The role of biopredictive dissolution method in the selection of CMA, CPPs, and verification of design space (s) - Case Studies

M-CERSI - Dissolution and Translational Modeling Strategies
Enabling Patient-Centric Product Development
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Outline

- **Objectives**
- **Case Studies**
  1. **Level A IVIVC obtained**
  2. **No IVIVC obtained, but a clinical/PK “safe space” established**
- **Points to consider**
- **Q&A/Discussion**

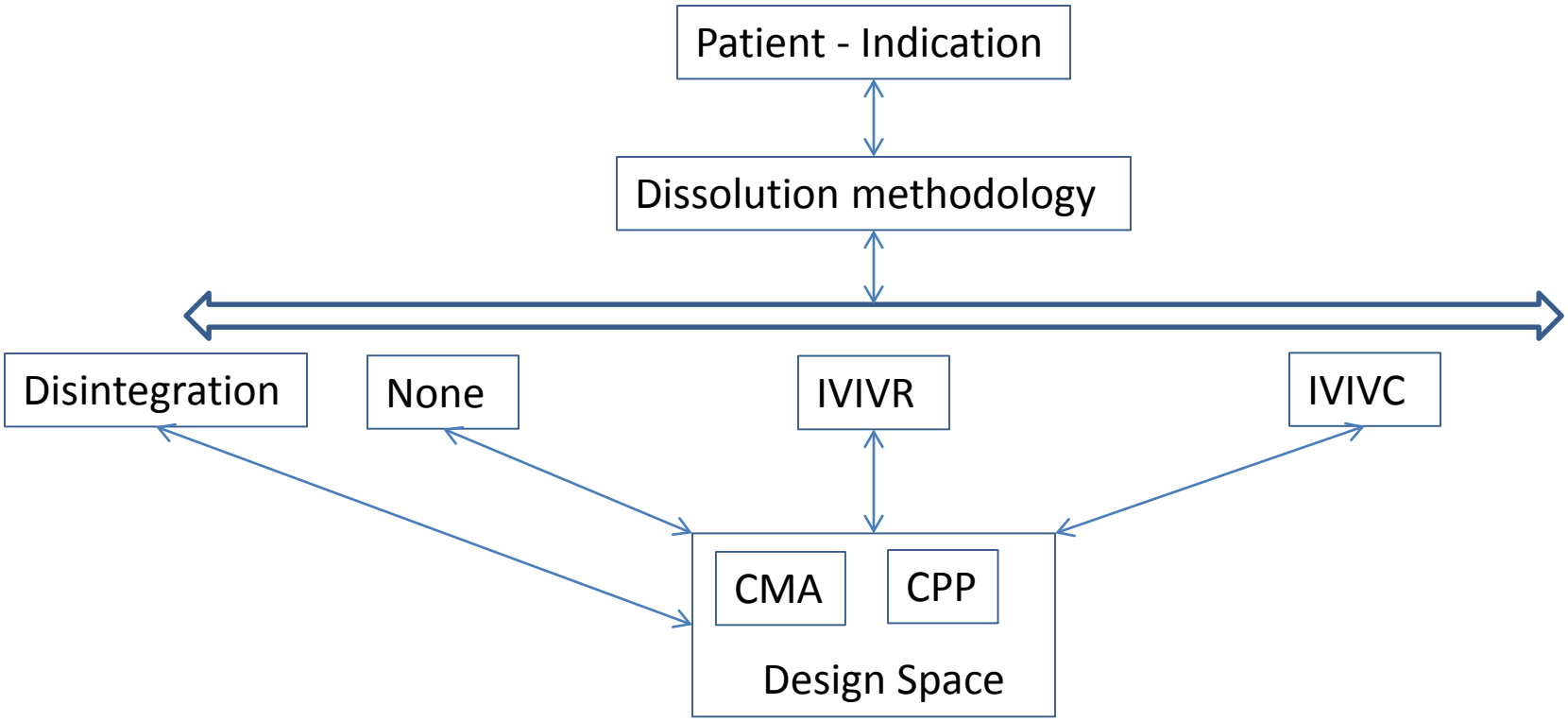
Objectives

- **To highlight two case studies using biopredictive (i.e., clinically relevant) dissolution methodology for design space verification**
  - **Demonstrating that dissolution is a valuable tool for confirming manufacturing consistency**

Why clinically relevant dissolution?

