Approaches to the Investigation of Dissolution Testing Changes and Failures

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Acknowledgements

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- Vivian Gray: V.A. Gray Consulting
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- Raimar Loebenberg: University of Alberta
- Jian-Hwa Han: Abbvie Inc.
- Juan Castaneda-merced: Genzyme, a Sanofi Company

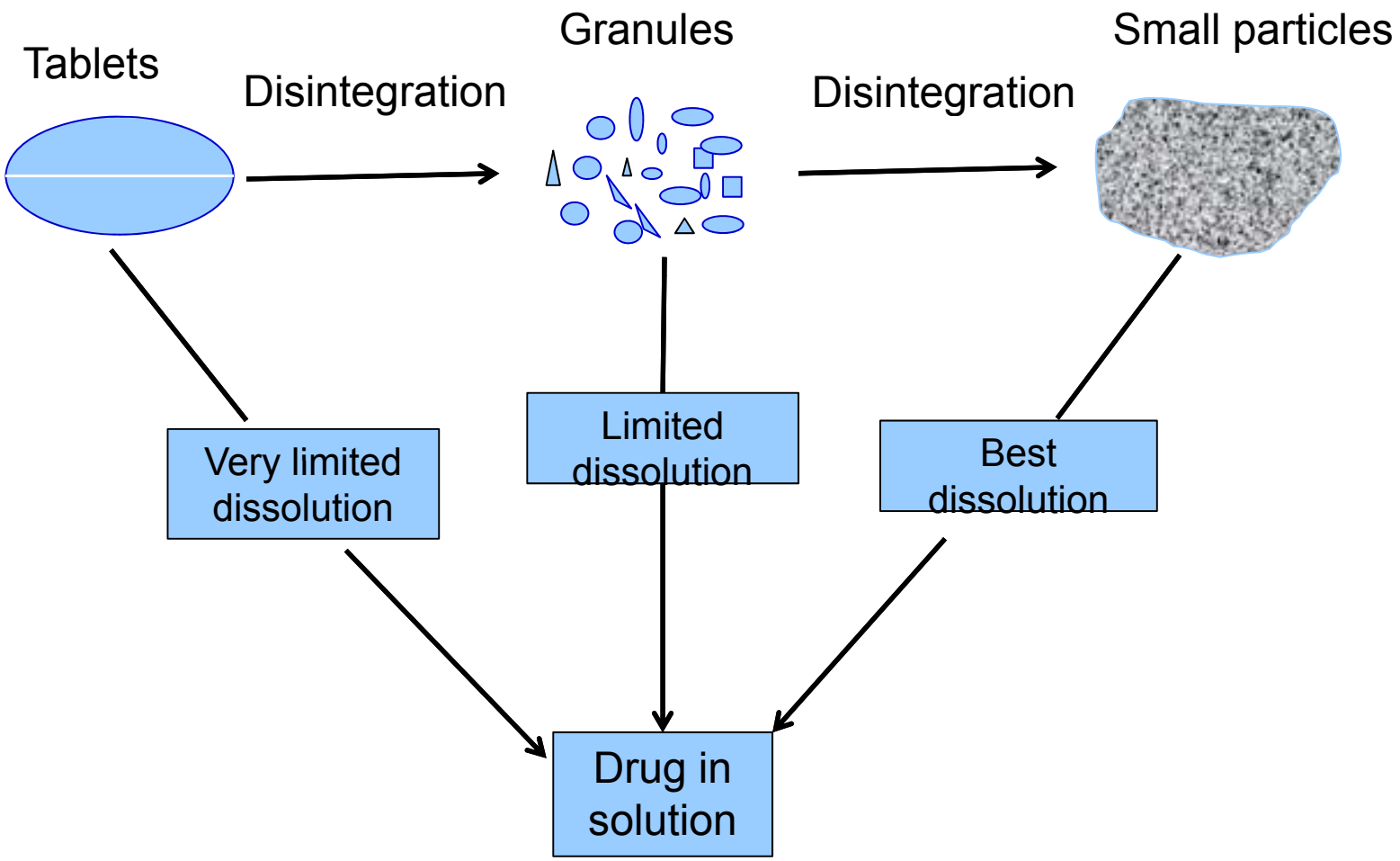
Purpose

- Understand possible factors that can cause dissolution changes and failures
- Investigate that whether the dissolution changes are caused by drug product or dissolution method

Solid Dosage Formulation Development Progression

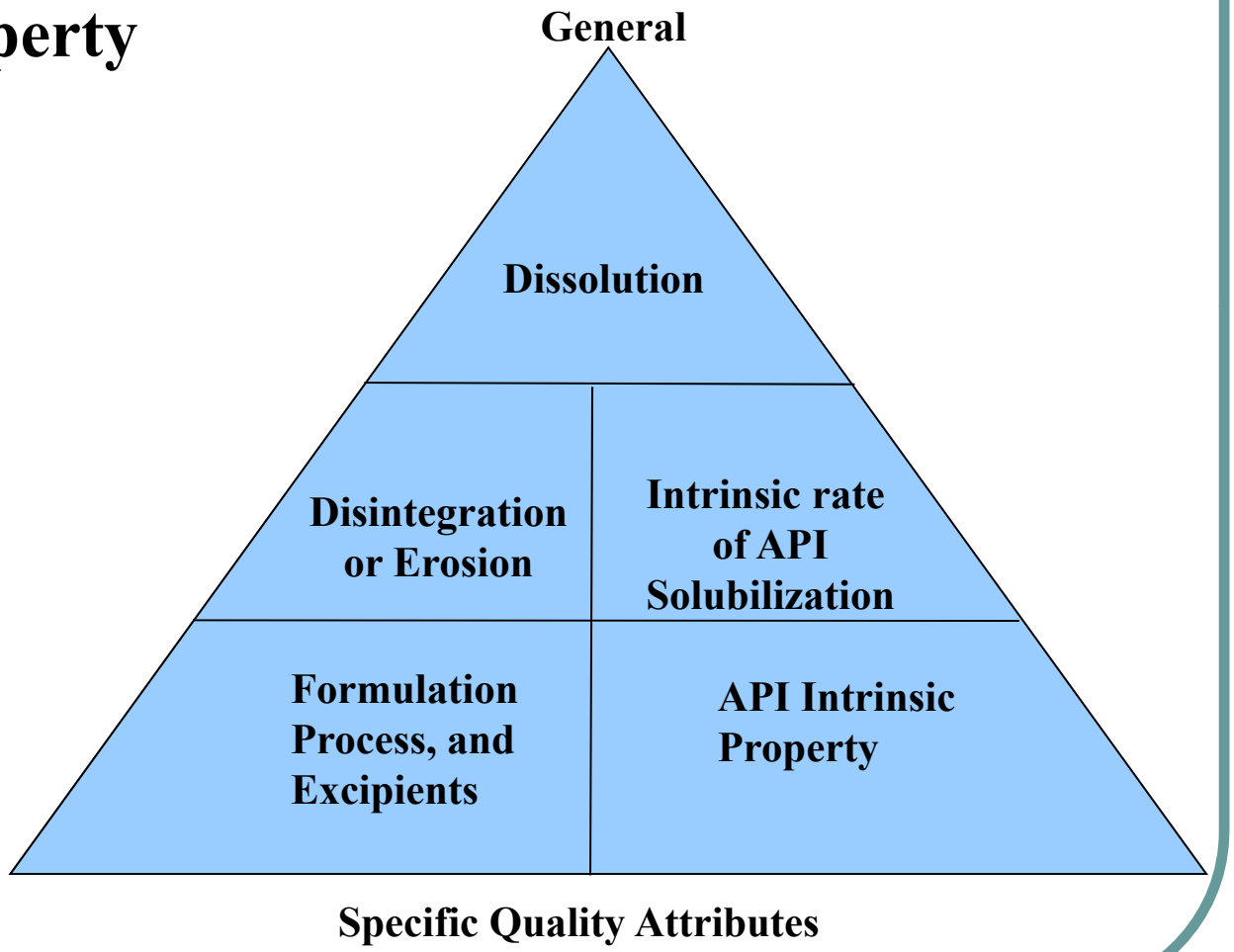
- Phase 1: first in man, oral solution, suspension, drug in bottle, capsules, or tablets
- Phase 2: more mature oral dosage forms
- Phase 3: oral dosage form optimization toward commercialization

Dissolution Mechanism



Factors That Affect the Dissolution of a Drug Product

- **Intrinsic Property of API**
  - Solubility
  - Wettability
  - Particle size
  - Polymorphs
  - Morphology
  - Surface area
  - Density
- **Formulation**
  - Excipients
  - Hardness
  - Process



Modified from C. Tong, Pharmaceutical Technology, 2009

Outline for Case Studies

Drug Product

- Drug load
- Particle size
- Tablet hardness
- Disintegration
- Excipient composition
- Gelatin capsules (cross-linking)
- Polymorph change on stability

Dissolution Method

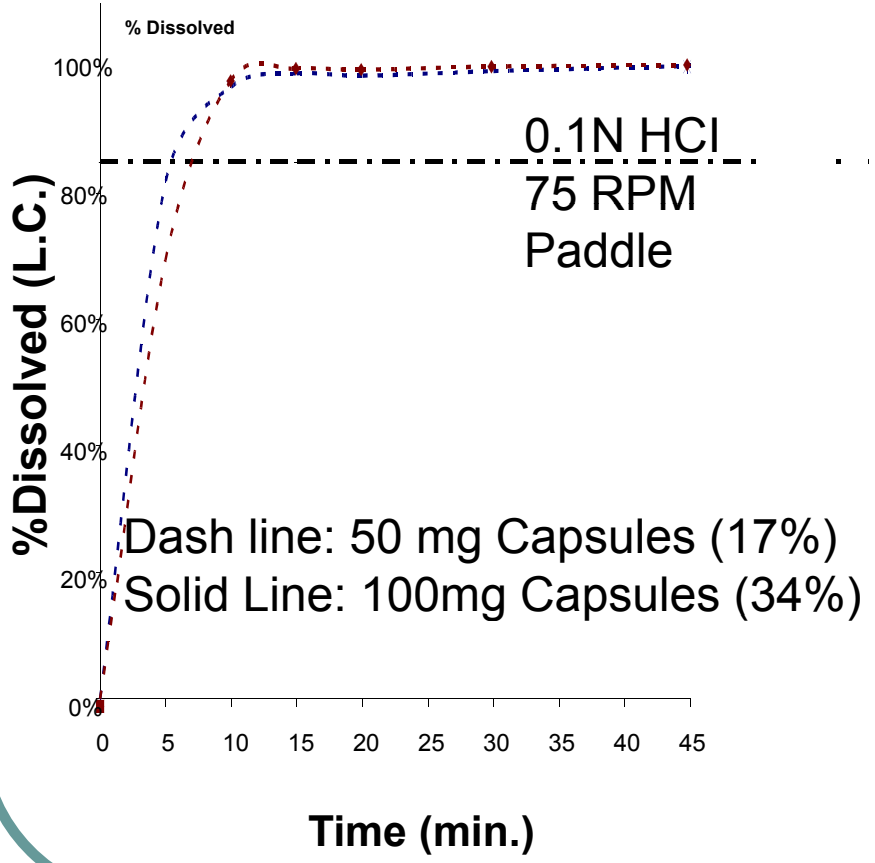
- Coning and gelling
- Agitation speed
- Sinker
- Buffer (composition and pH)
- Deaeration
- Surfactant amount and type

Biopharmaceutical Compound Classification

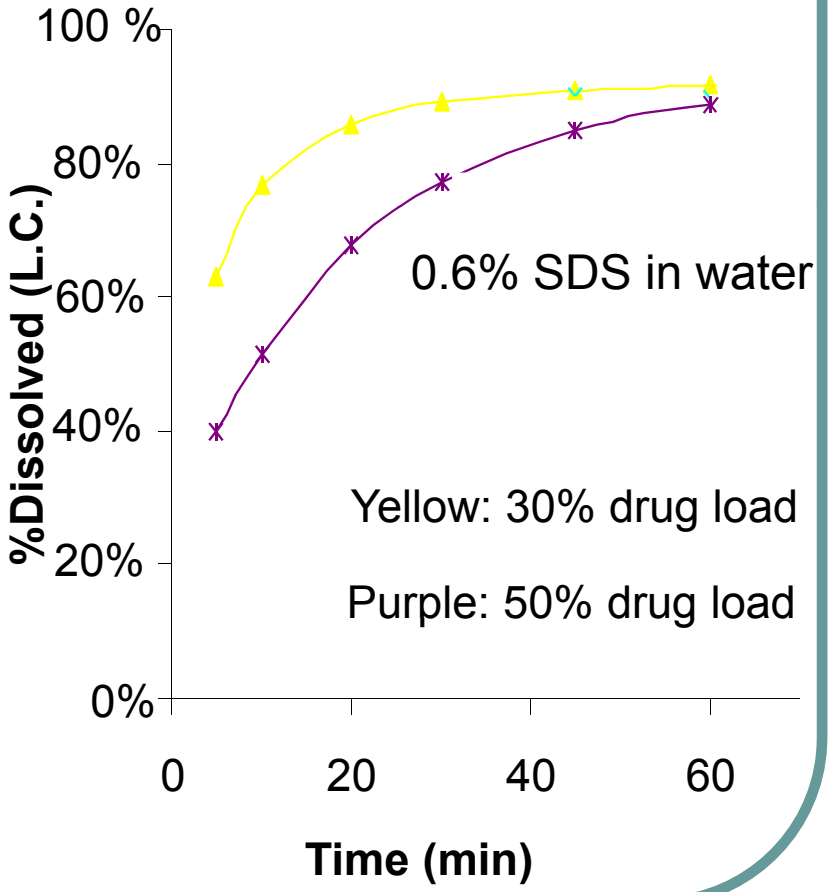
- BCS I: high solubility, high permeability
- BCS II: low solubility, high permeability
- BCS III: high solubility, low permeability
- BCS IV: low solubility, low permeability

