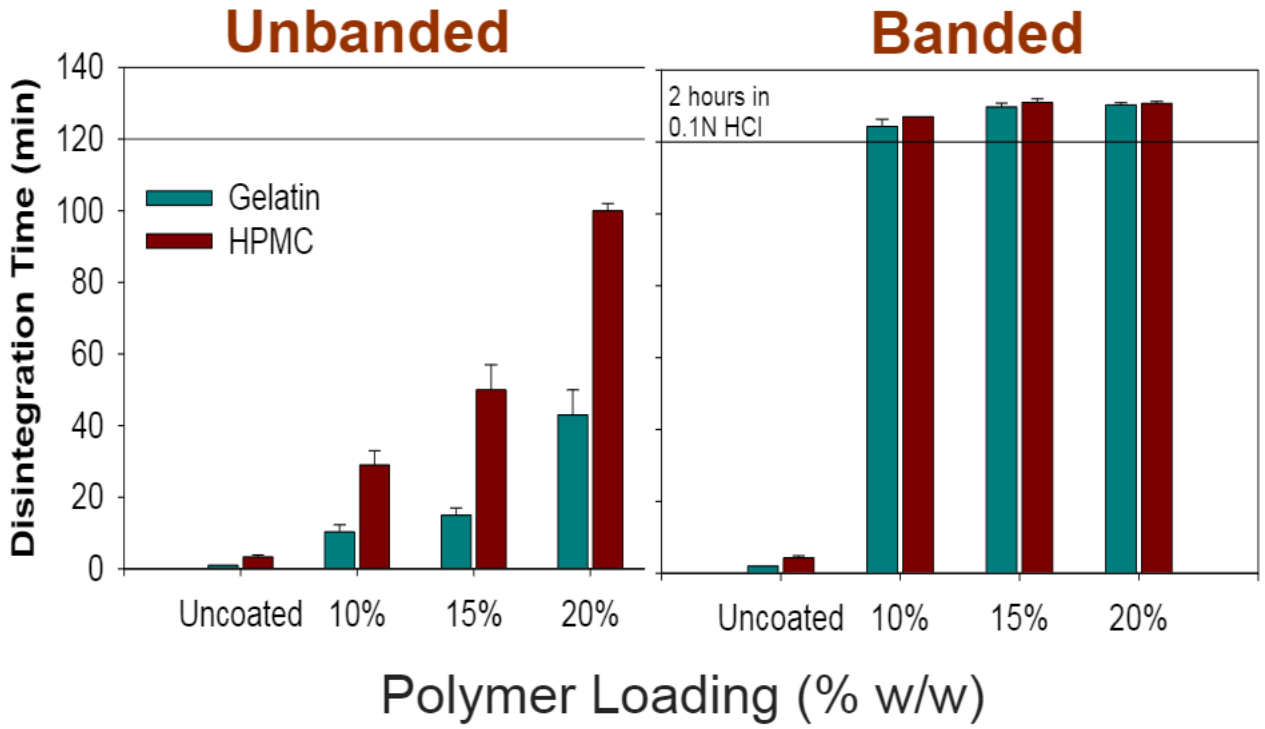


Gelatin

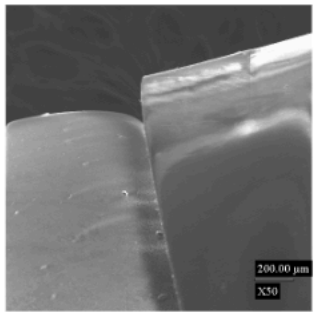


HPMC

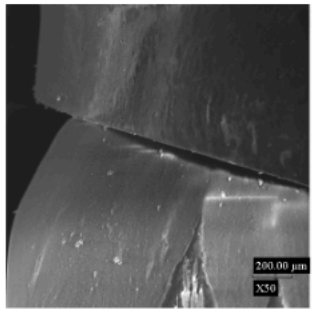
Banding of Capsule Shells Required for Enteric Protection