- **The objective of a clinically relevant dissolution method for the selection of CMAs, CPPs, and verification of design space is an obvious extension of the overall goals of Quality by Design, to link the performance of the drug product to patient safety and efficacy, through in-vivo prediction.**
- **In essence, a clinically relevant method, in conjunction with appropriate acceptance criteria, could help confirm the boundaries of the design space, with respect to in-vivo performance**
- **This should remove the need to confirm movements within the design space with in vivo studies**

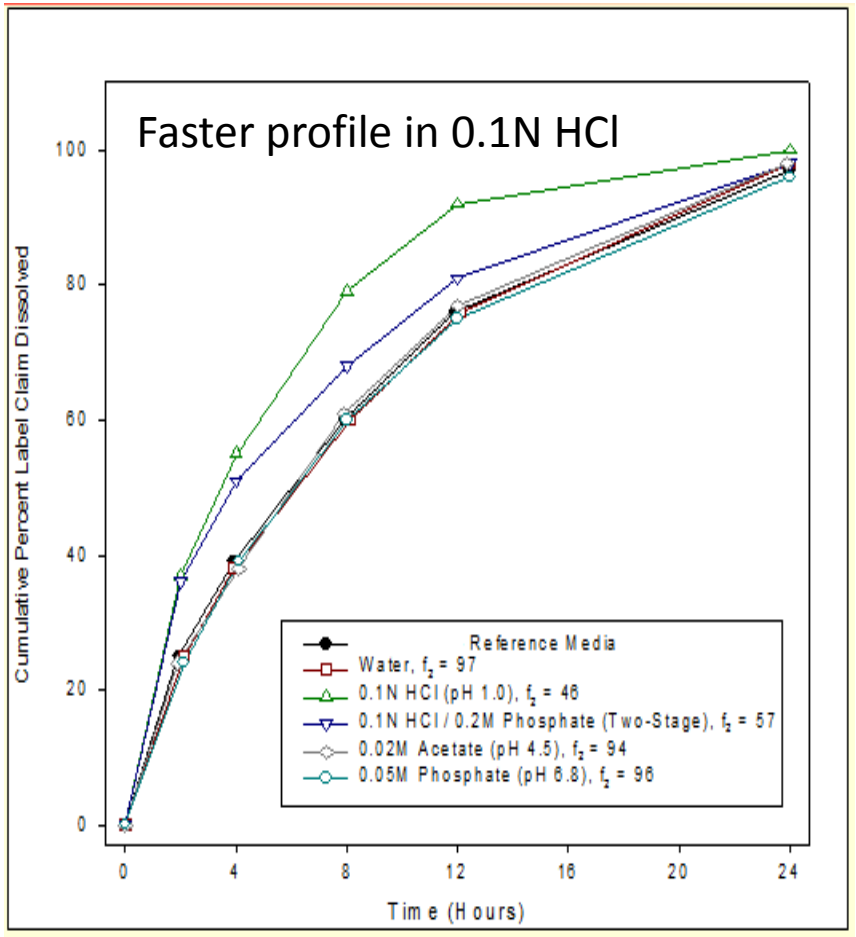