Drug Load Affects BCS I and BCS II Compound Dissolution Differently

Dissolution Profile Did Not Change, BCS I

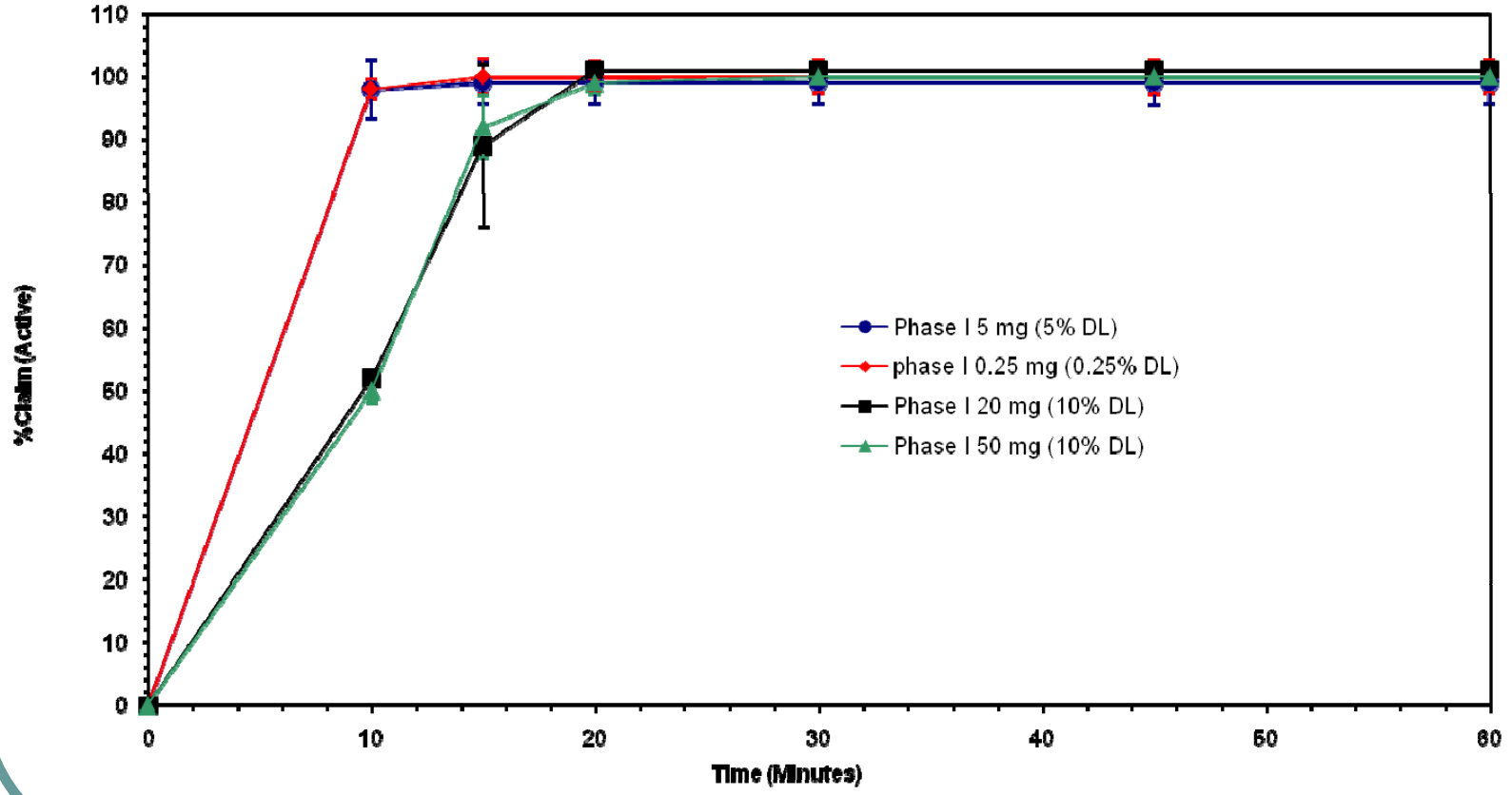


Dissolution Profiles Change, BCS II



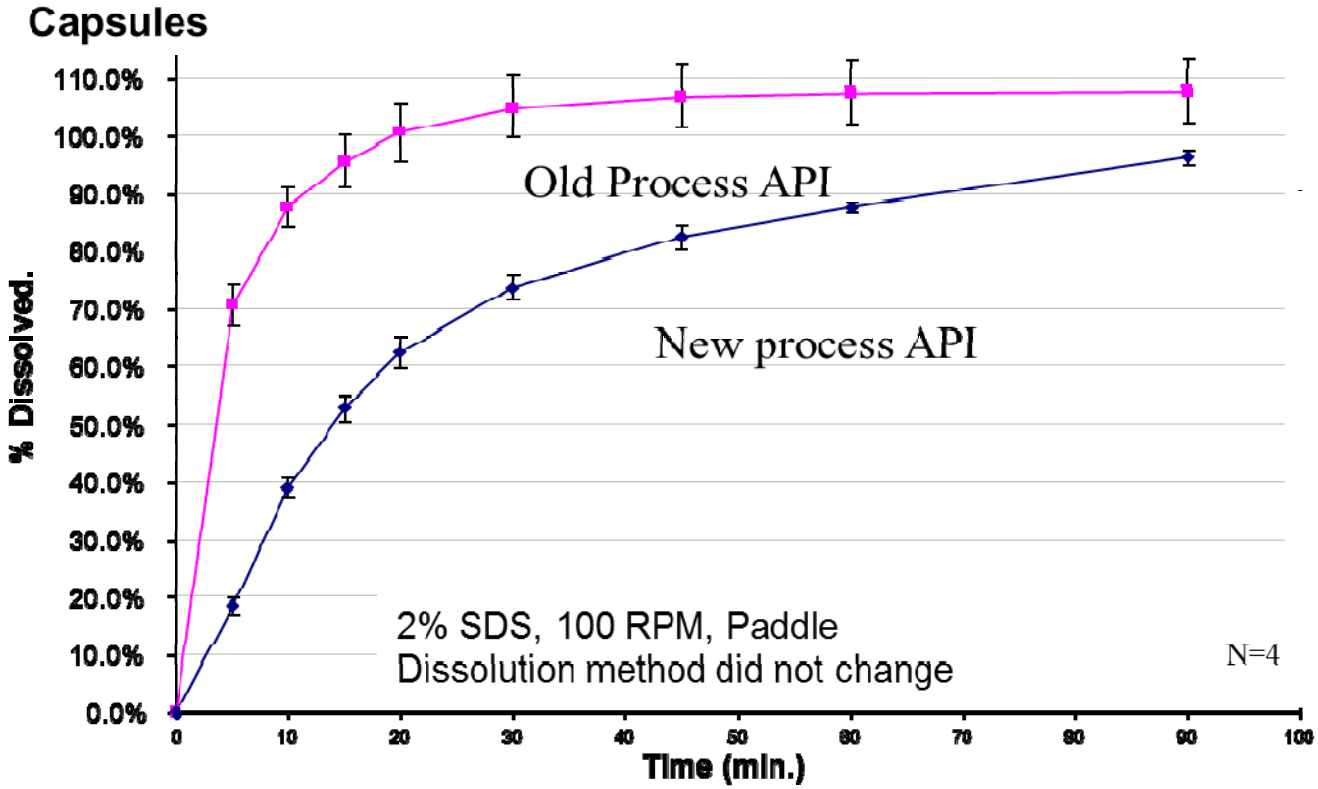
Drug Load Effect on Dissolution

Correct method can differentiate drug load difference



Courtesy of Greg Martin

Particle Size Effect-Drug Substance Process Change Resulting in a Dissolution Profile Change

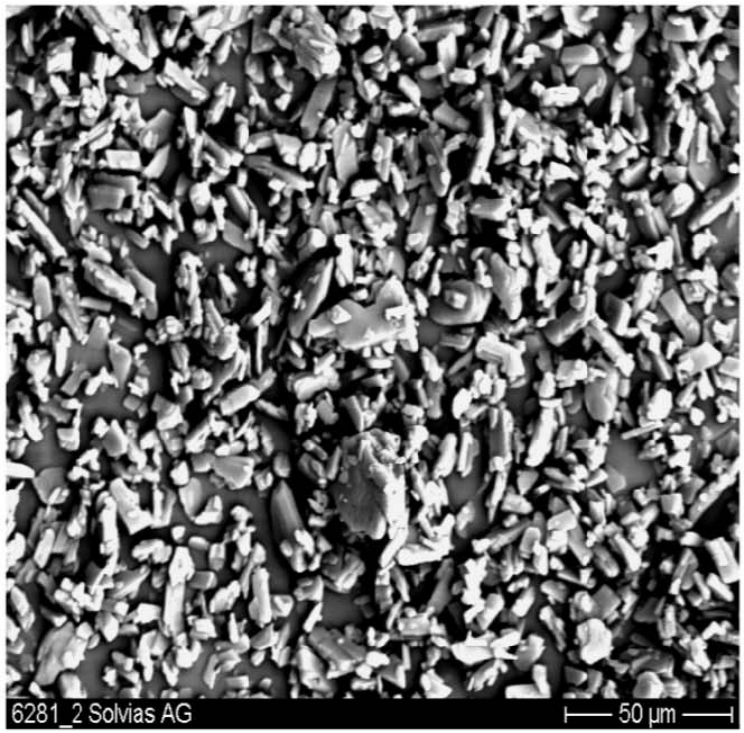


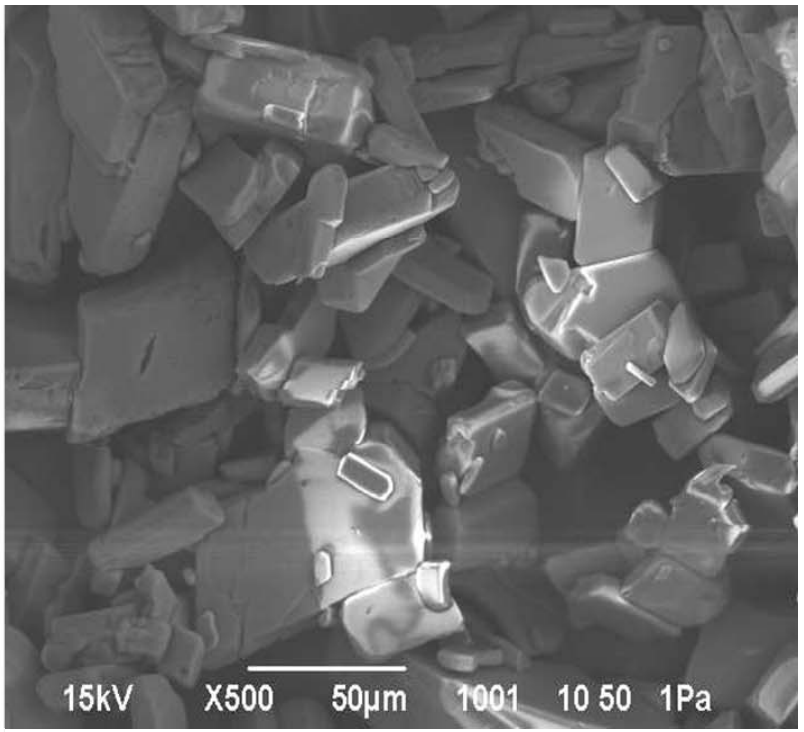
Drug Substance Characterization After Process Change

Old lot: small particle size

SEM

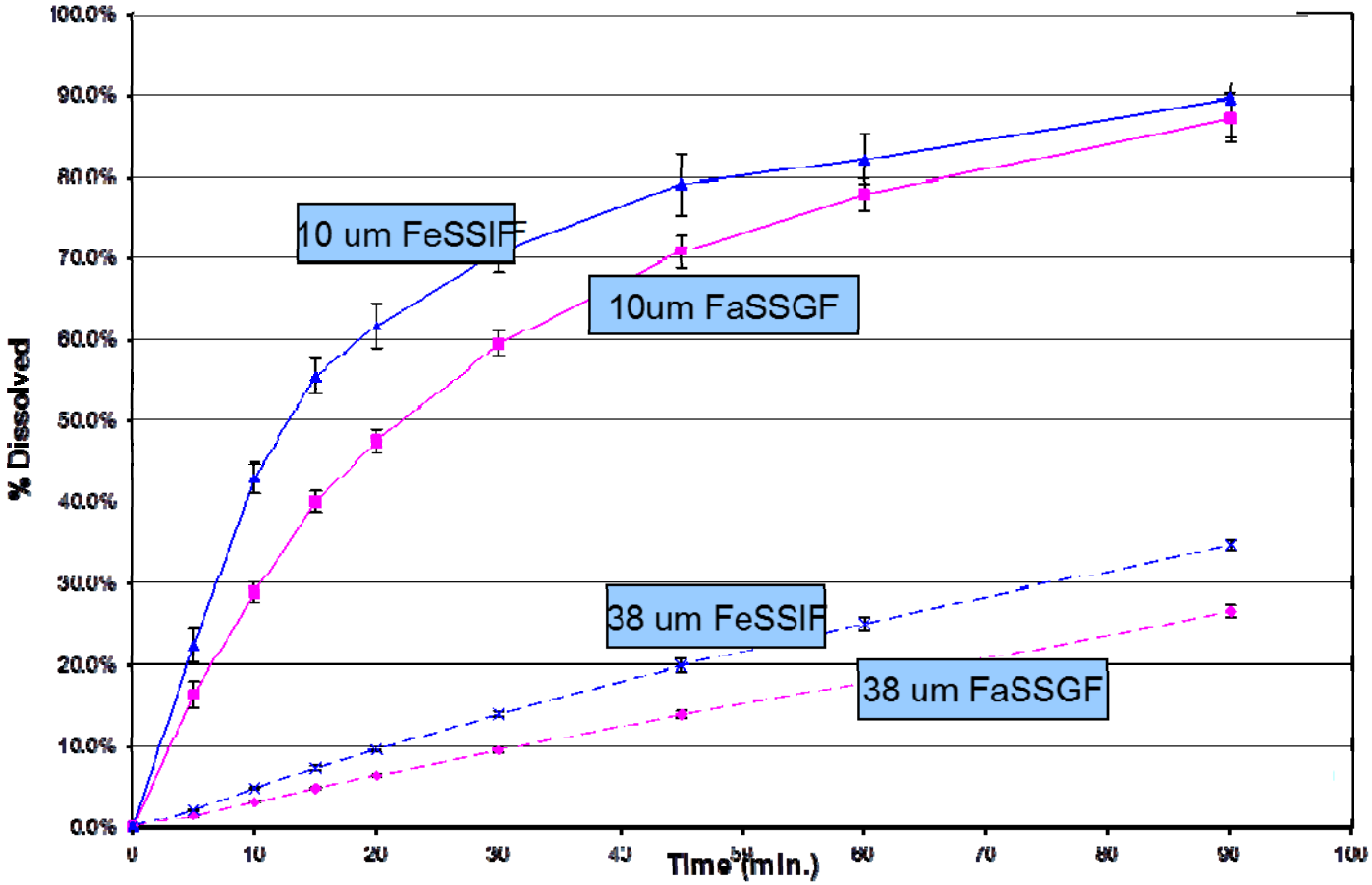
New lot: large particle size





D(0.5)=10 um D(0.9)=20 um	D(0.5)=38 um D(0.9)=74 um

Differentiating Particles Using Biorelevant Media

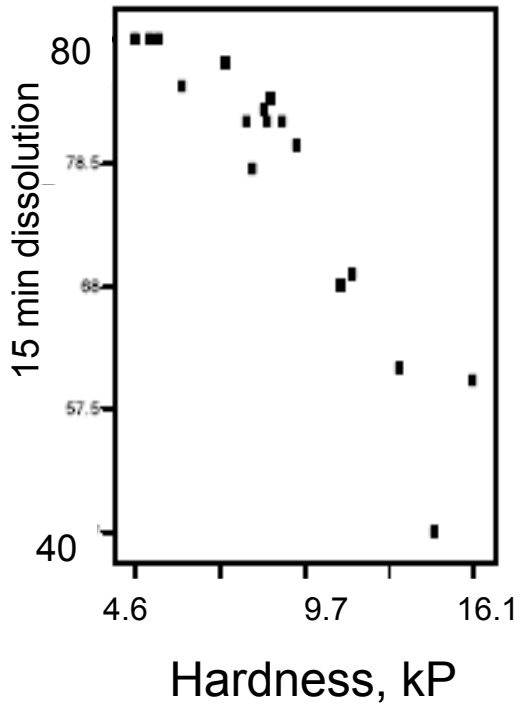


Hardness vs Dissolution

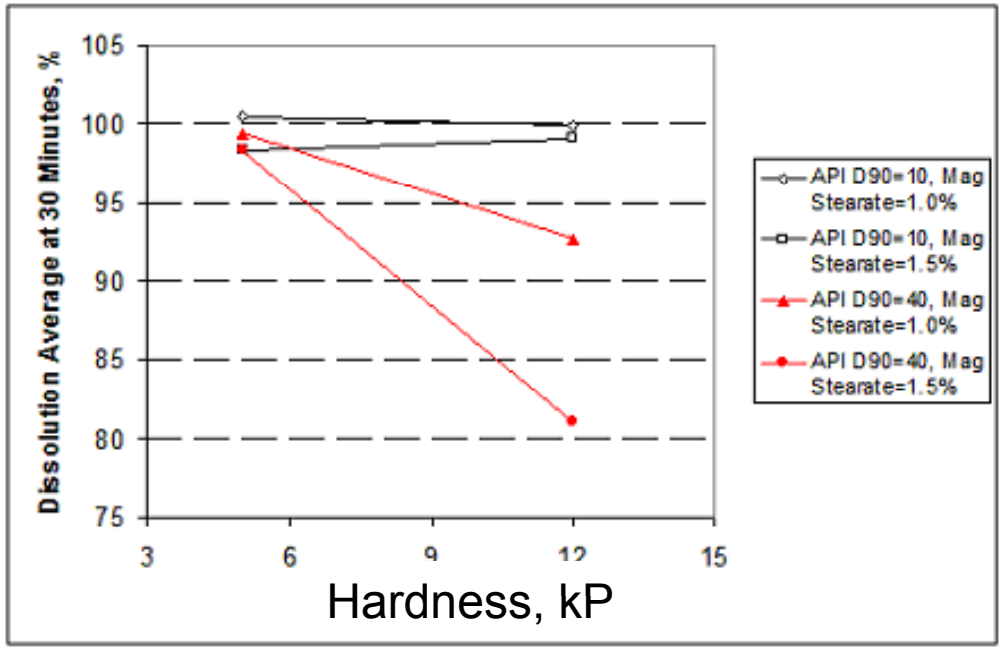
- Hardness change impacts dissolution profiles
- What changes tablet hardness?
  - Exicipients
  - Process
  - Storage (when hardness is affected by moisture penetration)