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



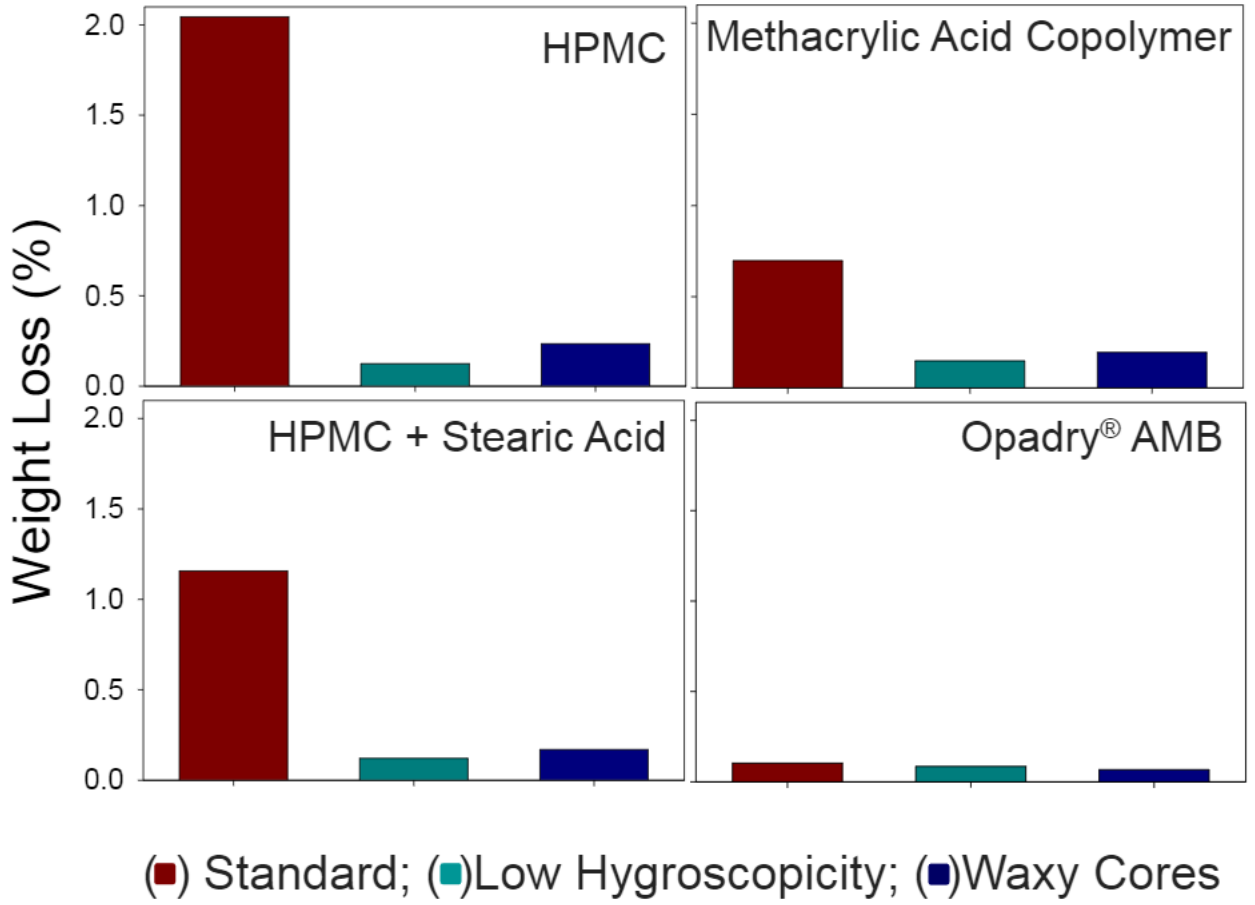
Gelatin



HPMC

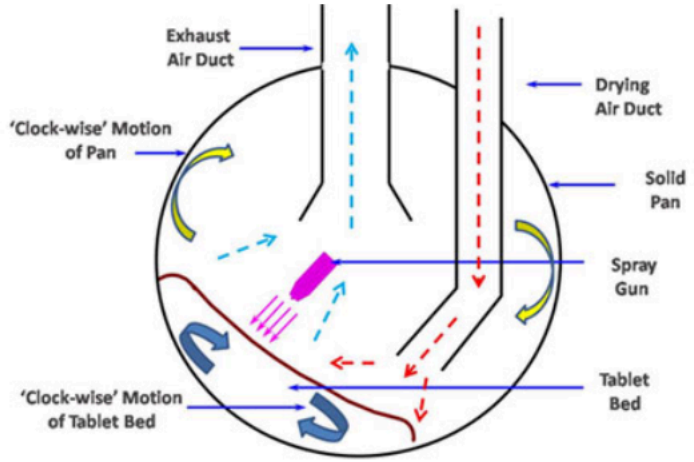
Felton et al., AAPS Annual Meeting, 2002

Substrate Can Influence Vapor Sorption Properties of Films

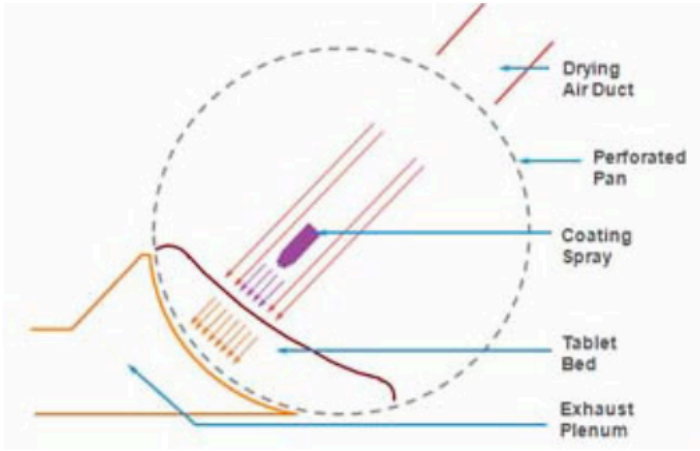


Colorcon Technical Data; Opadry AMB Sorption & Desorption Study; 2003

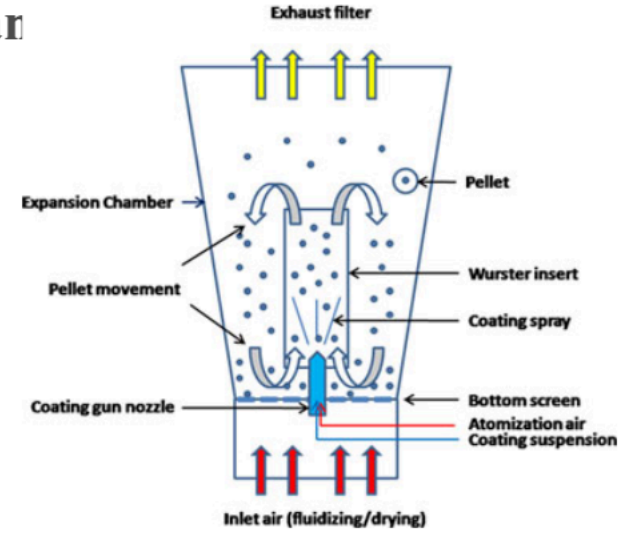
Coating Equipment



Conventional
Coating Pan



Perforated
Coating Pan



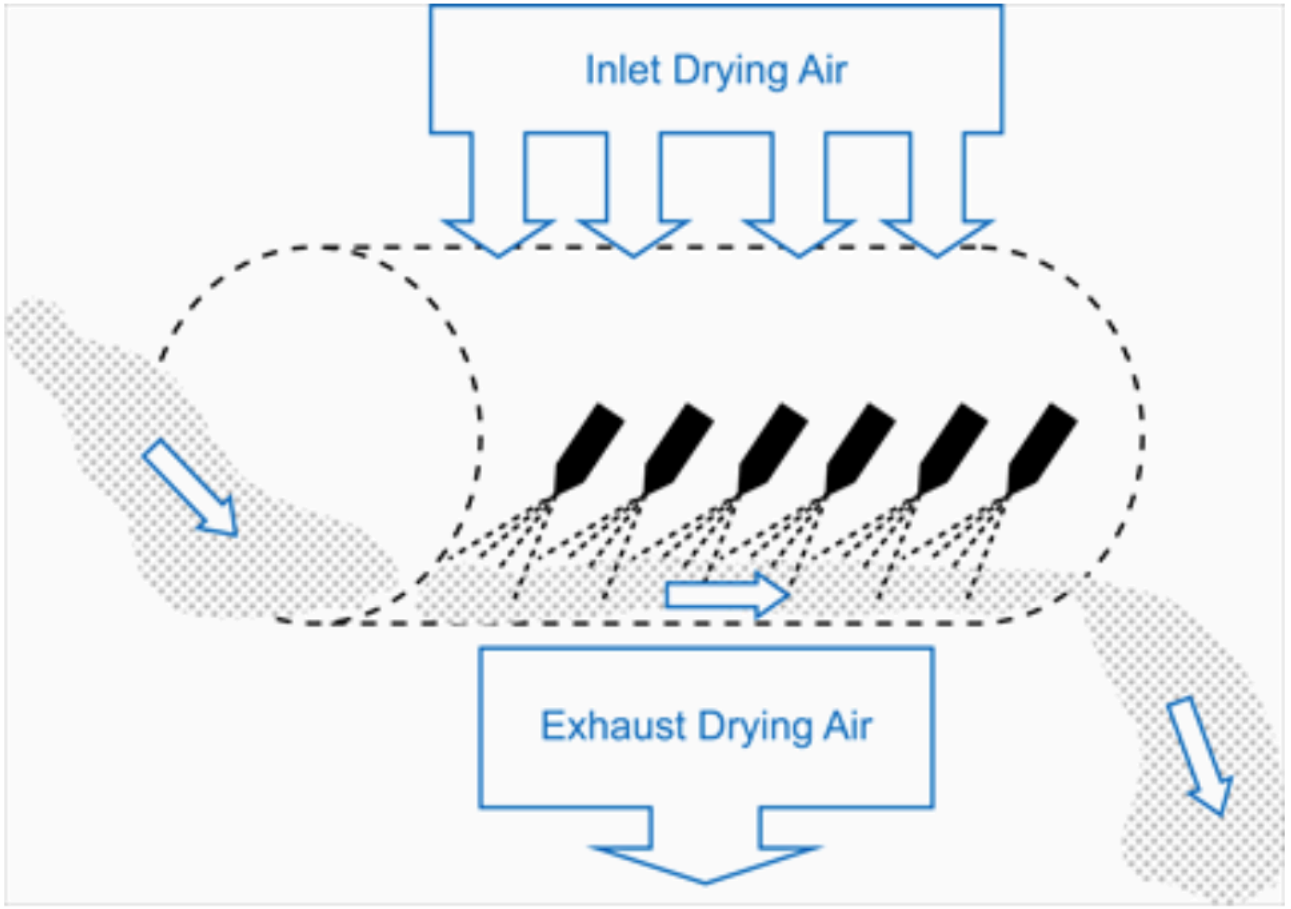
Fluidized Bed
Coating

Common Features of Coating Equipment

- Atomization of the polymer liquid
- Movement of substrate
- Heat to evaporate solvent
  - Drying capacity of process air
    - Volume of air; Temperature and relative humidity
  - Surface area from which drying takes place
    - Droplet size (atomization air pressure and properties of the coating liquid); Substrate surface area
  - Rate at which solvent is introduced
    - Spray rate; Solvent properties