Selection of dissolution methodology

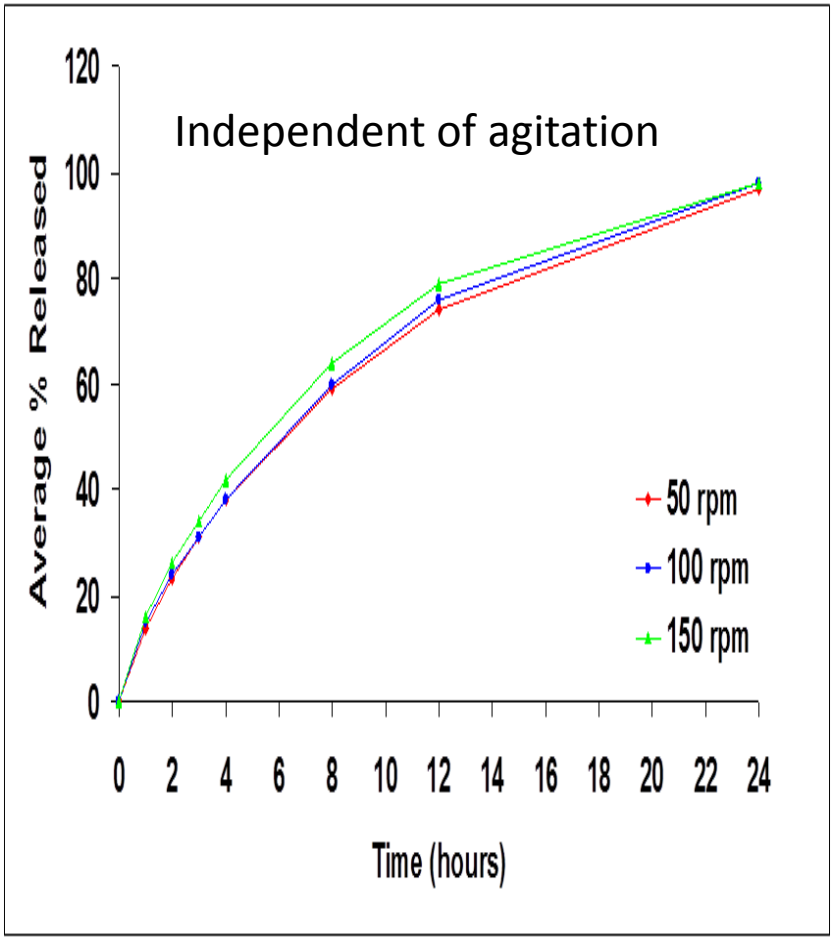


Case Study 1

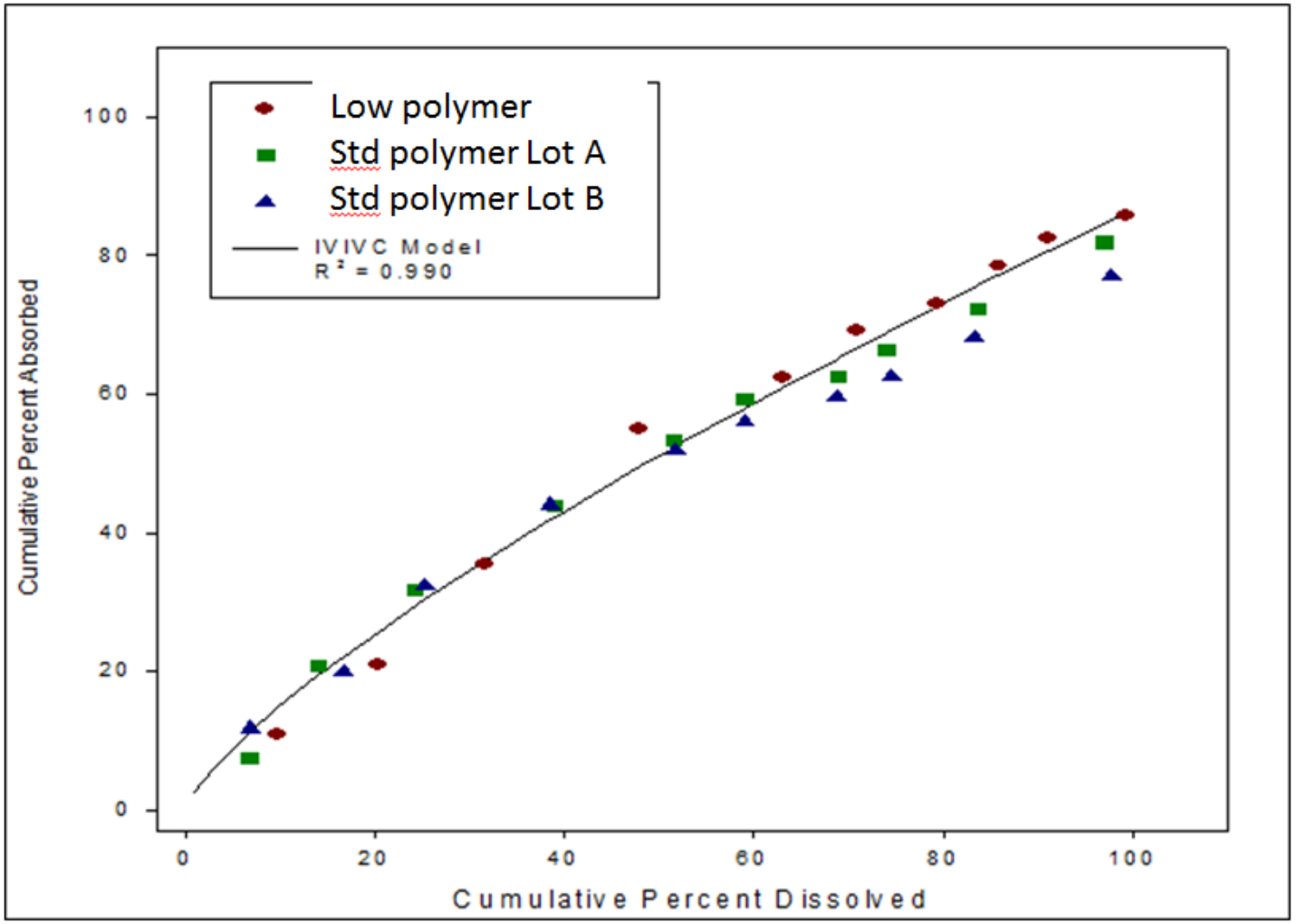
- Weak base, BCS 3 compound
- Moderate dose levels (>10, <1000 mg)
- Polymer matrix sustained release tablet
- Release rate independent of stirring conditions
- Release rate independent of medium except slightly faster in $HCl_{(aq)}$
- Final method USP Apparatus 1 (baskets) at 100 RPM; medium = 900 mL
- Level A IVIVC developed by changing level of rate-controlling polymer
- Successful design space verification was performed using this method
  - Material attributes
  - Processing parameters
  - CPPs
- Conclusion