Hardness Impact on Dissolution

Process Change

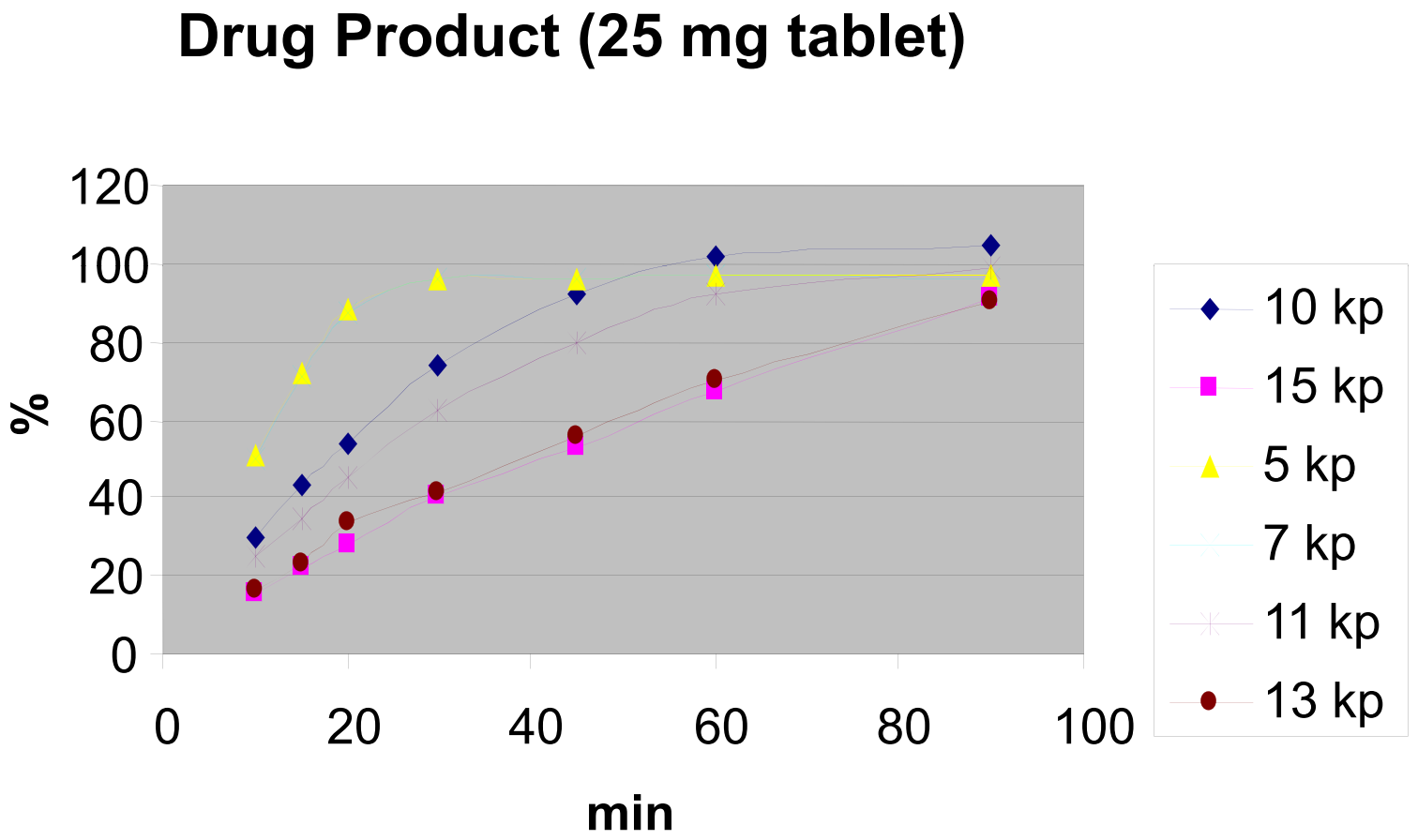


Formulation Excipients Change



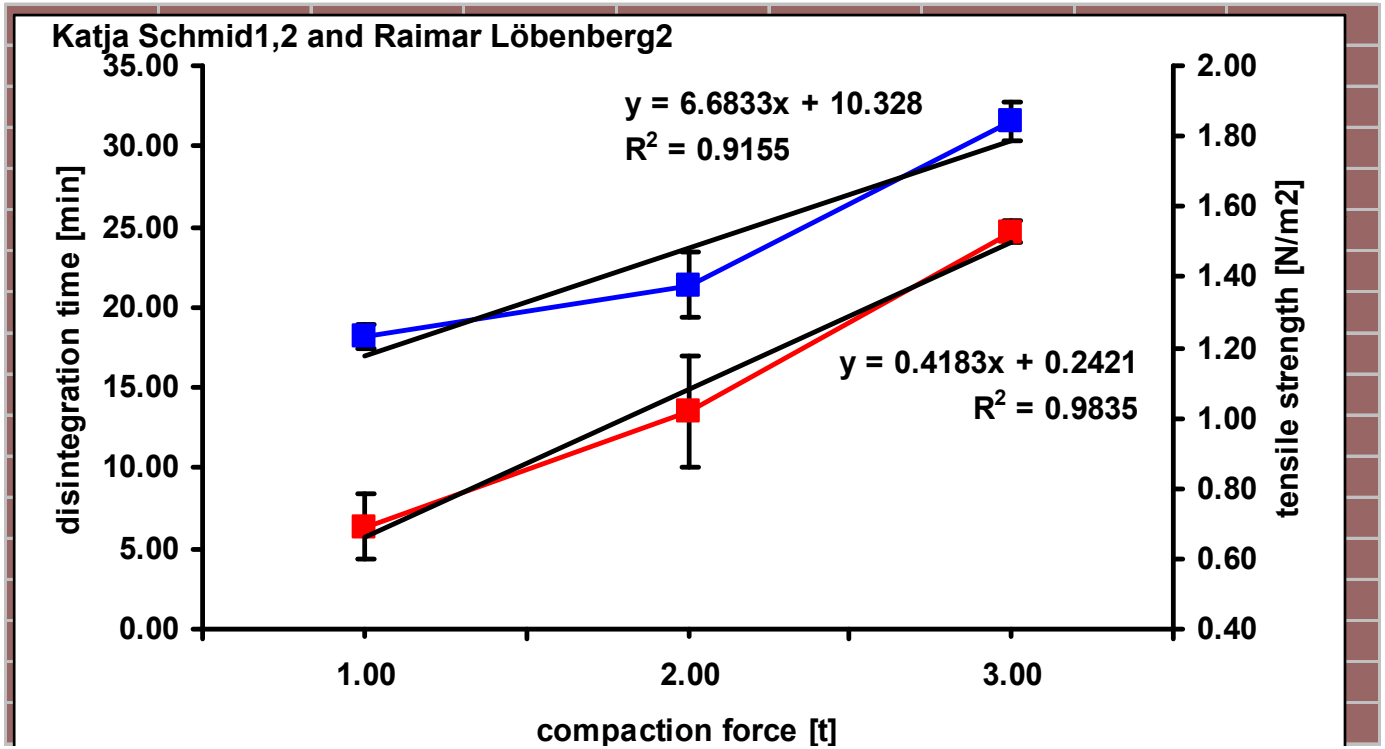
Pharmaceutical Development Case Study: “ACE Tablets”, Conformia, CMC-IM working group
www.**ispe.org**/pqli/case-study-**ace-tablets**.pdf

Impact of Tablet Hardness on Dissolution



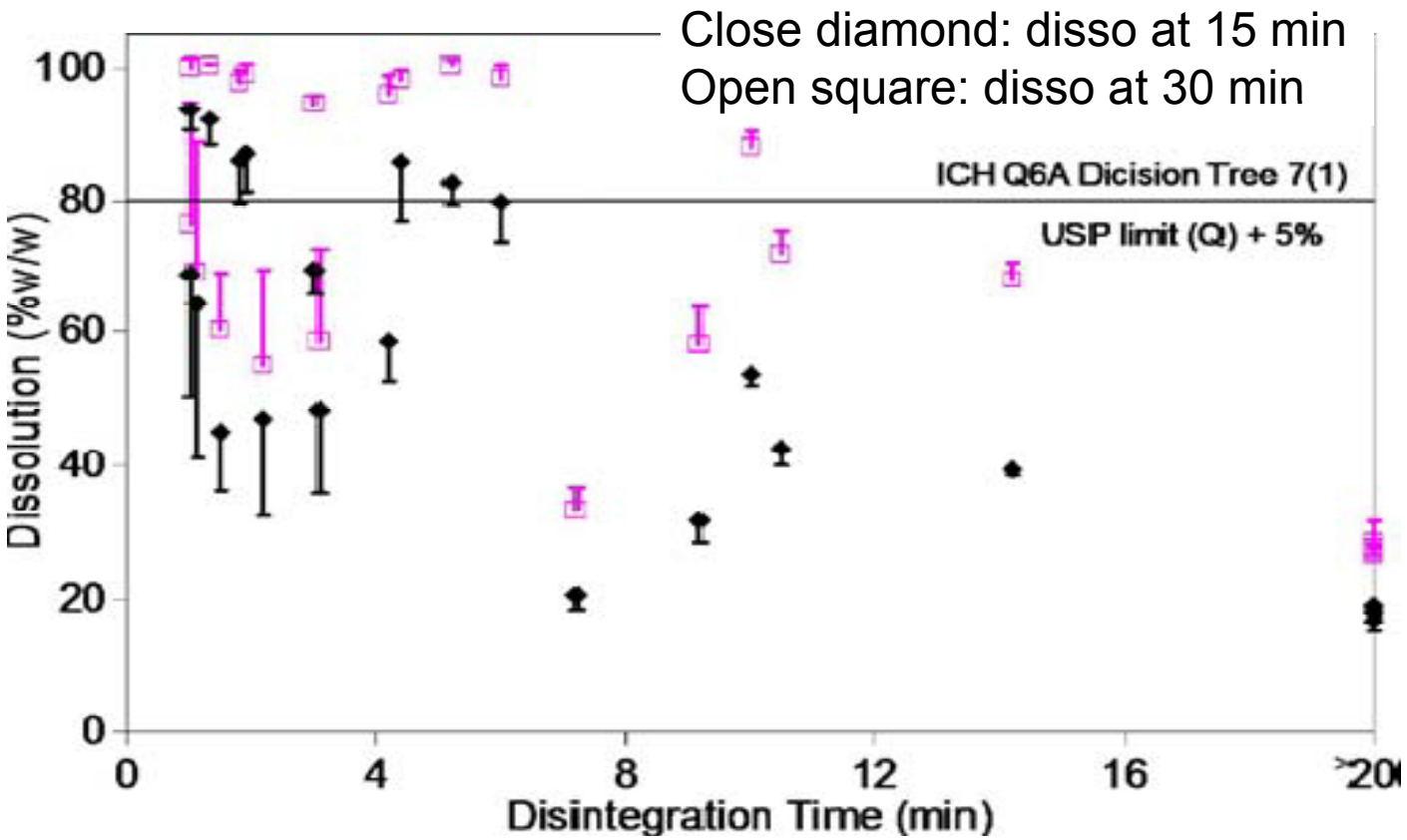
Courtesy of Greg Martin

Process Changed the Disintegration of Tablets



Courtesy of Raimer Loebenberg

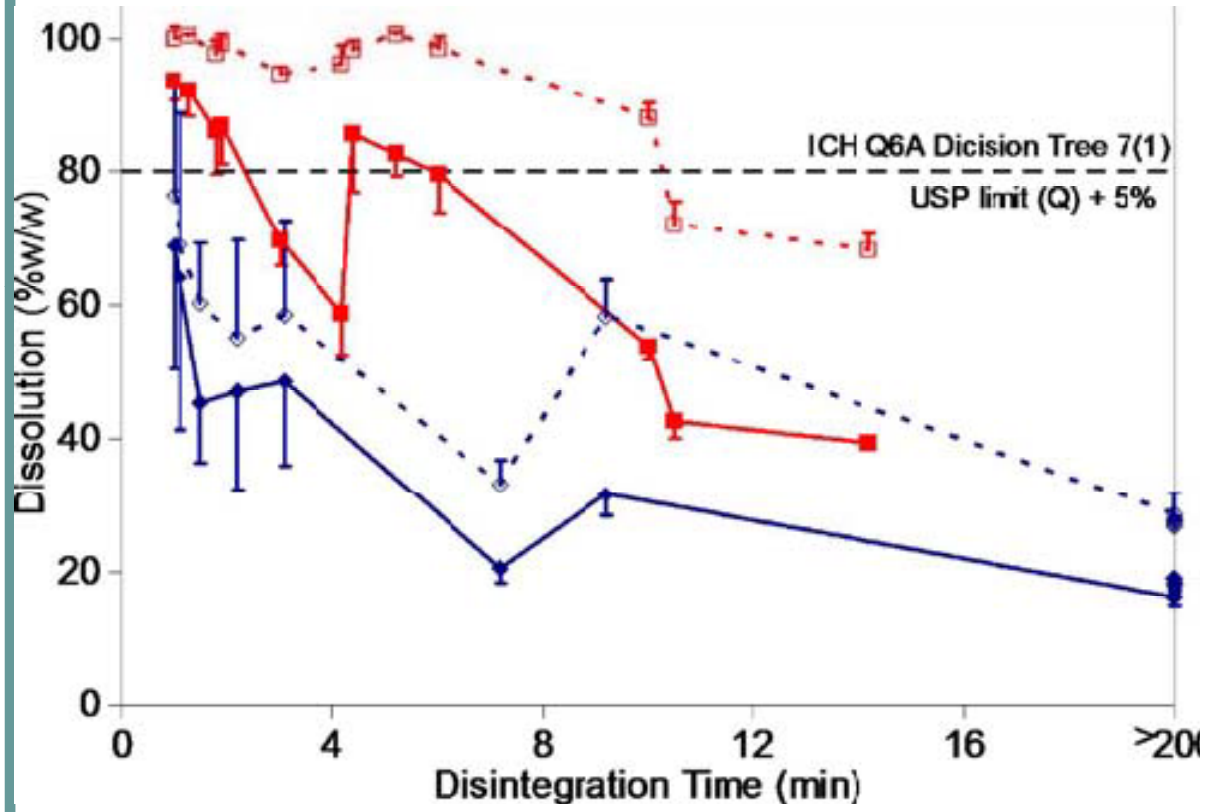
No Relationship Between Tablet Dissolution and Disintegration Time



The 24 set of tablets prepared using different filler, binder, and disintegrating agent and compressed into tablets to different hardness showed large variation in the dissolution and disintegration time.