Continuous Coating Operations

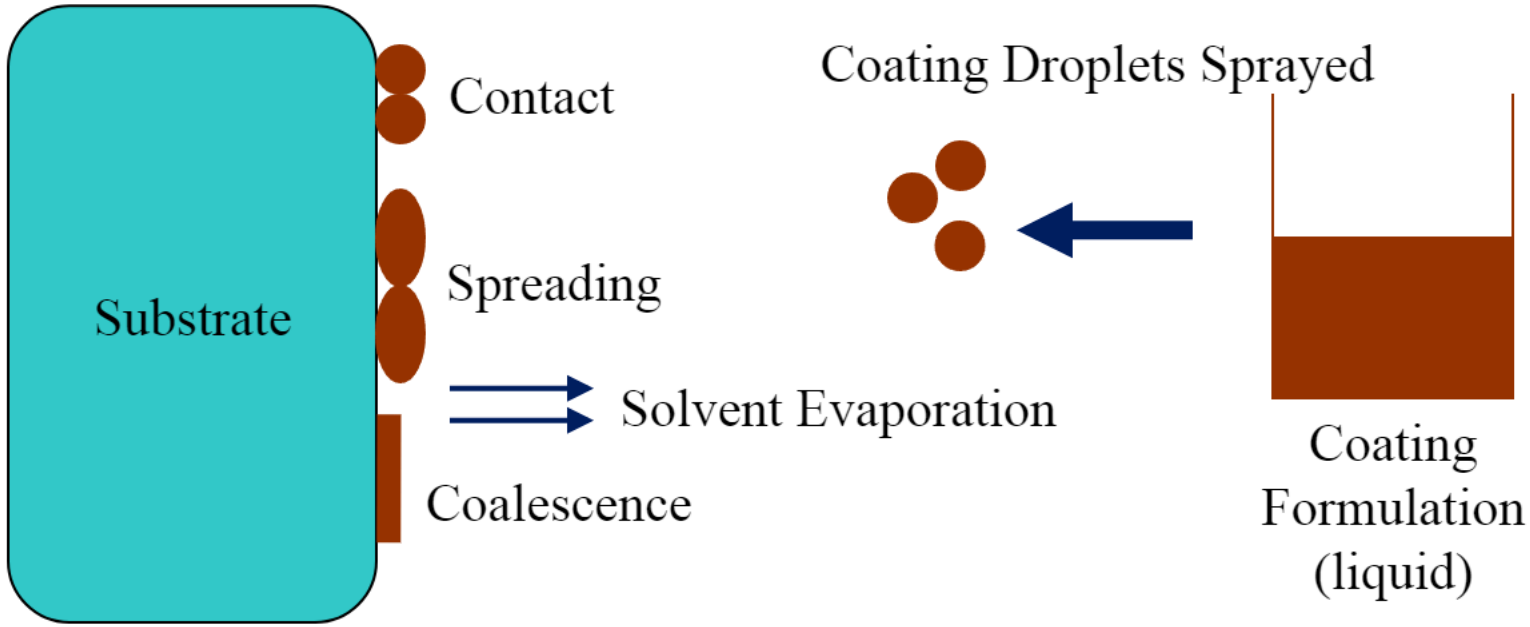
- Adaptation of conventional perforated pan



Advantages of Continuous Coating

- Higher output = fewer batches = cost savings
  - Outputs in the range of 500 kg to 2000 kg/hr
- Eliminates scale up issues
- Potentially more uniform coating
  - Shallow bed depth and more frequent presentation of product to the spray zone
  - Possible reduction in the total amount of coating required for IR products
- Less tablet attrition
  - Shorter residence time