Abhay Gupta et al, AAPS PharmSciTech, Vol. 10, No. 2, June 2009 495-499

Relationship Between Disintegration Time and the Tablet Dissolution When Changing LMH and DCP

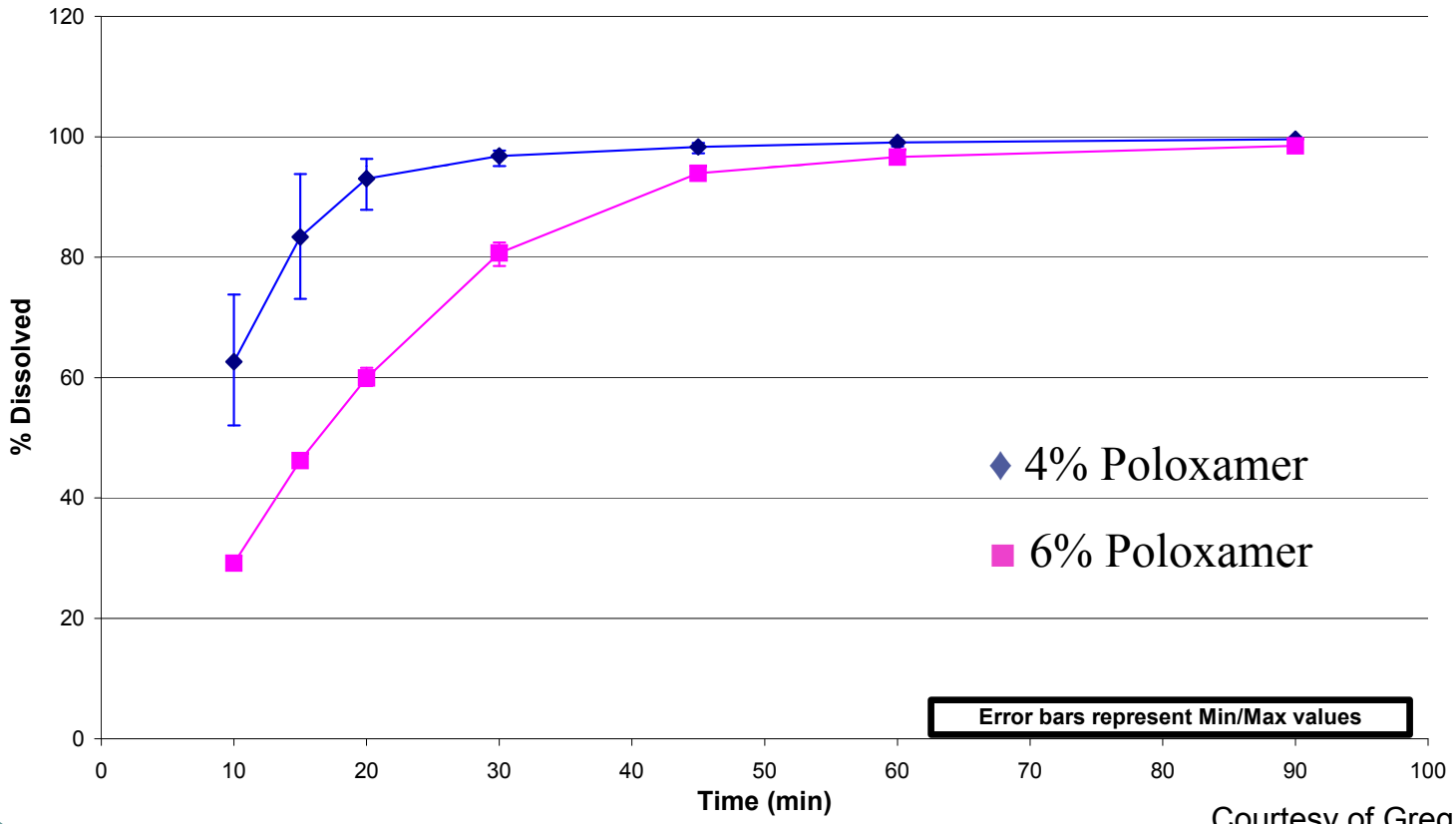


in 15 min (closed symbols) and at 30 min (open symbols) as function of filler used in the formulation (red squares-Lactose Monohydrate (LMH); blue diamonds-Dicalcium phosphate Dihydrate (DCP)). Results are expressed as mean ± standard deviation for n=6

Type of filler affects dissolution rate and disintegration time.

Abhay Gupta et al, AAPS PharmSciTech, Vol. 10, No. 2, June 2009 495-499

Dissolution Impacted by Varying Levels of an Excipient



Courtesy of Greg Martin

Example of Gelatin Cross Linking

Courtesy of Greg Martin

Cross-linking

USP Description

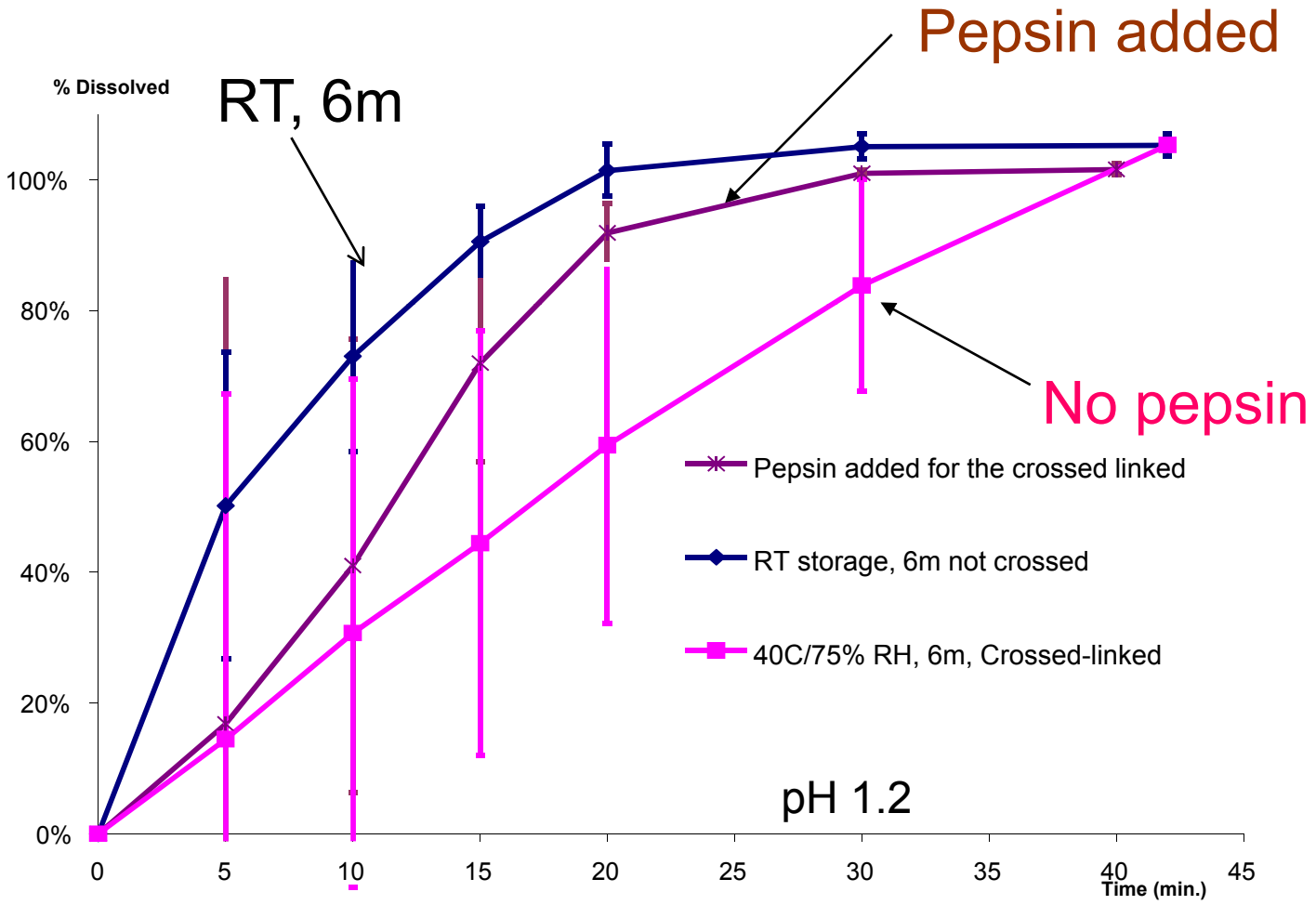
- Cross-linking (Pellicle) can be caused by agents or impurities present in the capsule shell, thereby rendering the entire shell matrix insoluble under conditions that normally would dissolve the gelatin shell. One of the strongest and most common types of cross-linking involves the covalent bonding of the **amine group** of a lysine side chain of one gelatin molecule to a **amine group** on another molecule. This reaction generally is caused by trace amounts of reactive aldehydes. Formaldehyde, glutaraldehyde, glyoxal, and reducing sugars are the most common cross-linking agents. The covalent bonding produced with this type of cross-linking is, for all practical purposes, irreversible, and dissolution of the shell must involve the breaking of other bonds such as the enzyme- mediated breaking of the peptide bonds in the protein chains.

See USP Chapter <1094>, <1724>, and <711>

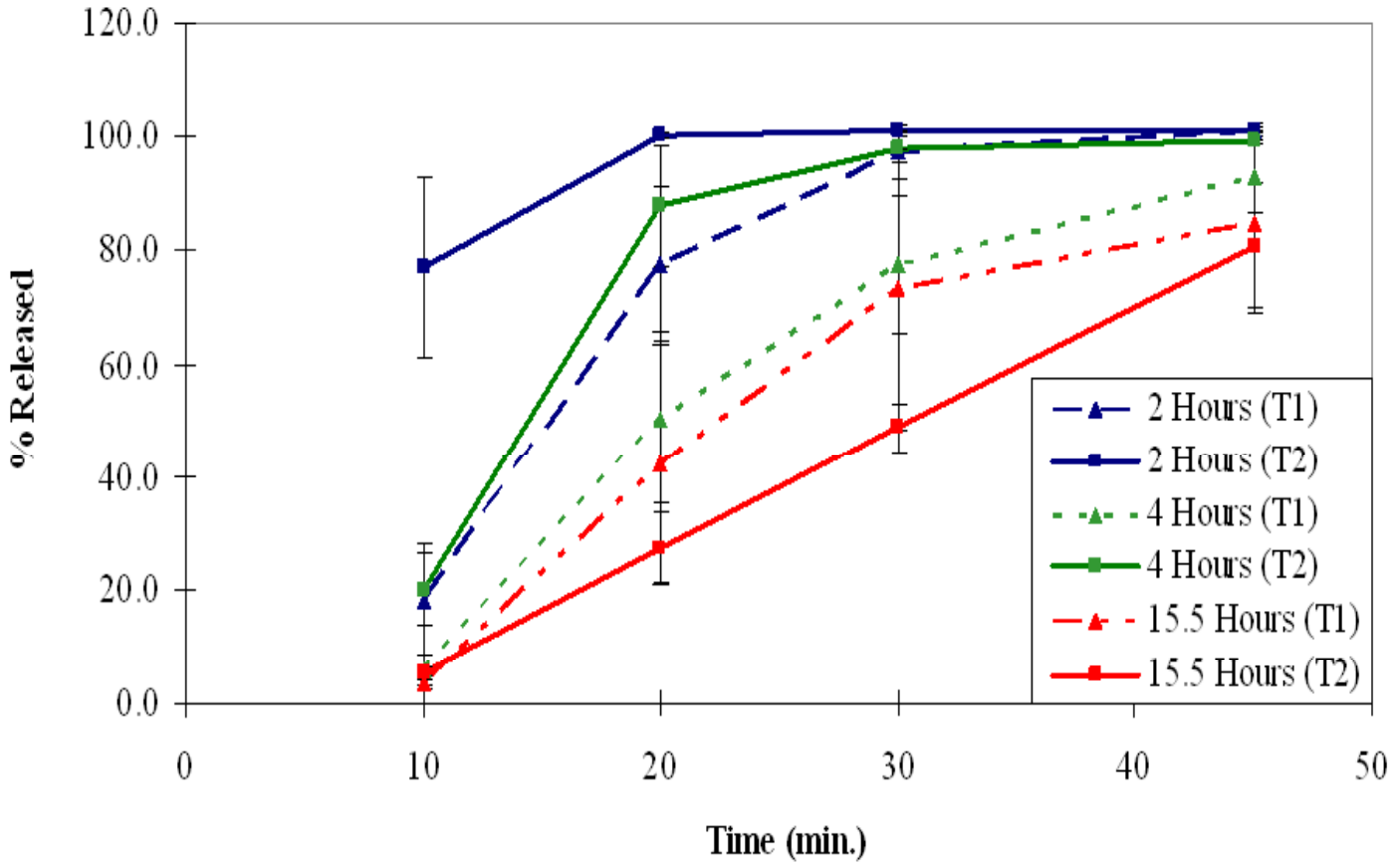
Current <711>

- For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the Dissolution specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the Medium in the individual monograph, the same Medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

Dissolution Testing with and without Pepsin Added



Enzyme Function Depends on the Degree of Cross-linking

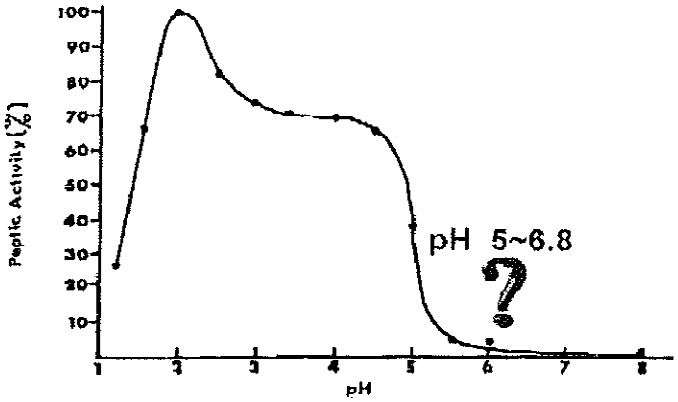


Courtesy of Dr. Jian-Hwa Han, Abbvie Inc

Enzyme Pepsin Behavior at Different pHs

Pepsin and Pancreatin Activity as a Function of pH

Pepsin



Ref: D.W. Piper and B.H. Fenton, "pH Stability and Activity Curves of Pepsin with Special Reference to Their Clinical Importance", *Gut (6)*: 506-508, 1965

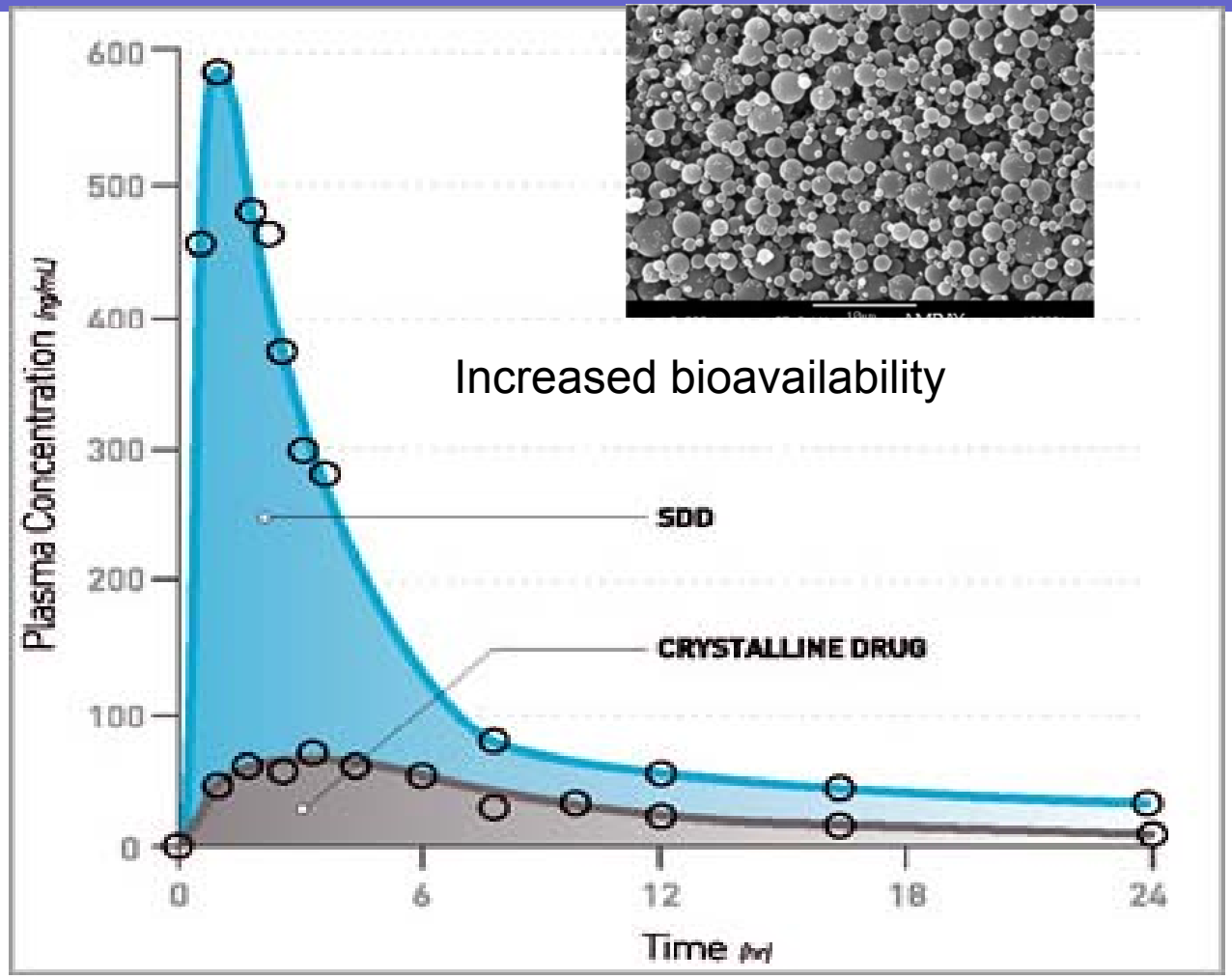
Pancreatin contains many enzymes, including trypsin, amylase, lipase, and protease.

Enzyme	pH Optimum
Lipase (pancreas)	8.0
Trypsin	7.8 ~ 8.7
Amylase (pancreas)	6.7 - 7.0

Suggestions for QC Dissolution Testing

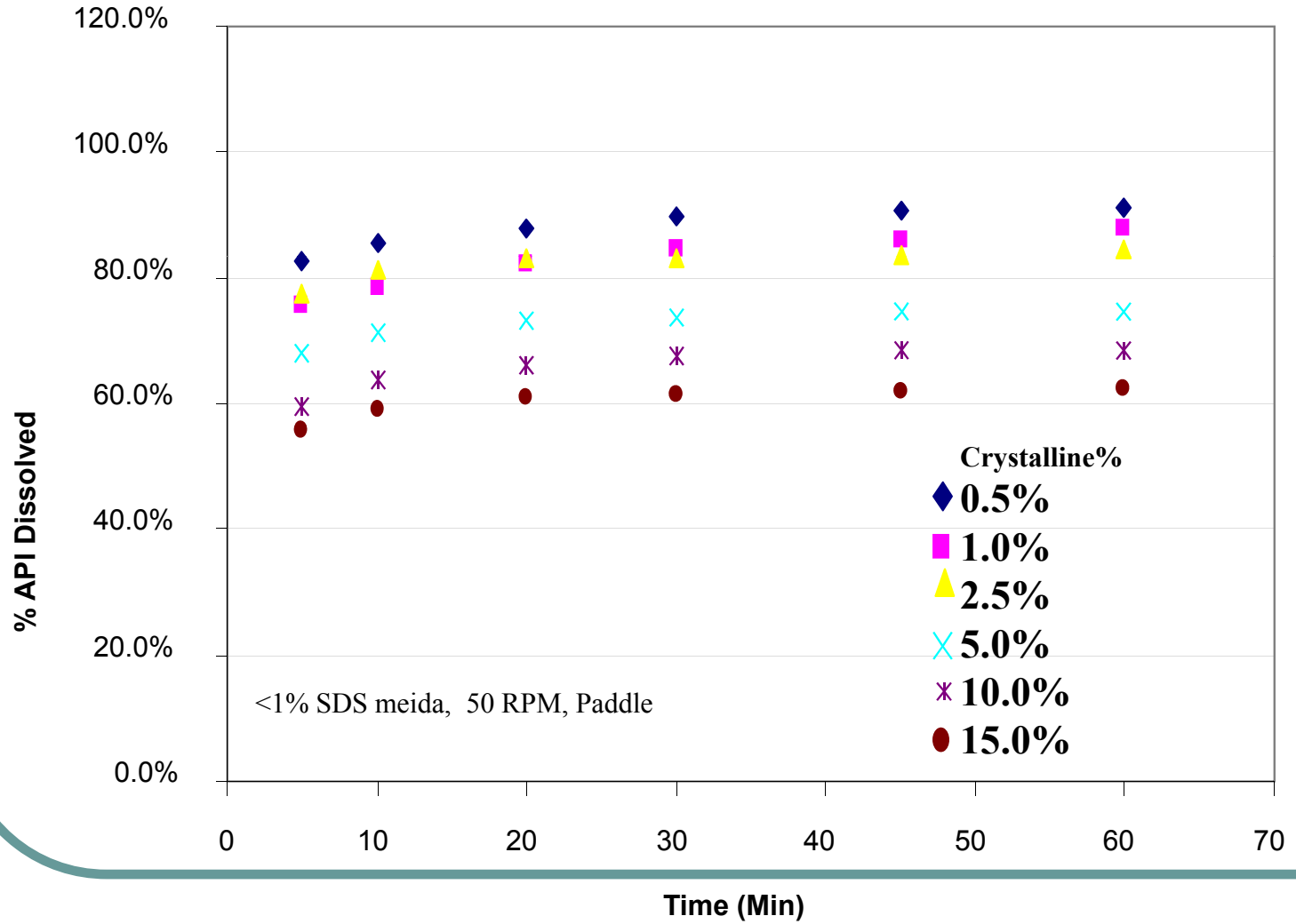
- Tier1:
  - Use the current dissolution method as is
  - Continue to stages 2 and 3 testing if failing stage 1 test due to cross linking.
- Tier 2
  - If fails Tier 1, then go to Tier 2 test by adding enzymes to remove cross linking.
- If stability at previous time has already failed, go to Tier 2 directly.

Crystalline Formation from Amorphous Spray Dispersion

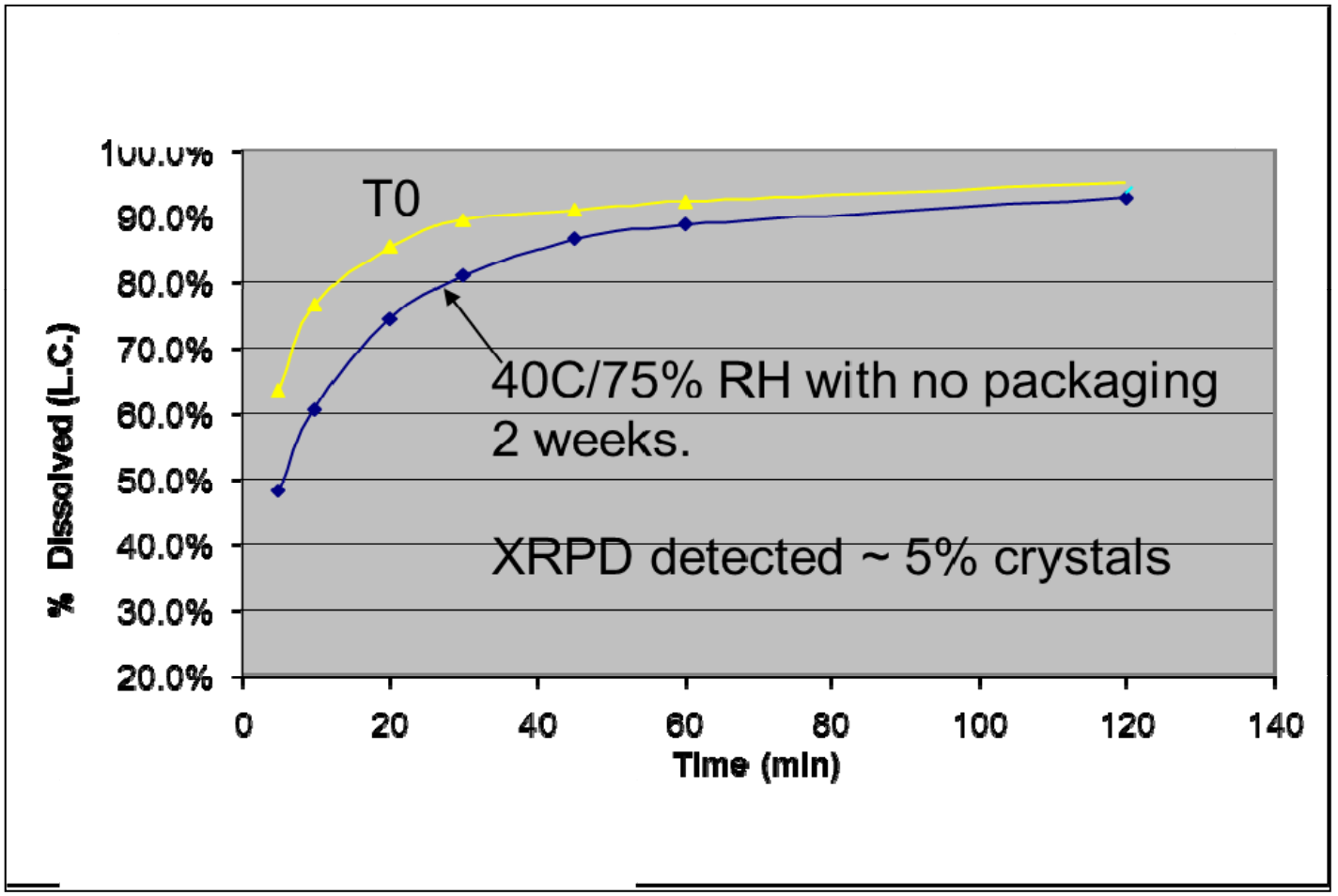


Increased bioavailability

A Discrimination Dissolution Method :Detect Crystalline Polymorphs at ~5%



Tablet Dissolution Change due to Amorphous Crystalline Conversion



Outline for Case Studies

Drug Product

- Drug load
- Particle size
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Dissolution Method

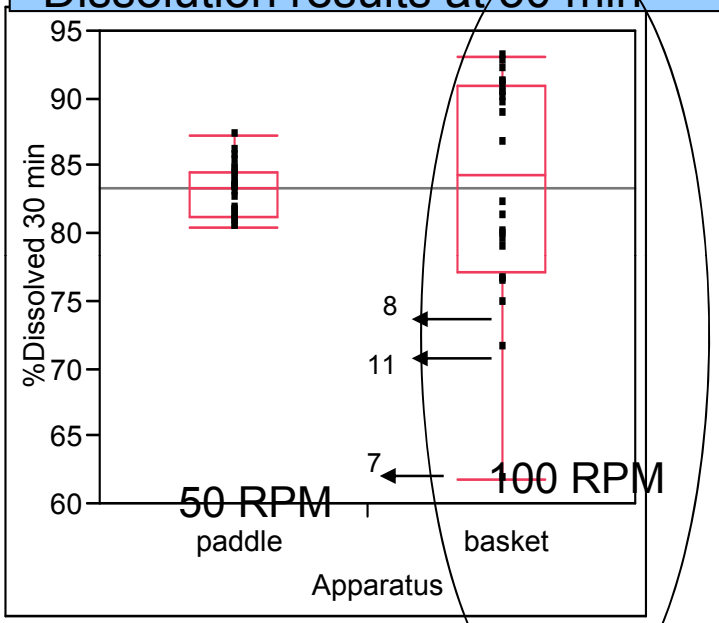
- Coning and gelling
- Agitation speed
- Sinker
- Buffer (composition and pH)
- Deaeration
- Surfactant amount and type

Coning or Gelling During Dissolution

- Formulation dependent
- Method dependent
- Two are intertwined
- Investigation can result in a leading cause depending on which factor is dominant

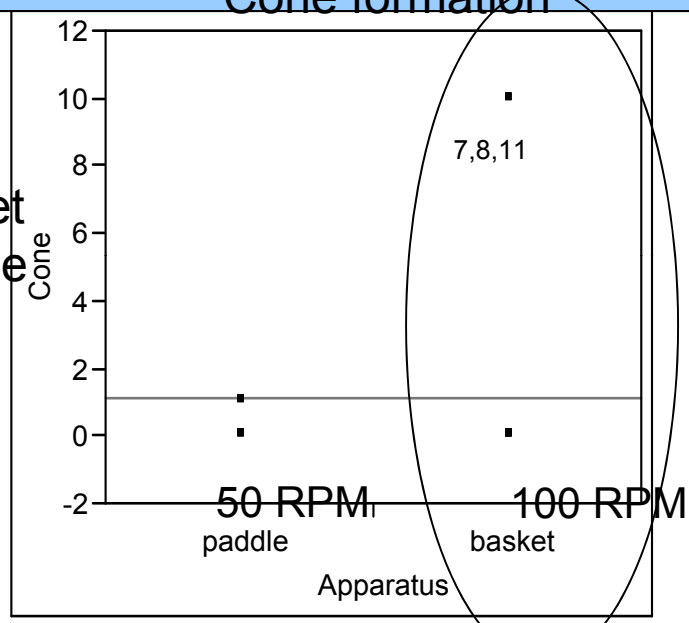
Coning: Method Dependent
Changing Apparatus is Important

Dissolution results at 30 min



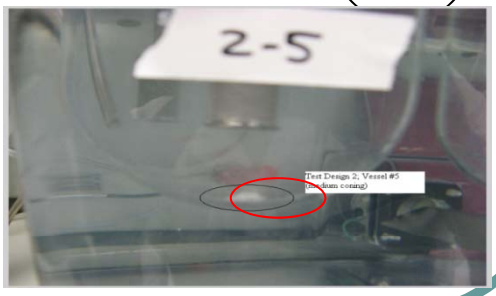
USP I: Basket
USP II Paddle

Cone formation



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
paddle	80.5	80.7	81.275	83.35	84.525	85.9	87.2
basket	61.8	73.1	77.1	84.4	90.85	92.4	93.1

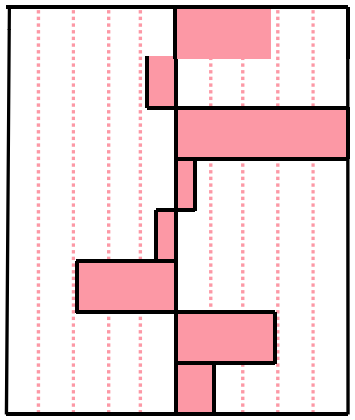


Use Statistical Design to Examine Method Robustness

Scaled Estimates

Nominal factors expanded to all levels

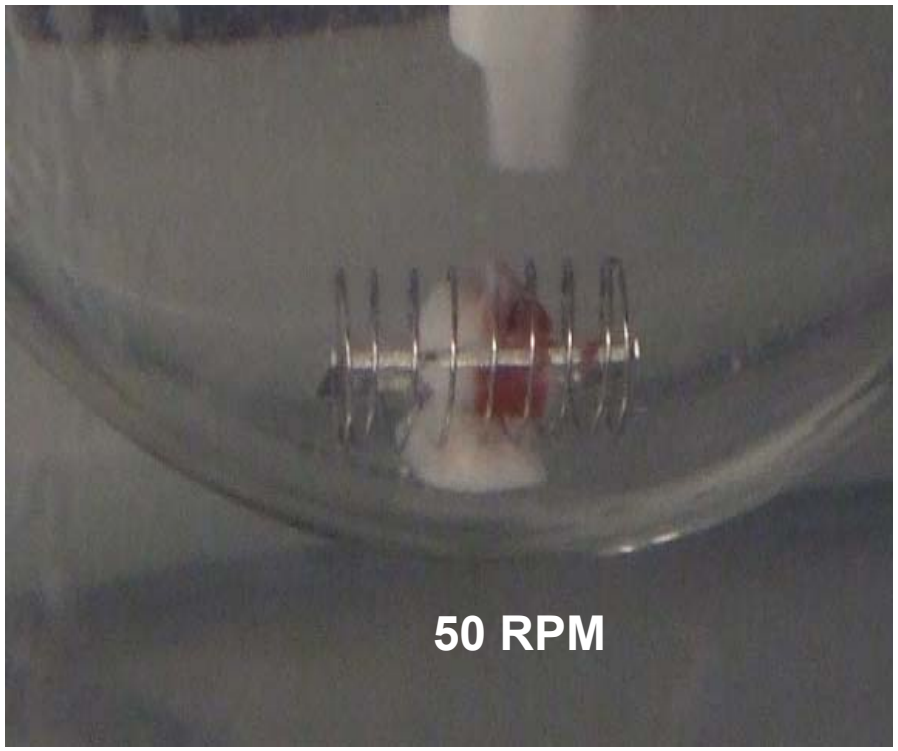
Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	83.6	0.366125	228.34	<.0001*
Height(20,30)	-0.714583	0.391404	-1.83	0.0735
SLS(0.5,0.7)	4.2520833	0.391404	10.86	<.0001*
Air[yes]	0.5125	0.366125	1.40	0.1674
Air[no]	-0.5125	0.366125	-1.40	0.1674
Speed[low]	-2.4875	0.366125	-6.79	<.0001*
Speed[high]	2.4875	0.366125	6.79	<.0001*
Temp(35,39)	0.96875	0.391404	2.48	0.0166*