Overview of the Coating Process

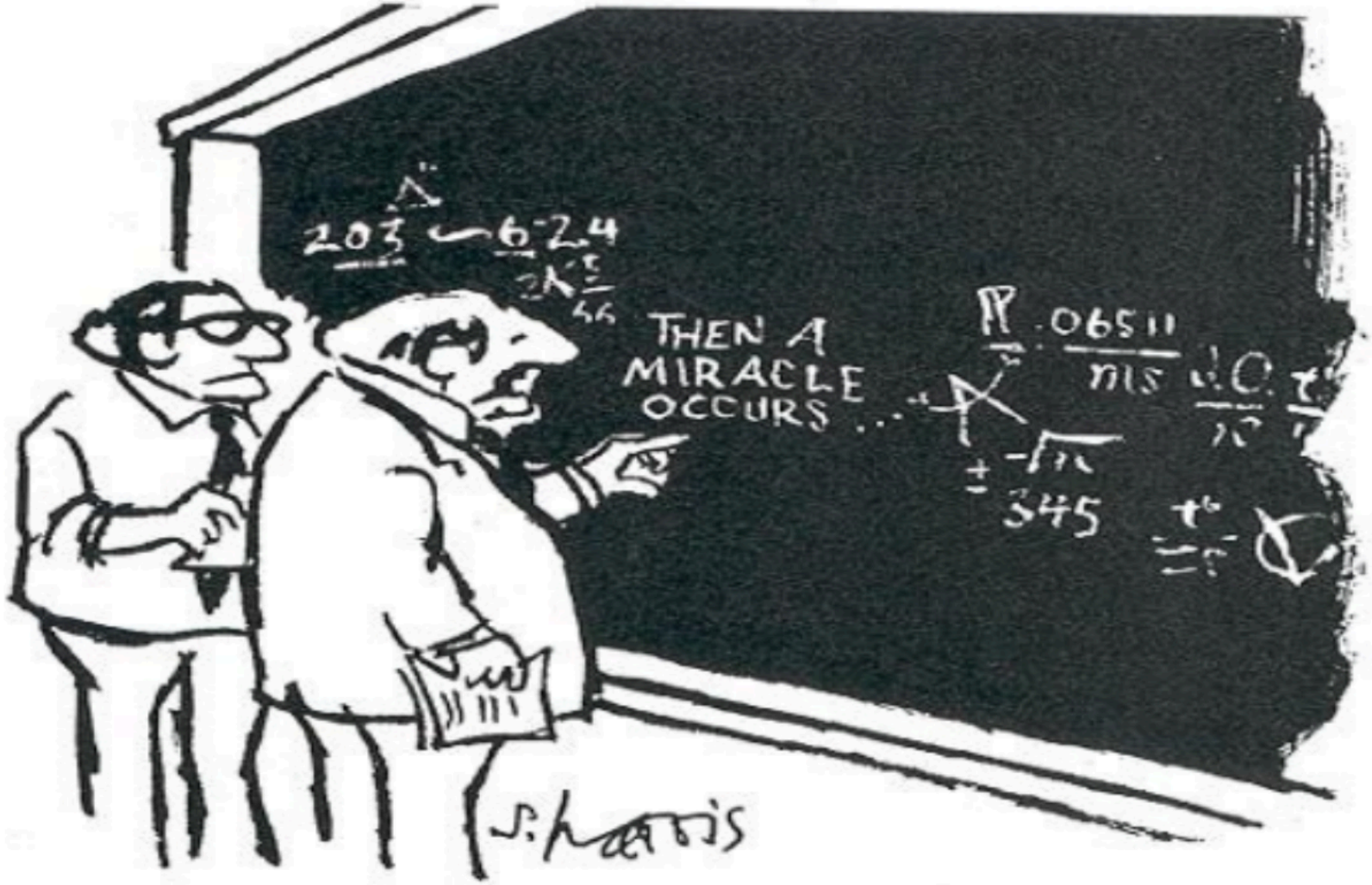


Substrate Variables

Processing Variables

Coating Variables

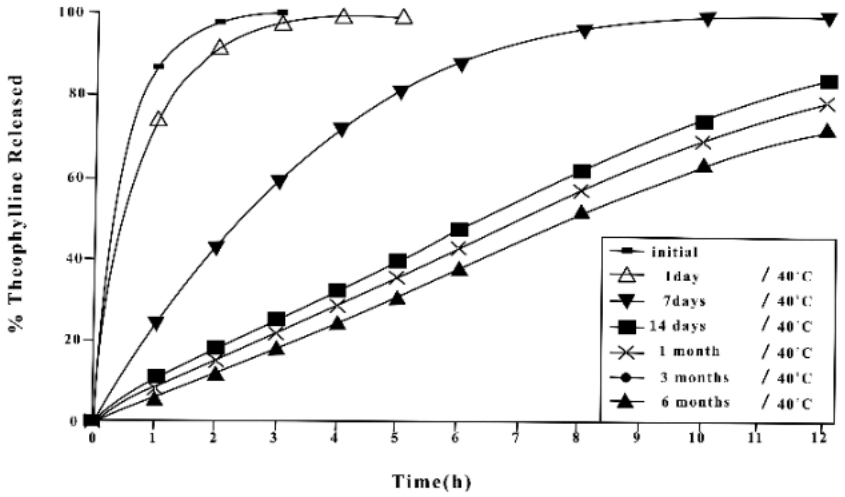
Variables often inter-related



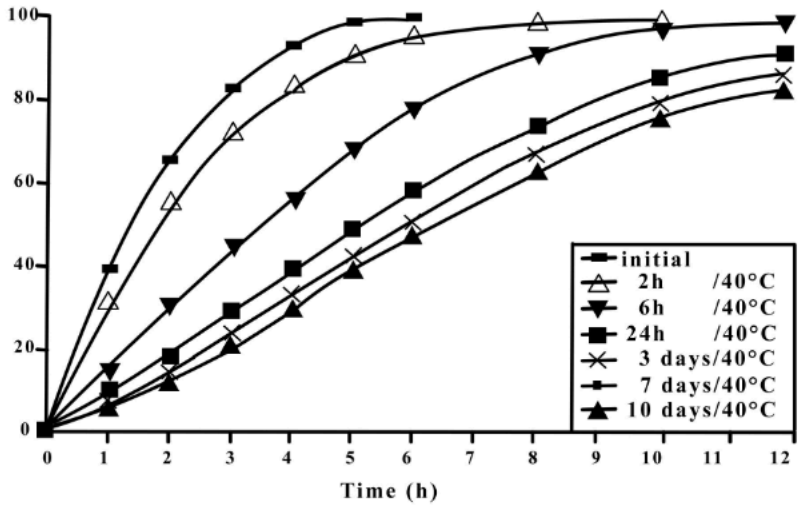
"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

Drug Release Changes Over Time with Aqueous-Based Dispersions

10% TEC in coating



20% TEC in coating

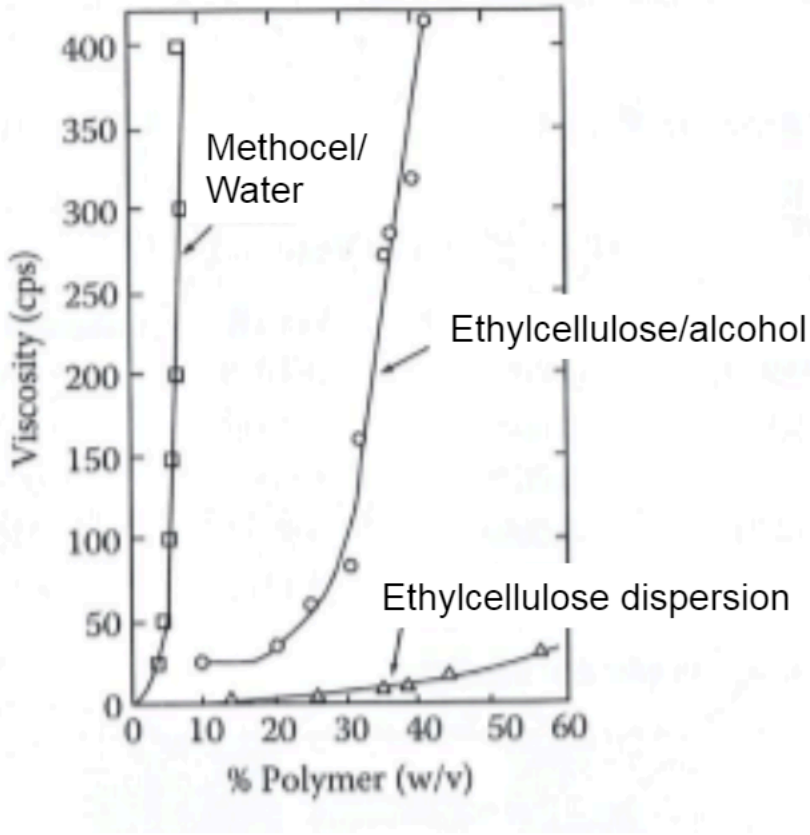


Pellets coated with Eudragit RS 30 D containing 5% Pharmacoat 505
Approximately 10% weight gain

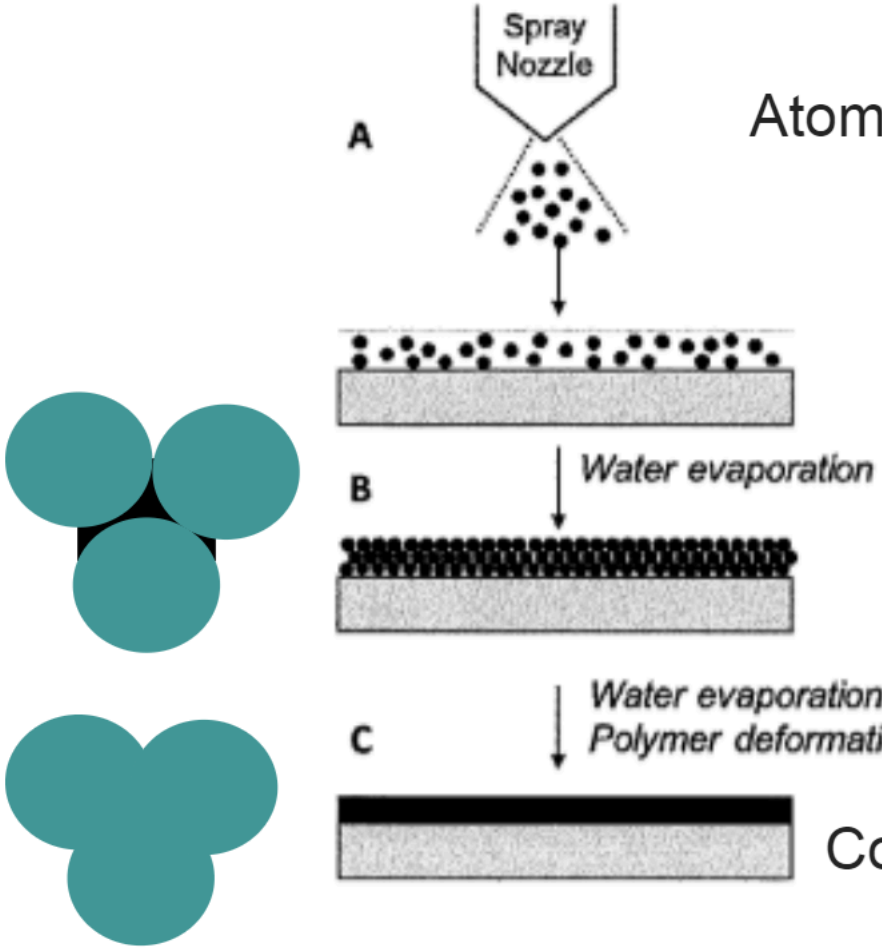
Kucera, McGinity, and Felton, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, Informa, 2008