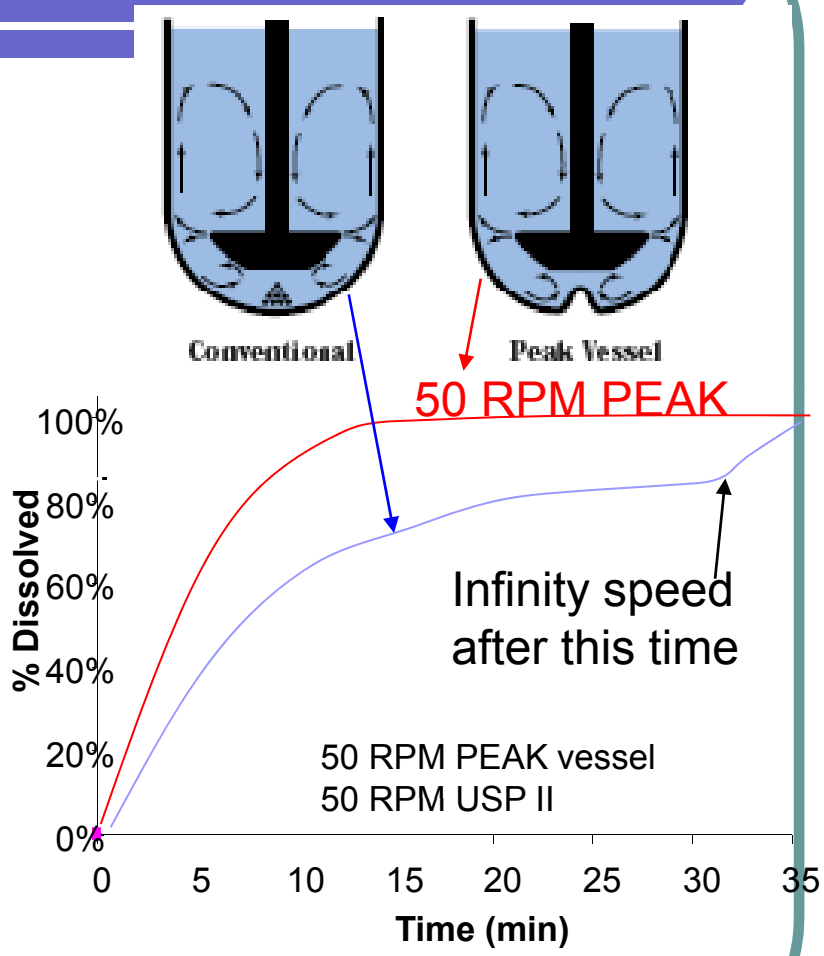
Ranking of Impact on Method Robustness

amount of surfactant > agitation speed > temperature

Coning - Formulation and Method

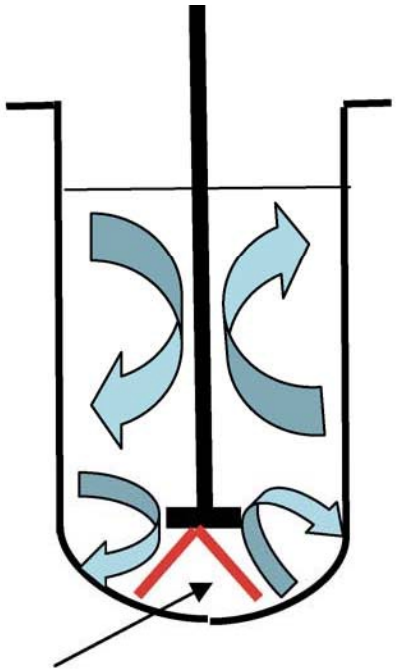


Heavy insoluble excipients causing coning
Changing method speed is important

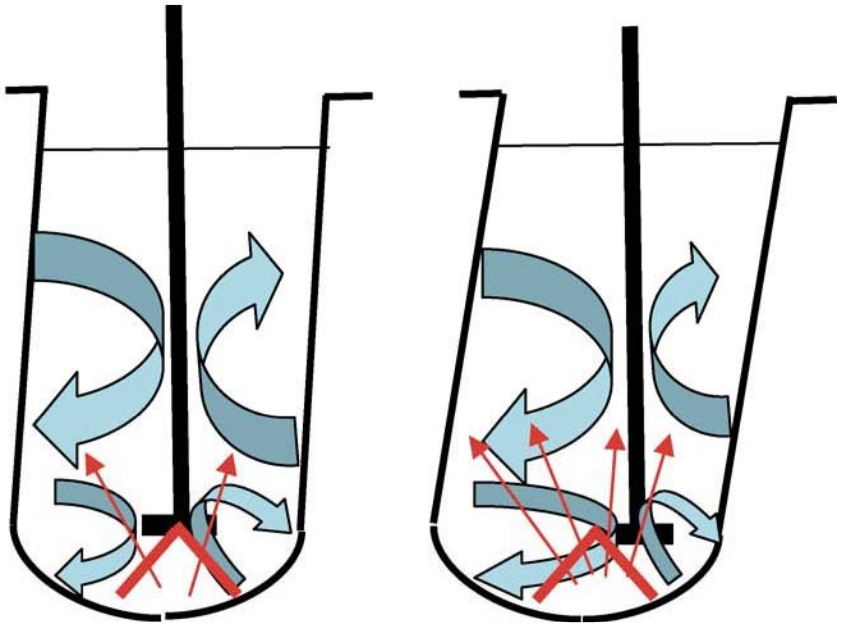


Data extrapolated from
real exptl data

Schematic of the Perturbation Study Demonstrating the Existence of a Dead Zone at the Bottom of the USP Vessel



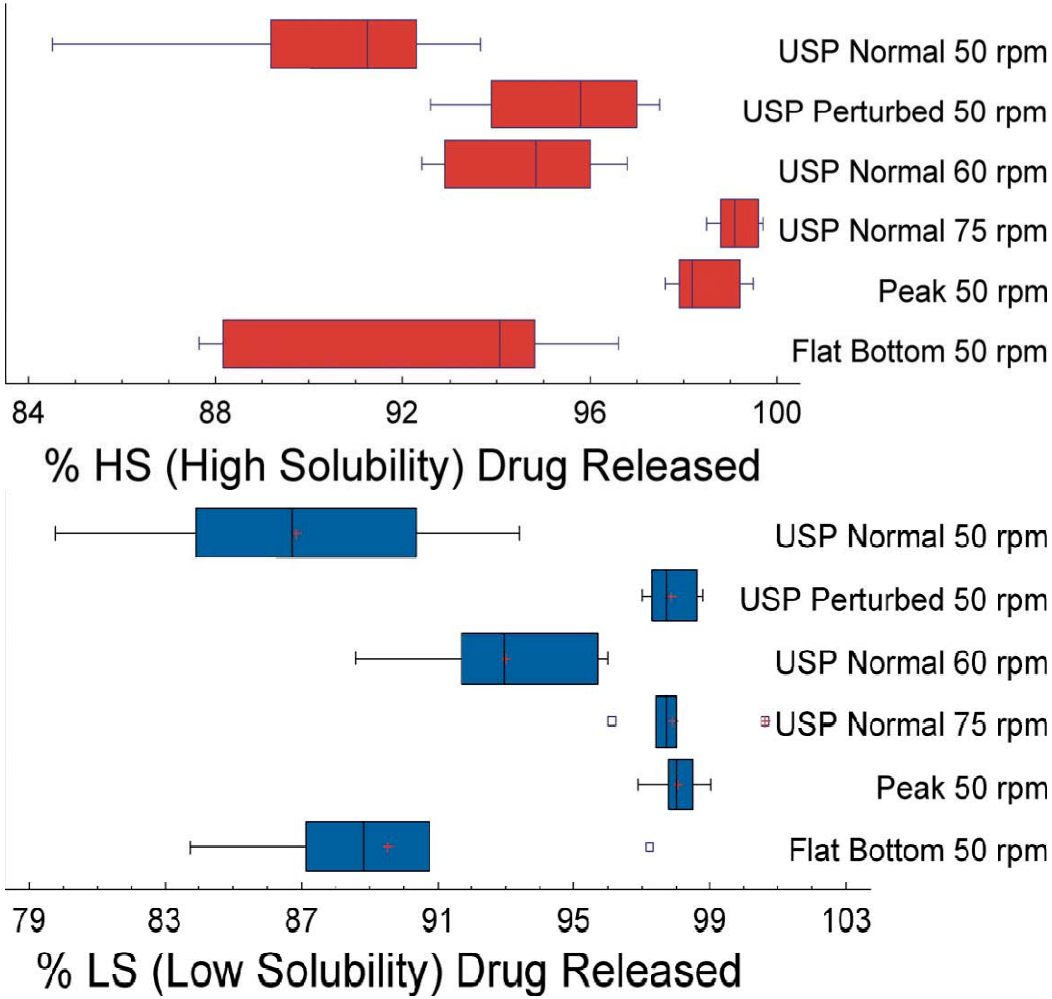
A 'cone' of disintegrated mass forms in the 'dead zone' trapping the drug particles



As the vessel is progressively tilted while keeping the paddle straight, the 'dead zone' experiences increasing agitation causing the 'cone' to disperse. The trapped drug is released and goes into solution.

Tahseen Mirza, et al, Dissolution Technology, *FEBRUARY 2005, 11-16.*

Dissolution Rate Comparison

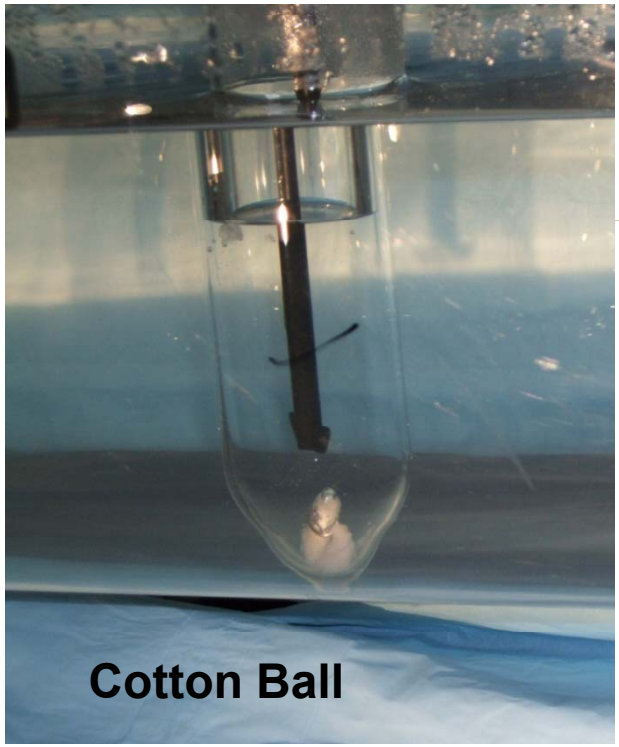


Tahseen Mirza, et al, Dissolution Technology, *FEBRUARY 2005, 11-16.*

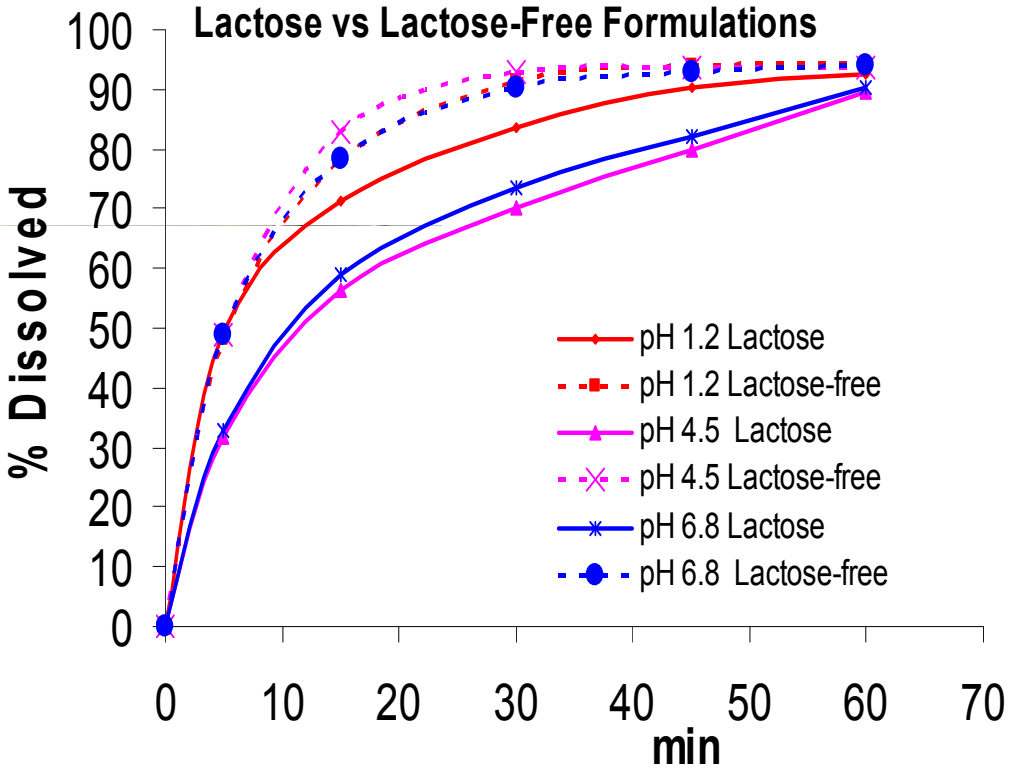
Gelling

- Usually is formulation dependent
- Selection of apparatus is important
- Apparatus I (rotating basket) issues
  - Granules get caught inside the basket
  - Formulation gels up and get caught inside the basket

Lactose Gelling Effect



100 RPM Basket



Examples of Sinkers

3-prone

O-Ring Style Sinker, 316 SS

Spiral Capsule Sinker, Coated Music Wire, 1.10" L x .41" W capacity, 6.5 coils

Spiral Capsule Sinker, 316 SS, .84" L x .385" W capacity, 5 coils

CAPWHT-Breath Film cSinker, PC 316 SS

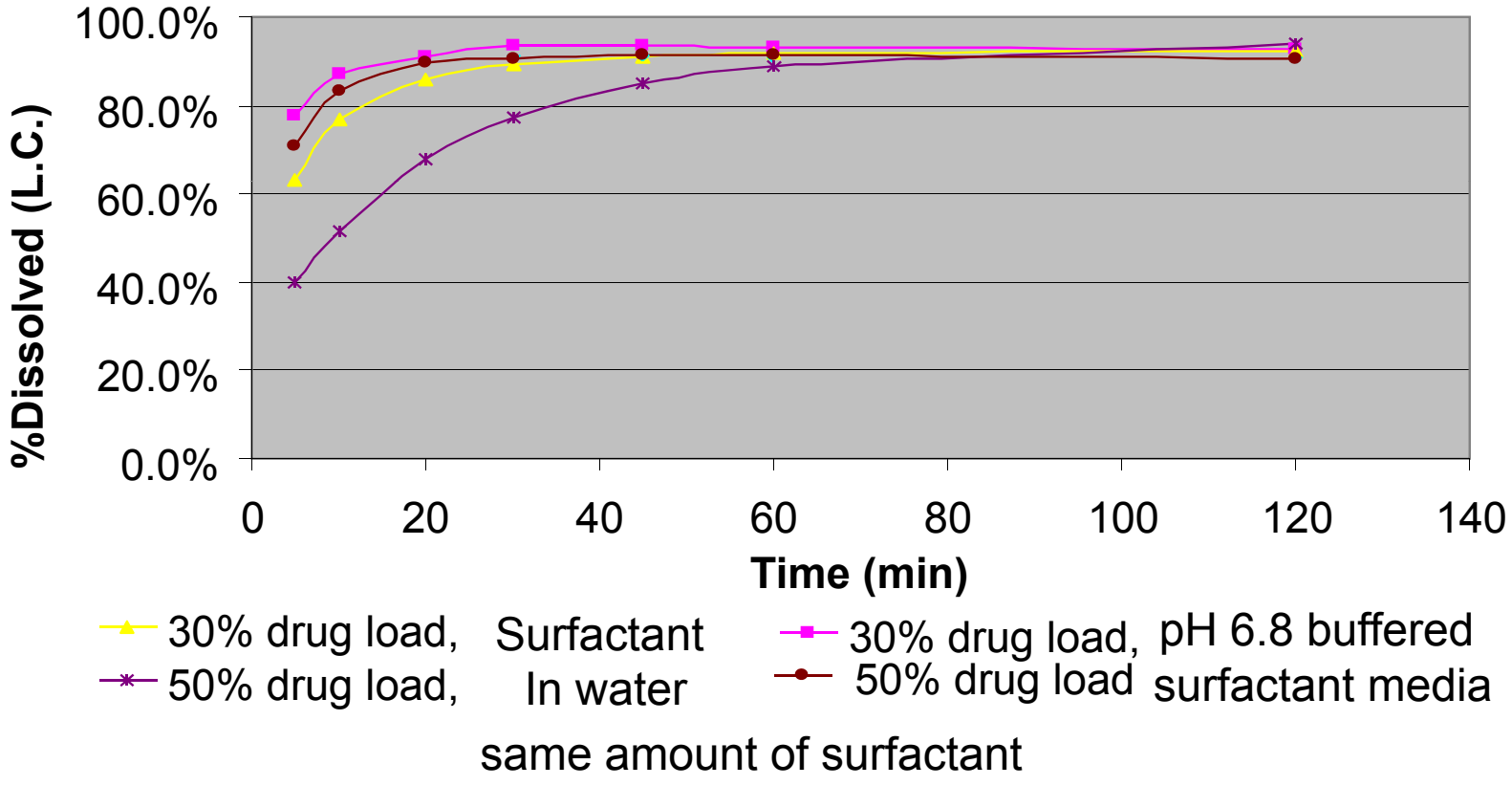
8 Mesh Basket Sinker, .90" L x .51" W capacity

8 Mesh Basket Sinker, 1.06" L x .62" W capacity

Same Type of Sinker but Fit Differently Can Results in Different Dissolution Results

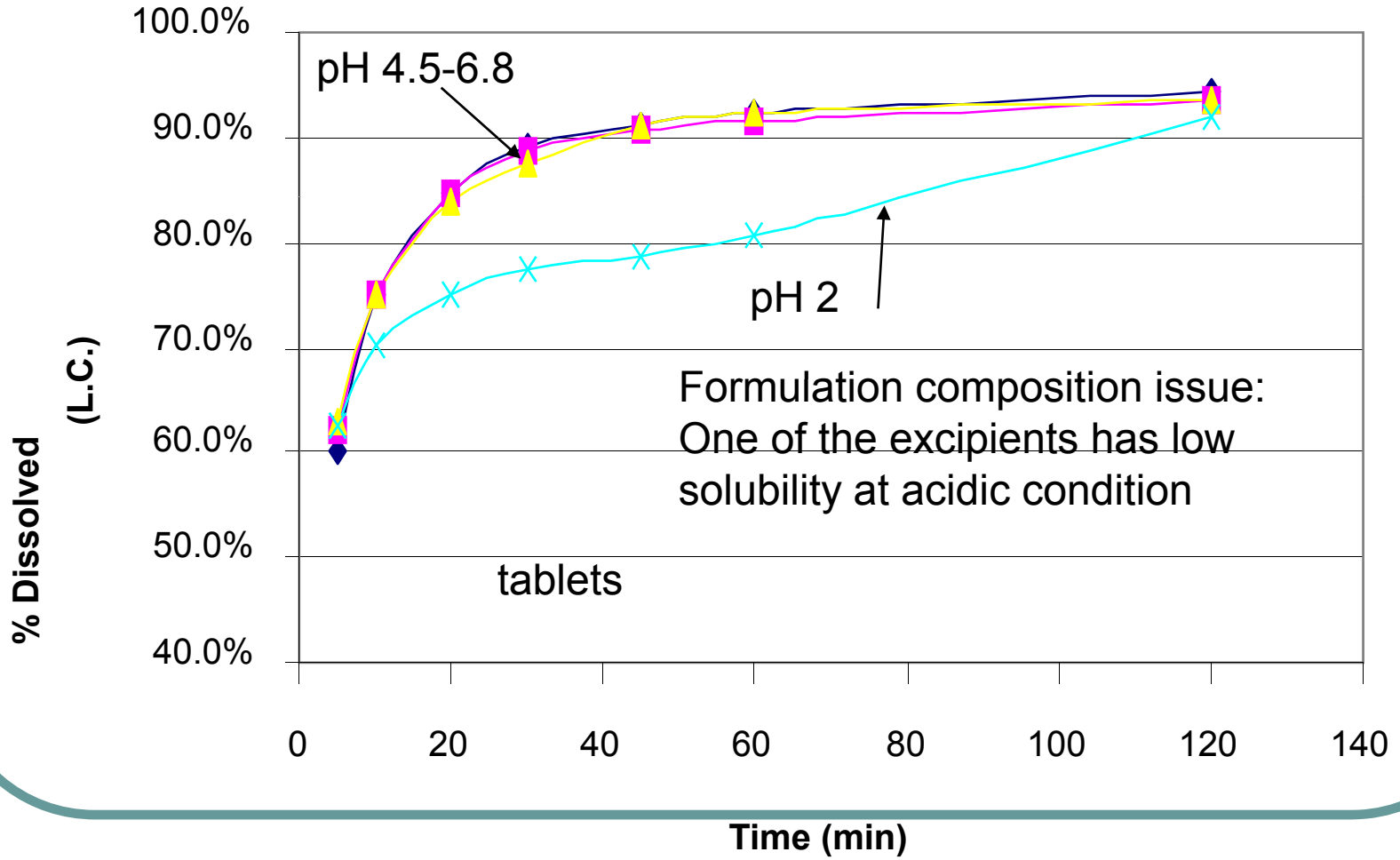
Buffer Effect : Formulation Change Requires a Correct Method to Detect Difference

Buffered pH with surfactant removed the dissolution differentiation power

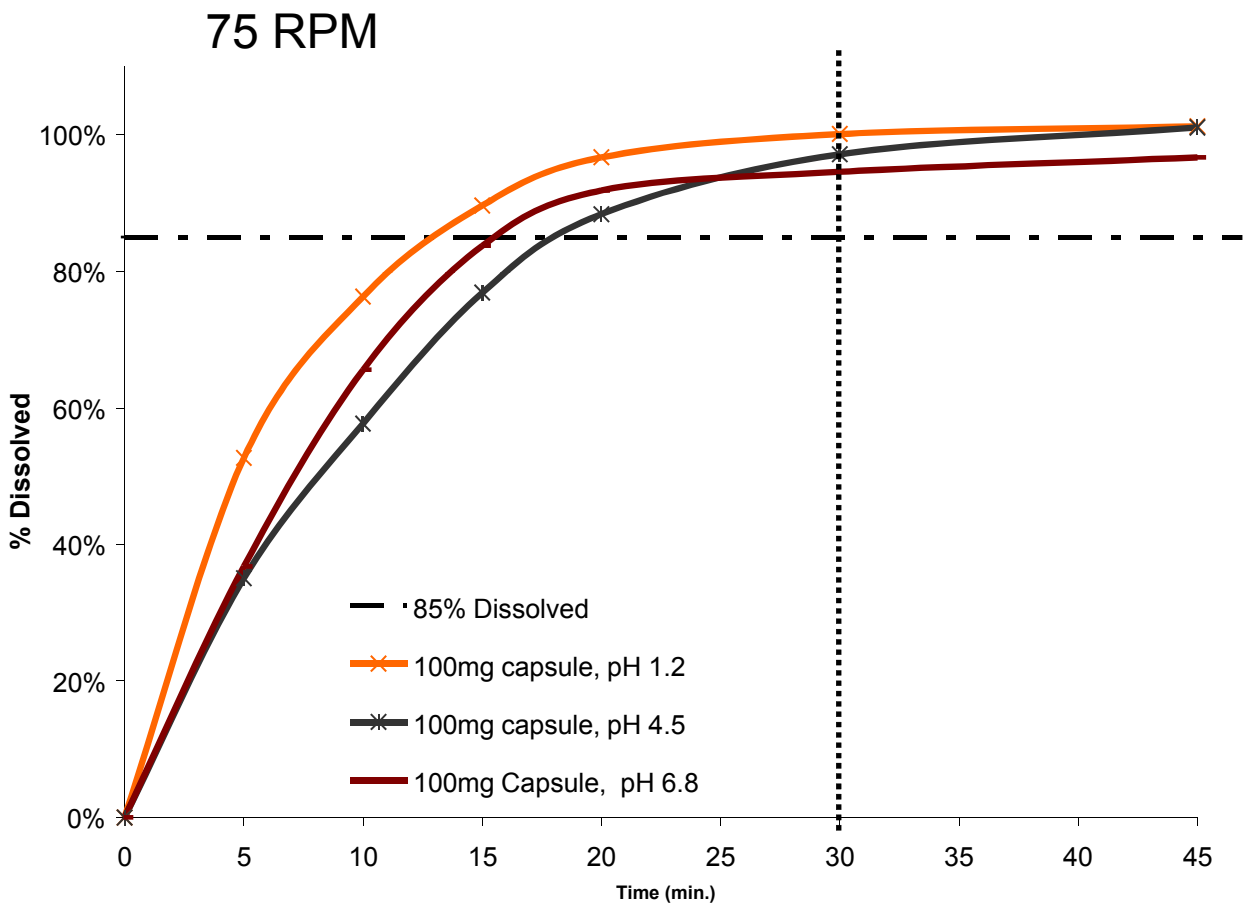


pH Effect: Same Drug in Different pH Dissolution Media

Understand the Property of Each Component in Formulation



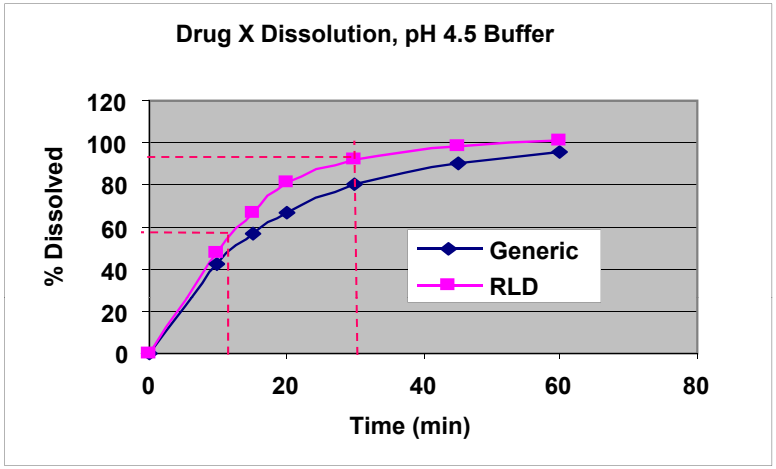
Dissolution of a BCS I Compound, Gelatin Capsule at pH 1.2, 4.5, and 6.8

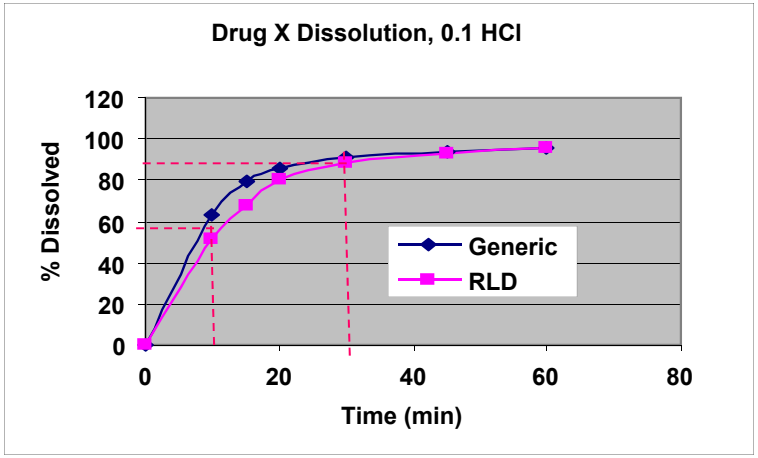


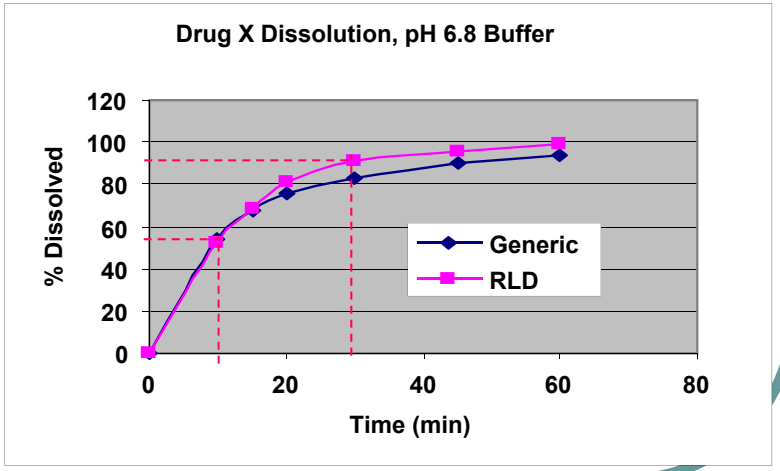
Tablet Example: No Dissolution Difference at pH 1.0, 4.5, and 6.8

Robert Lionberger
Office of Generic Drugs, FDA
ACPS-CP Meeting
July 23, 2008

Drug X; Highly soluble, IR tablet
The test and reference list drug products have the same formulations, qualitatively and quantitatively







Bubbles in Dissolution Medium

Variability in Dissolution Data

To eliminate this source of variability, the dissolution medium should be *degassed* or *deaerated*.