Advantages of Aqueous-Based Polymeric Dispersions

- No organic solvents
  - Cost savings
  - Environmental concerns
  - Toxicity
  - Regulatory issues
- Higher polymer concentrations without significant increase in viscosity



Film Formation from an Aqueous Polymeric Dispersion



Atomization of polymeric dispersion

Polymeric dispersion deposited onto substrate

Close packed polymer spheres; water in voids

Continuous film

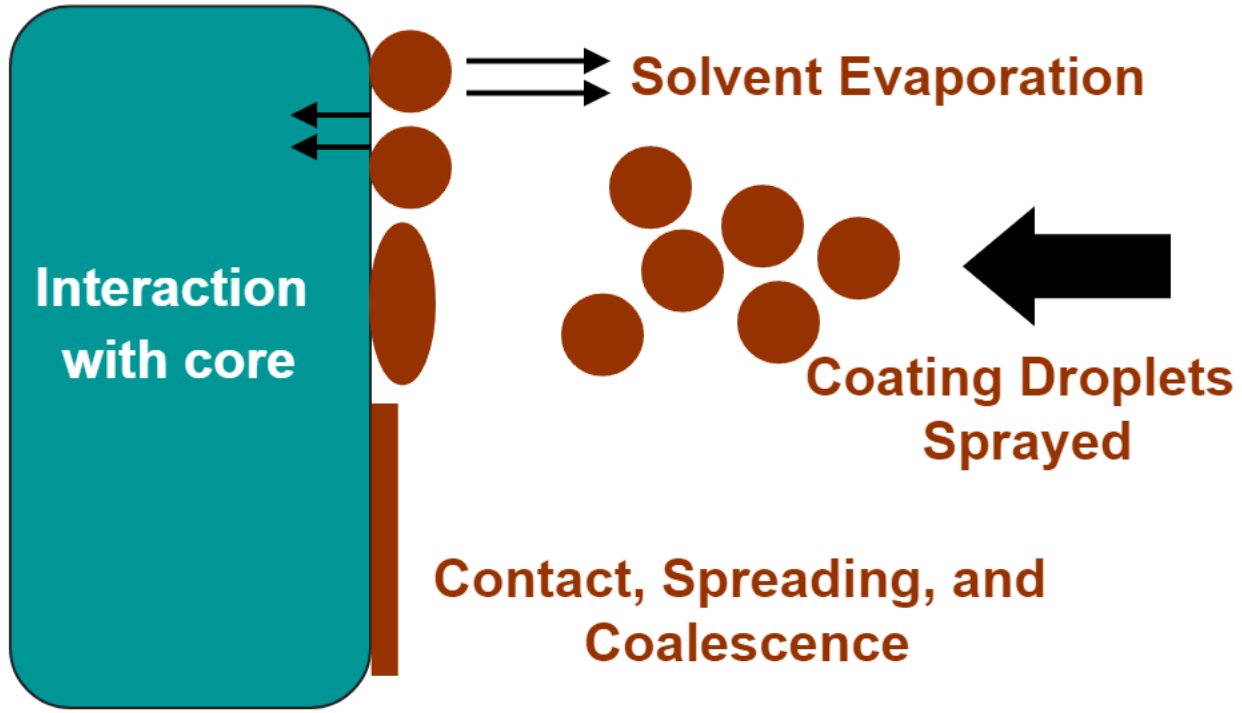
Felton, Int. J. Pharm. 2013

Variables Influencing Coalescence

- Processing conditions
  - Temperature
    - During coating: should be ~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
- Plasticizer
  - Type
  - Concentration

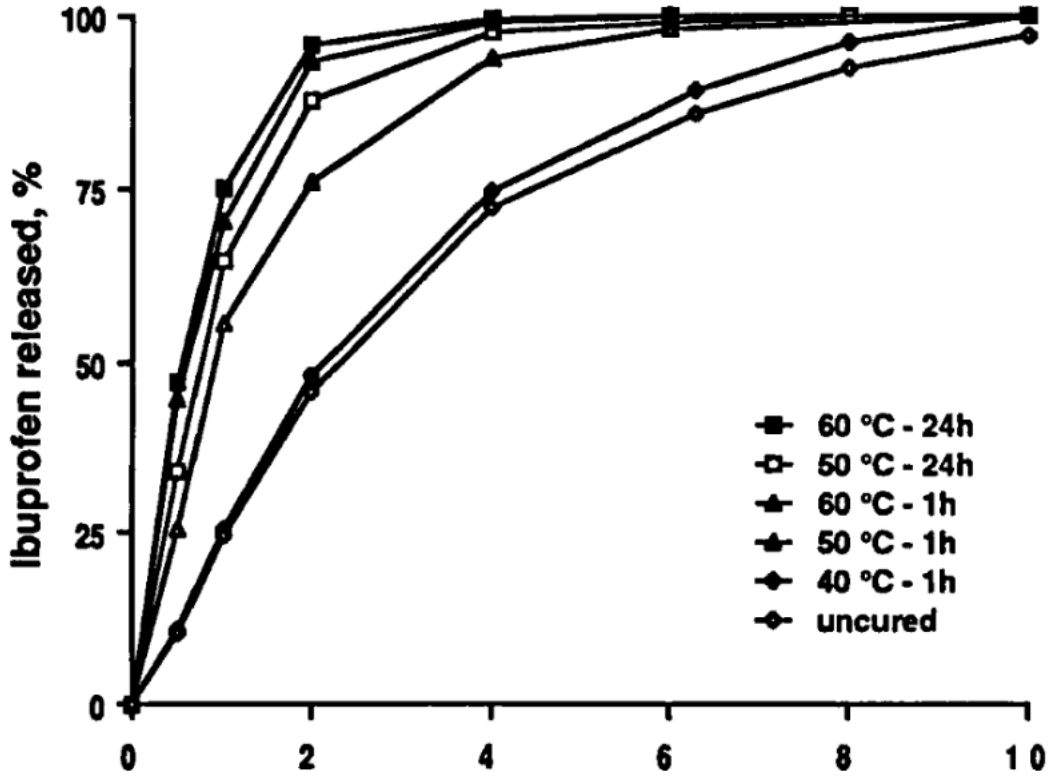
Physical Mixing at the Interface

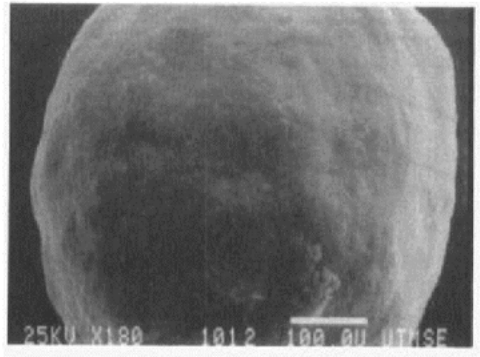
- Dissolution of the outermost tablet surface
  - Migration of drug/excipient into film



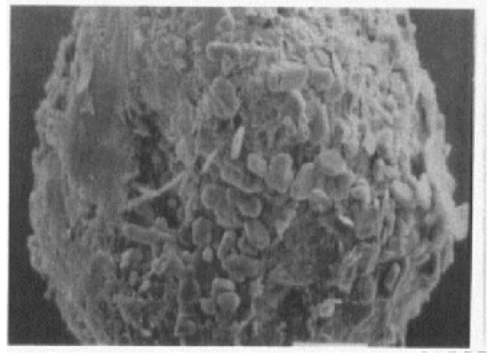
Migration and Recrystallization of API

Observed faster release rates after curing





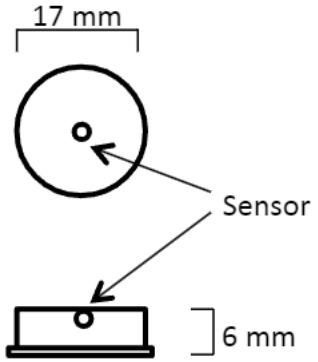
Uncured bead



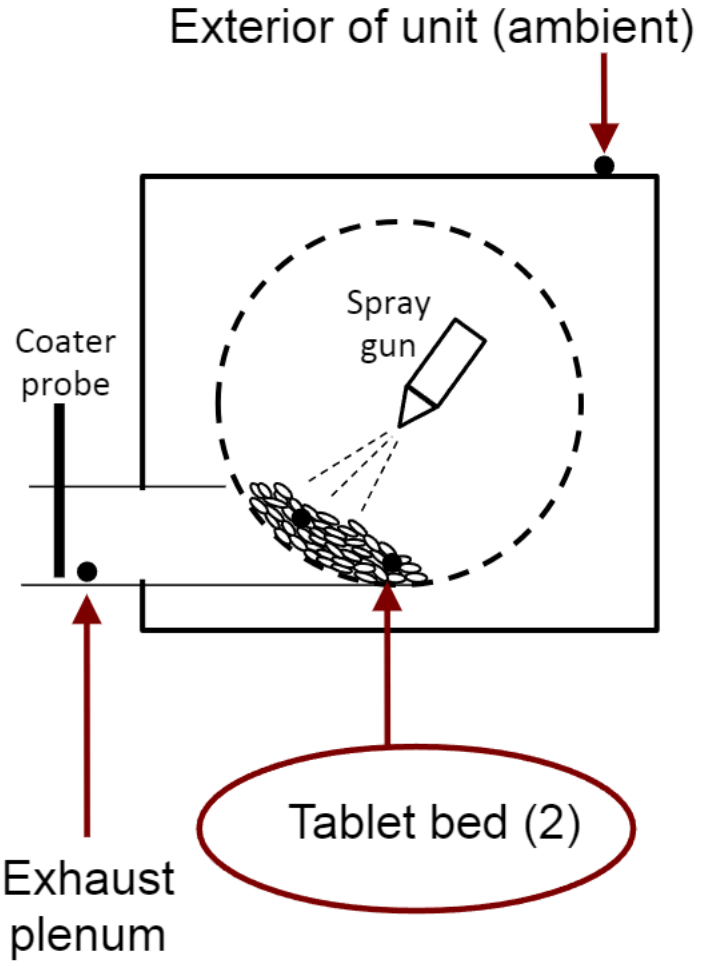
Cured bead

Bodmeier and Paeratakul, Drug Dev Ind Pharm, 1994

Opulus PyroButtons®

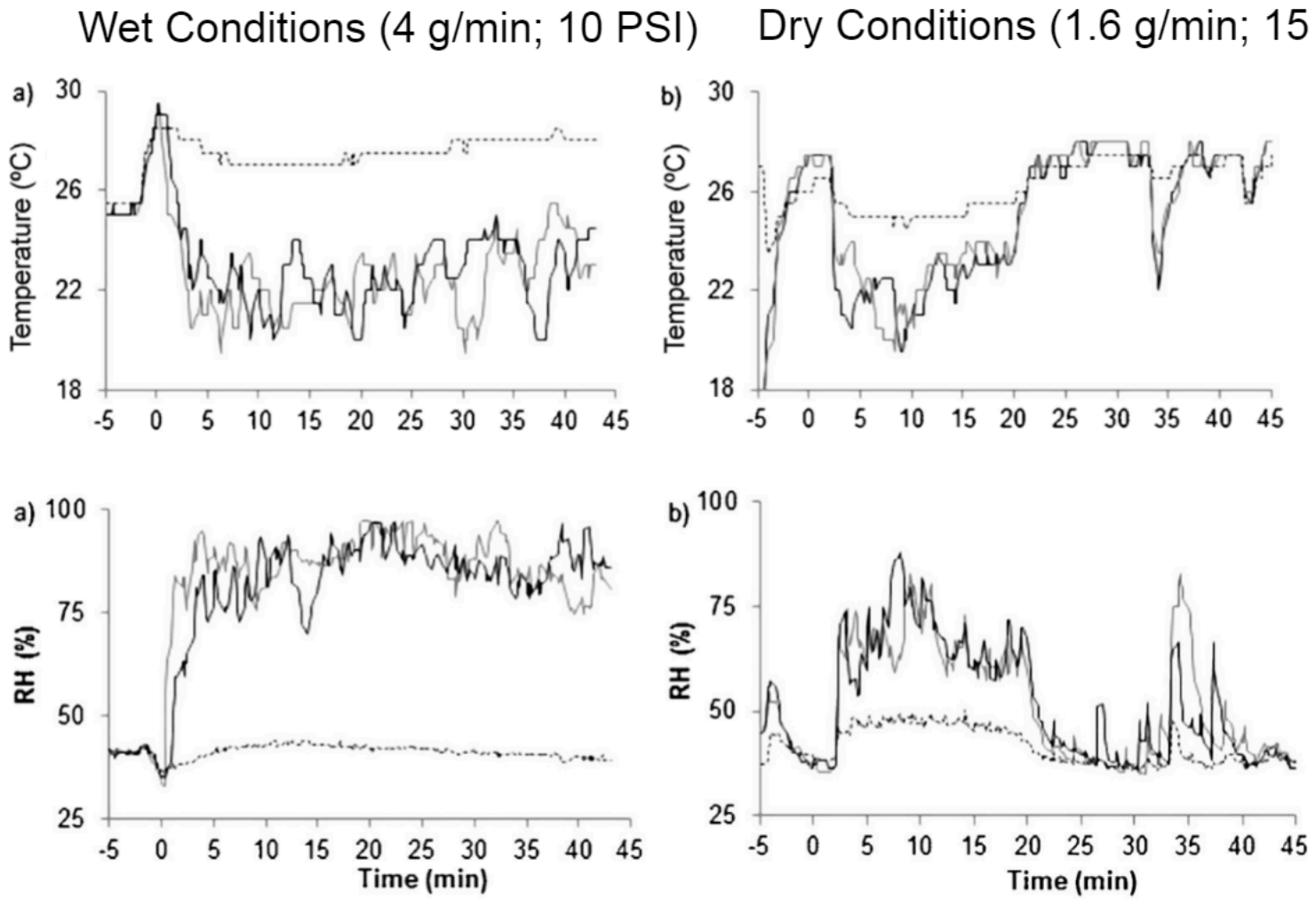


Schematic



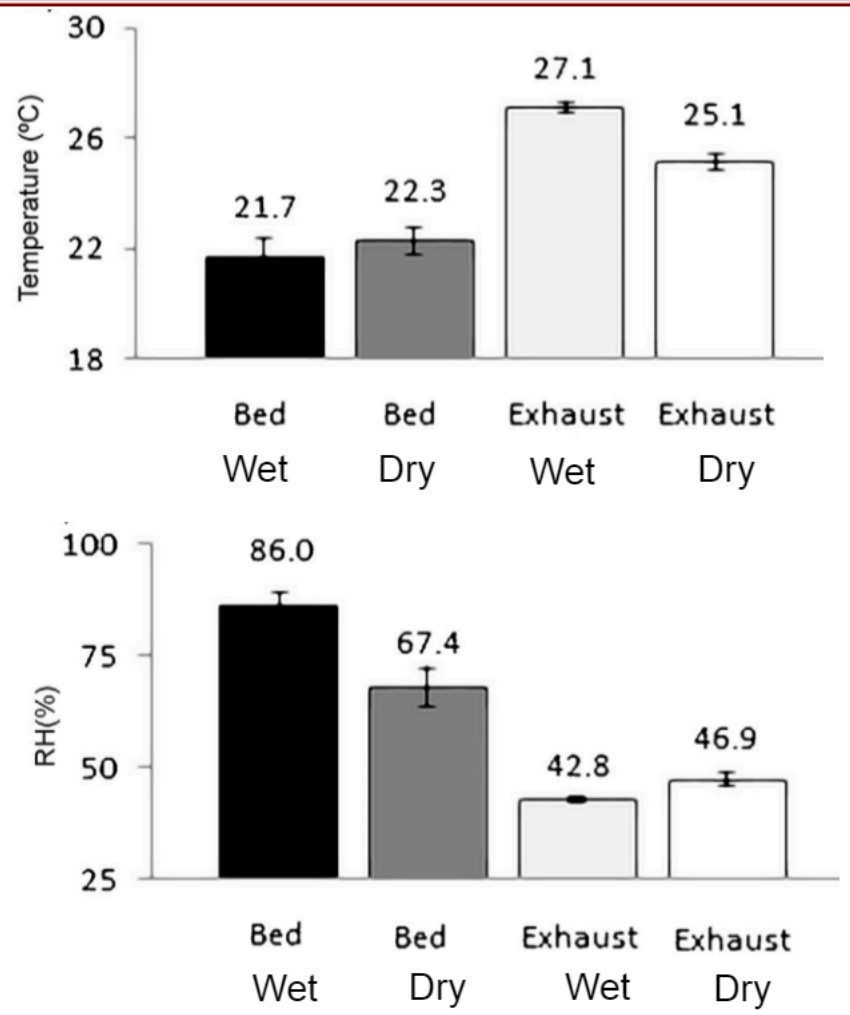
Macchi et al, Eur. J. Pharm. Biopharm, 2016

Coating Parameters Affect Coating Bed Environment



Macchi and Felton, Int. J. Pharm., 2016

Coating Parameters Affect Coating Bed Environment



Macchi and Felton, Int. J. Pharm., 2016

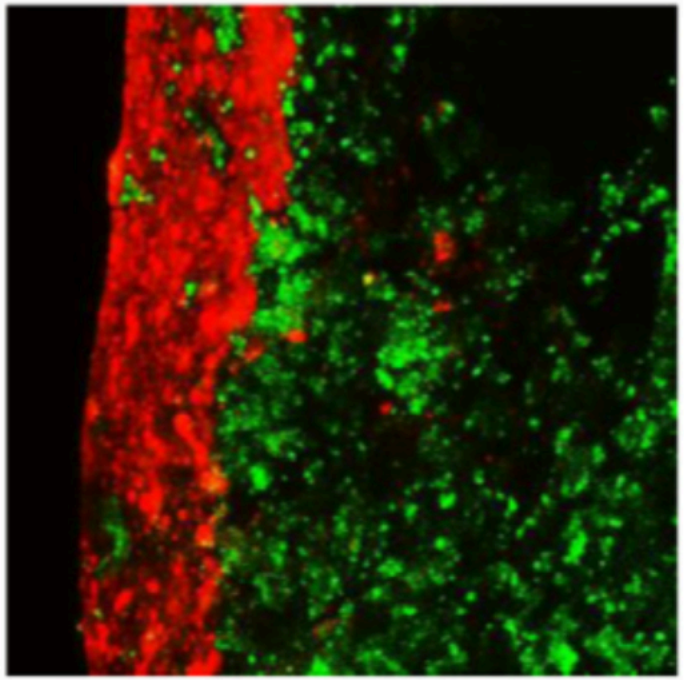
Wet Conditions: 4 g/min; 10 PSI

Dry Conditions: 1.6 g/min: 15 PSI

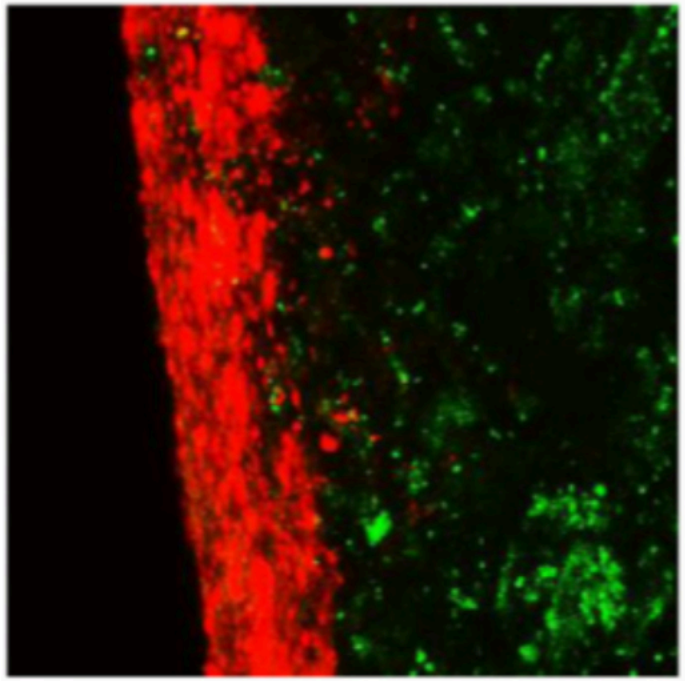
- Exhaust temp/RH is not representative of actual conditions (microenvironment) to which substrates are exposed during coating
- RH for two coating conditions differed

Coating Conditions Influence Surface Dissolution/Physical Mixing

Wet Conditions (4 g/min; 10 PSI)



Dry Conditions (1.6 g/min; 15 PSI)



16.7% Acetaminophen; 82.6% Avicel PH 302; 0.2% Fumed Silica; 0.5% Magnesium Stearate
Tablets compressed to a hardness of 10kp; Confocal laser scanning microscopic images

Macchi and Felton, Int. J. Pharm., 2016

Current Study

Tablet Formulations

A	B
16.7% Acetaminophen 81.8% Avicel 302 1.0% Cab-O-Sil 0.5% Mag. St.	16.7% Acetaminophen 78.3% Avicel 302 1.0% Cab-O-Sil 4.0% Mag. St.
C	**D**
16.7% Acetaminophen 40.9% Avicel 302 40.9% Lactose SD 14 1.0% Cab-O-Sil 0.5% Mag. St.	16.7% Acetaminophen 39.15% Avicel 302 39.15% Lactose SD 14 1.0% Cab-O-Sil 4.0% Mag. St.