Guidance for Industry

The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (cGMP)

USP <711>

Bubble and coning 1

CLIP1584.AVI

Bubble and Coning 2

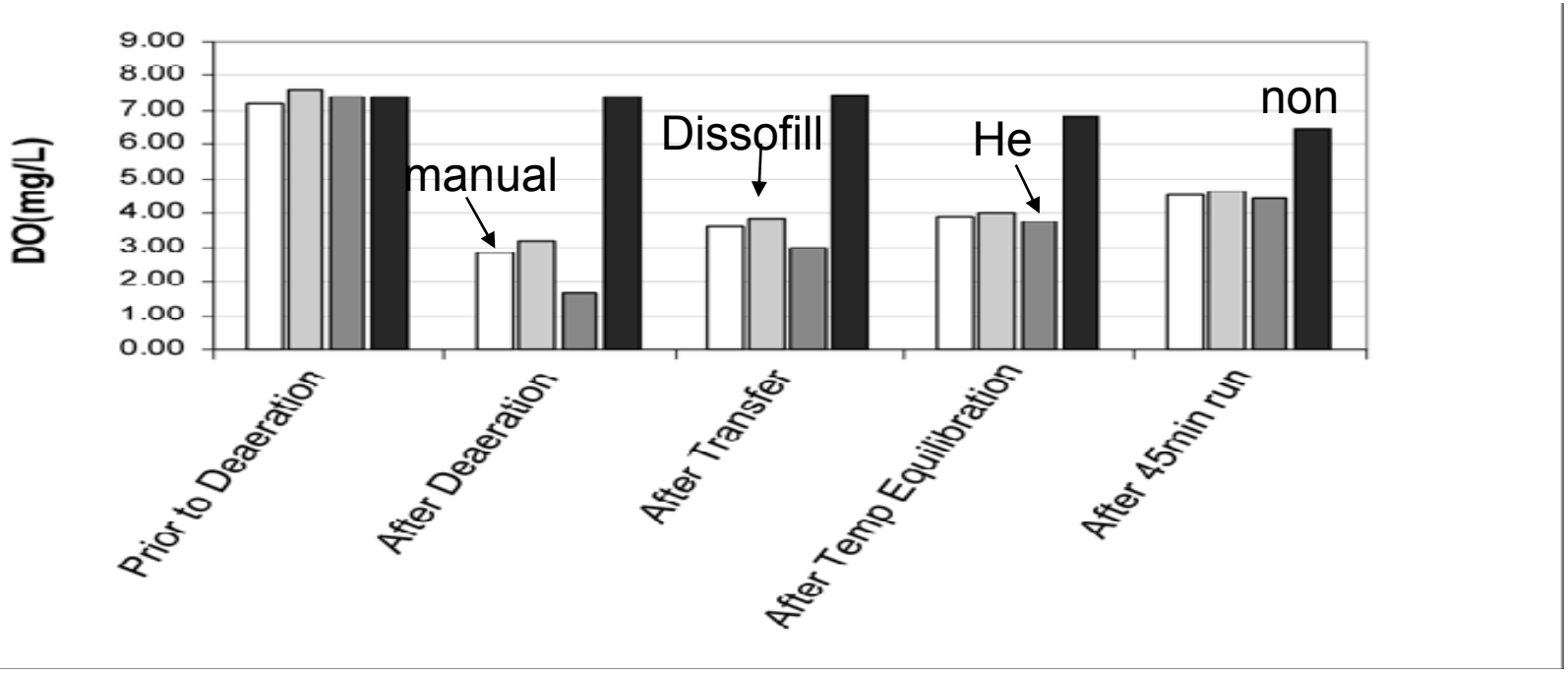
CLIP1582.AVI

Deaerated

Courtesy of Raimer Loebenberg

Deaeration Removes Dissolved Oxygen

- *Dissolution* <711> suggests heated vacuum filtration as one method of deaeration

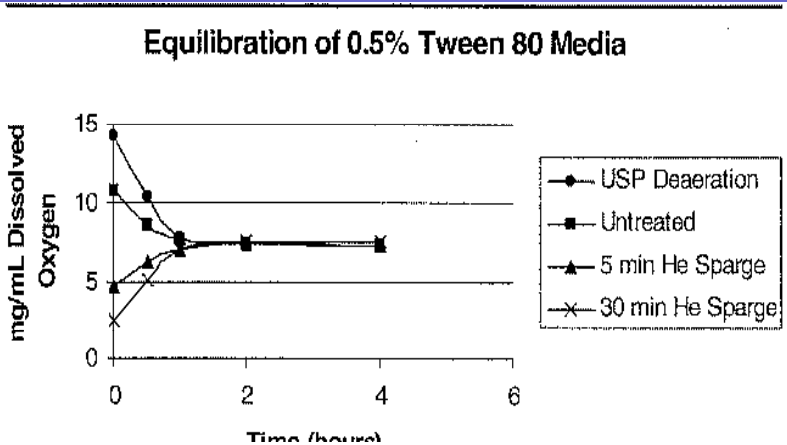


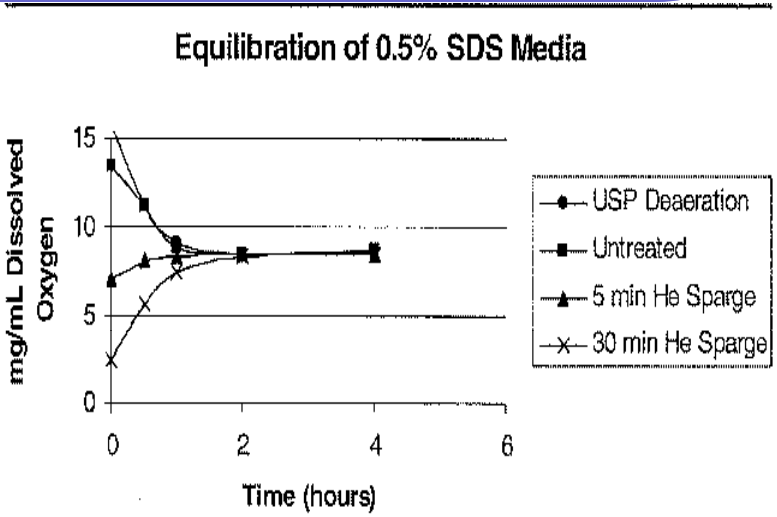
Levels of dissolved oxygen remaining after various stages of a dissolution run using (1) Manual vacuum filtration, (2) Dissofill automated filtration (3) Helium sparging, and (4) Non-deaerated media.

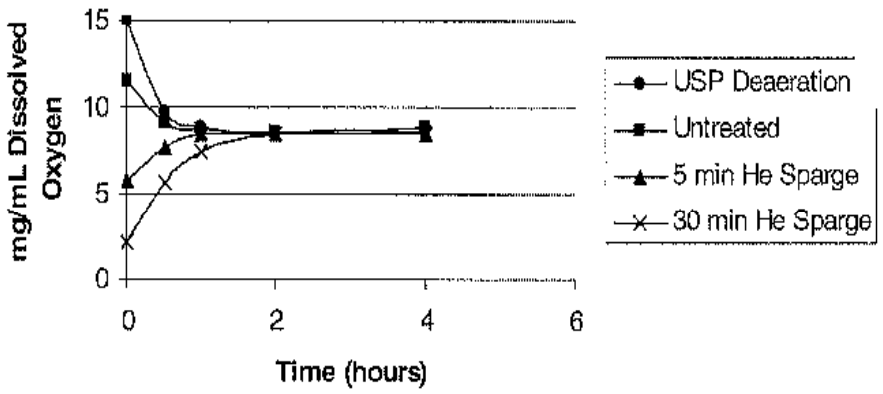
From left to right

Owen S. Degenhardt et al., Dissolution Technology, FEBRUARY 2004, 6-11

Degasing and Reaeration for a Surfactant-containing Dissolution Medium



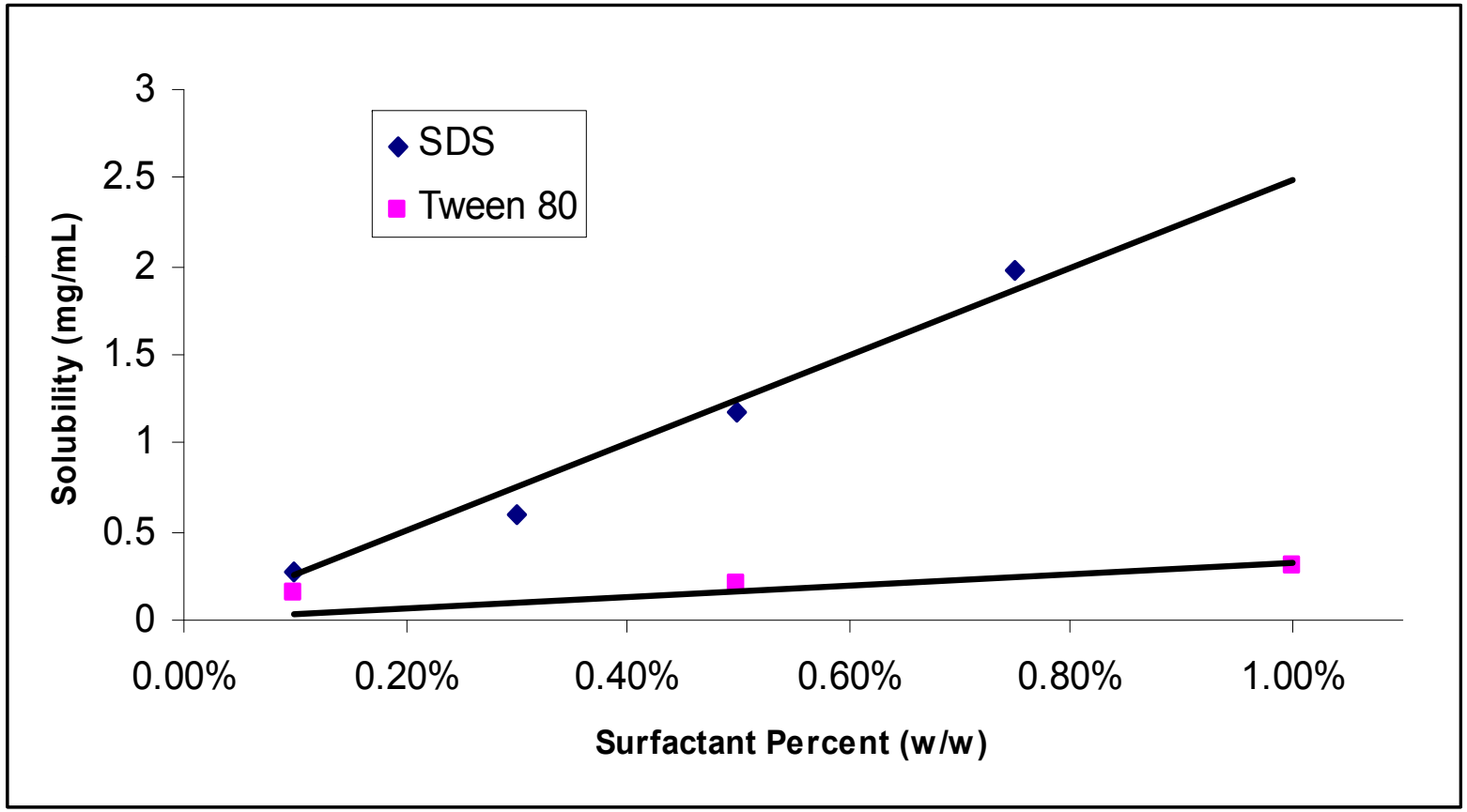




For method validation and transfer, equilibrate the media before test is recommended.

Fliszar, KA, Forsyth, RJ, Li, Z, Martin, GP., Dissolution Technology, Aug, 2005

Drug Solubility vs Surfactant Concentration



Solubility of Griseofulvin with and without Different Surfactants

Surfactant	Surfactant Concentration (mM)	Griseofulvin Solubility (mM)	f_f	f_m	n
No surfactant	—	0.0350 (±0.0001)	1.000	0.000	—
SDS	10	0.657 (±0.017)	0.053 (±0.001)	0.947 (±0.001)	3.30 (±0.09)
	20	1.367 (±0.016)	0.025 (±0.000)	0.975 (±0.000)	
	40	2.452 (±0.217)	0.014 (±0.001)	0.986 (±0.001)	
	60	3.759 (±0.223)	0.009 (±0.000)	0.991 (±0.000)	
CTAB	6.67	0.403 (±0.007)	0.086 (±0.001)	0.914 (±0.001)	3.56 (±0.12)
	13.32	0.717 (±0.016)	0.048 (±0.001)	0.952 (±0.001)	
	20	1.088 (±0.041)	0.032 (±0.001)	0.968 (±0.001)	
Tween 80	1.53	0.069 (±0.0012)	0.502 (±0.009)	0.498 (±0.009)	0.584 (±0.026)
	3.82	0.097 (±0.0001)	0.358 (±0.003)	0.642 (±0.003)	
	7.63	0.131 (±0.0005)	0.264 (±0.006)	0.736 (±0.006)	
Cremophor EL	0.80	0.052 (±0.0002)	0.654 (±0.017)	0.346 (±0.017)	3.84 (±0.04)
	1.99	0.085 (±0.0005)	0.406 (±0.015)	0.594 (±0.015)	
	3.98	0.109 (±0.0003)	0.317 (±0.005)	0.683 (±0.005)	

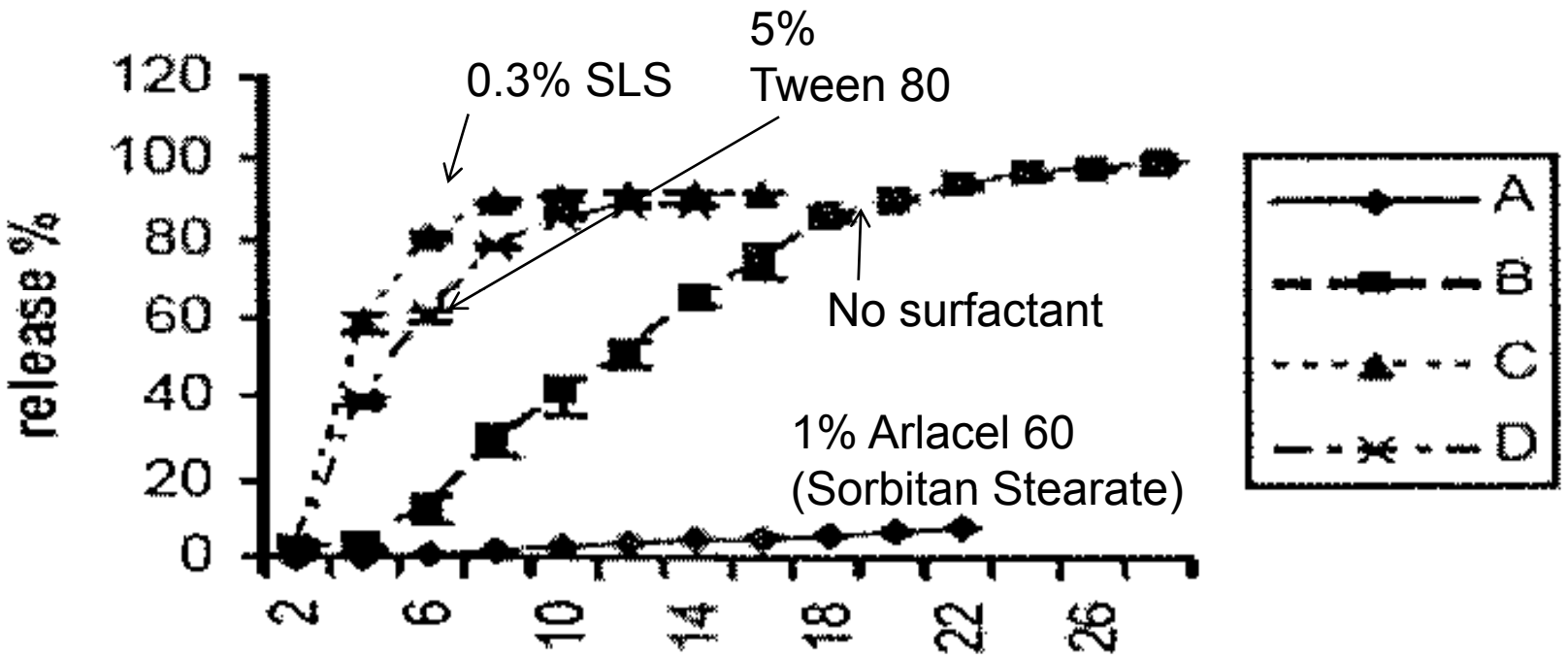
A linear increase in griseofulvin solubility was observed with increasing surfactant concentration. Resulting values for f_f, f_m, and n are also tabulated.

F_f: drug molecules that are free in solution
F_m: drug molecules that are micelle-incorporated
n: number of drug molecules per micelle

Aggregation Weight, g/mol of micelles
SDS< CTAB<Tween 80< Cremophor EL

Balakrishnan, A, Rege, B.D., Amidon, G.L., Polli, J.E., J. Pharm. Sci., 2004, 93, 2064.

Effect of Different Surfactants on Dissolution



Honary, S., Majidian, A., Naghibi, F., Iranian J. Pharm. Res. (2007), 6, 25-33

Conclusion

- Dissolution results changes or failures can be caused by many factors
- Need to investigate the root cause:
  - Drug product
  - Excipients
  - Process
  - Dissolution method
- General guideline for dissolution trouble shooting
  - Failure mode effect analysis (FMEA) for root cause analysis
  - Use statistical software to perform DOE and data analysis
  - Identify leading factors that contribute to the method robustness

Thank You

Any Questions ?