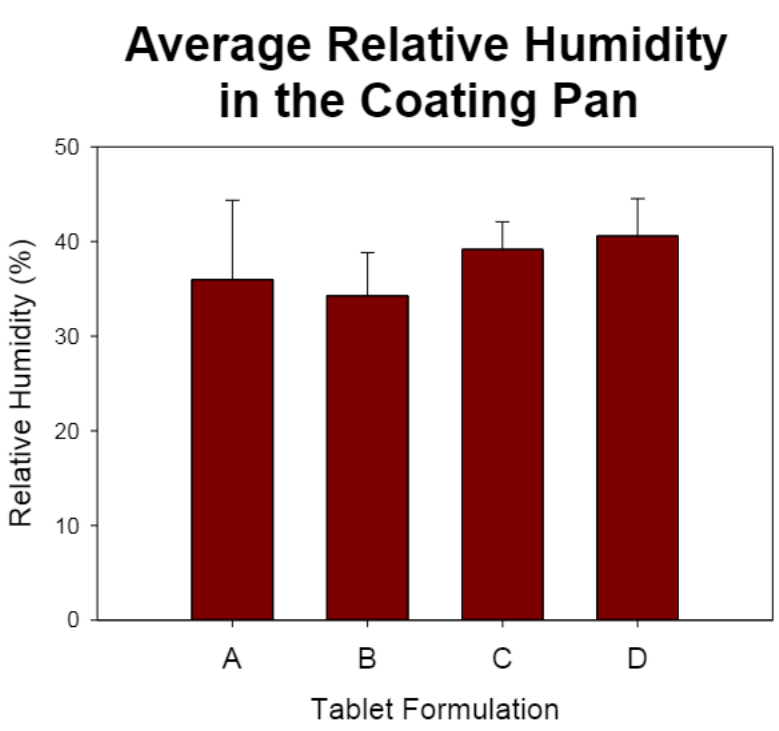
300mg tablets; Compressed to hardness of 10kp

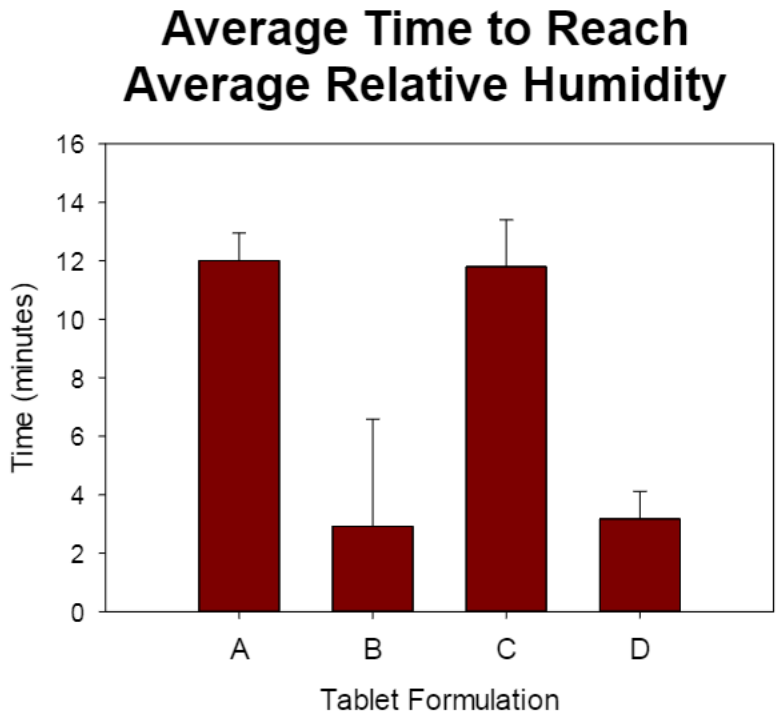
Coating

Formulation*
Eudragit RS/RL 4:1 20% TEC 50% Talc 0.001% Rhodamine B Water to reduce solids to 15%

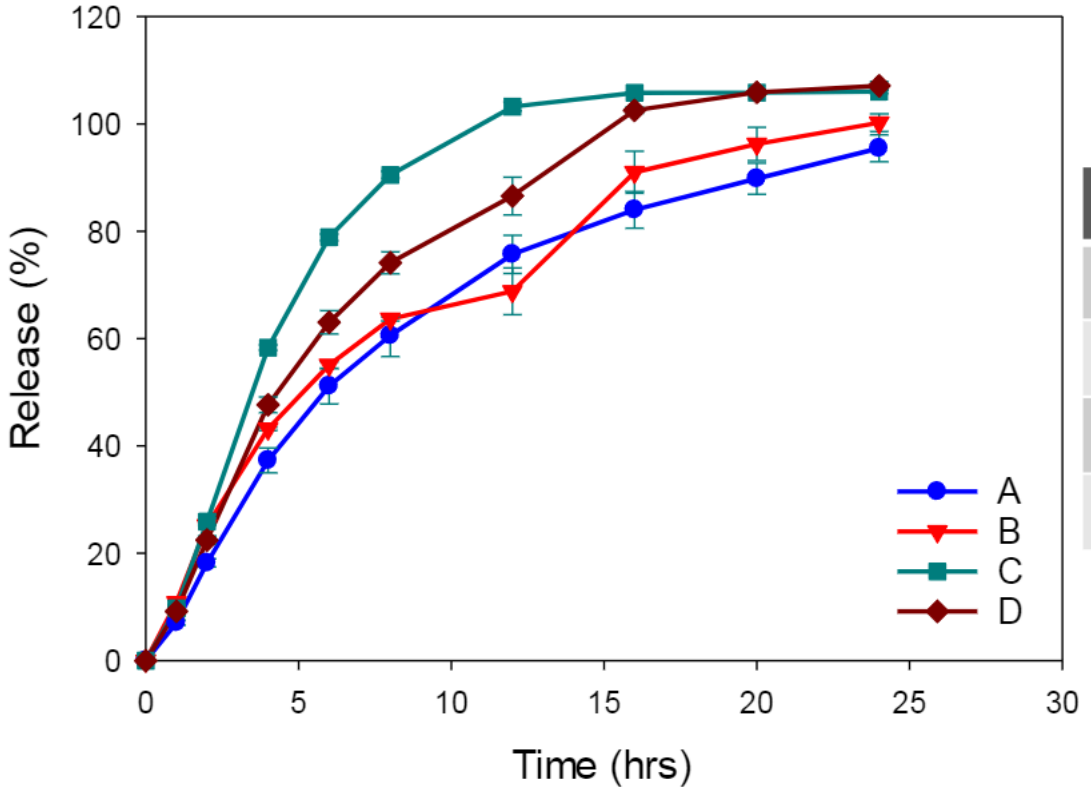
Processing Parameters
Inlet air temperature: 40C Pan speed: 15rpm Atomization air pressure: 10 PSI Spray rate: ~4g/min

Substrate Properties Affected Microenvironmental Conditions





Substrate Properties Affected Polymer Deposition/Drug Release



Formulation	Weight Gain
A	7.56%
B	7.33%
C	4.24%
D	6.31%

Summary

- Film coating is highly complex: Coating formulation, substrate characteristics, and processing conditions influence film properties
  - Variables often inter-connected
- Characterize system to understand process and avoid/resolve problems
  - Mechanism of film formation from polymer dispersions is different from solutions
  - Surface dissolution and physical mixing at interface
  - Using Pyrobuttons to measure actual environmental conditions in coating pan

Thank you