IVIVC: Dissolution as a function of medium and agitation rate





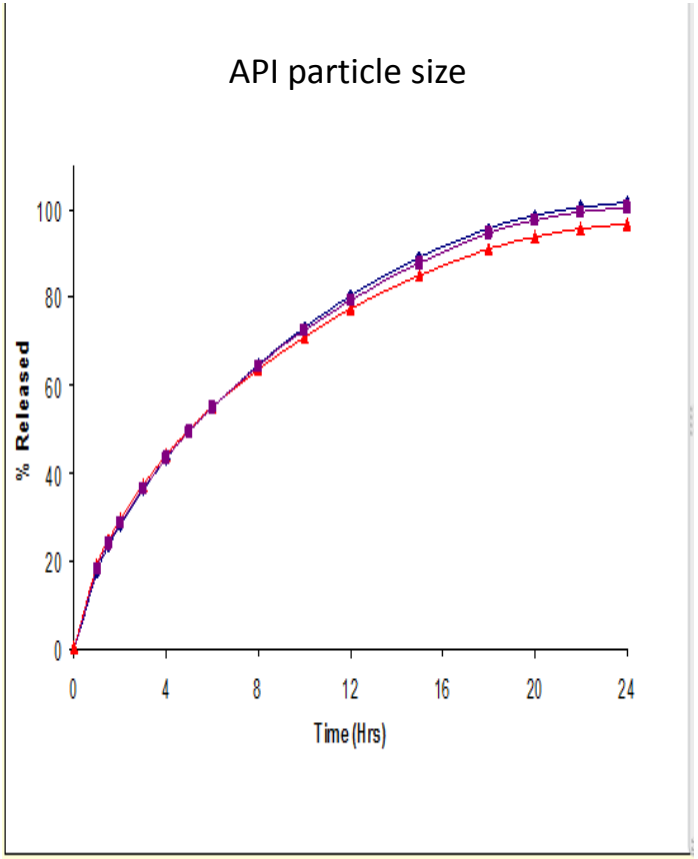
Successful level A IVIVC achieved



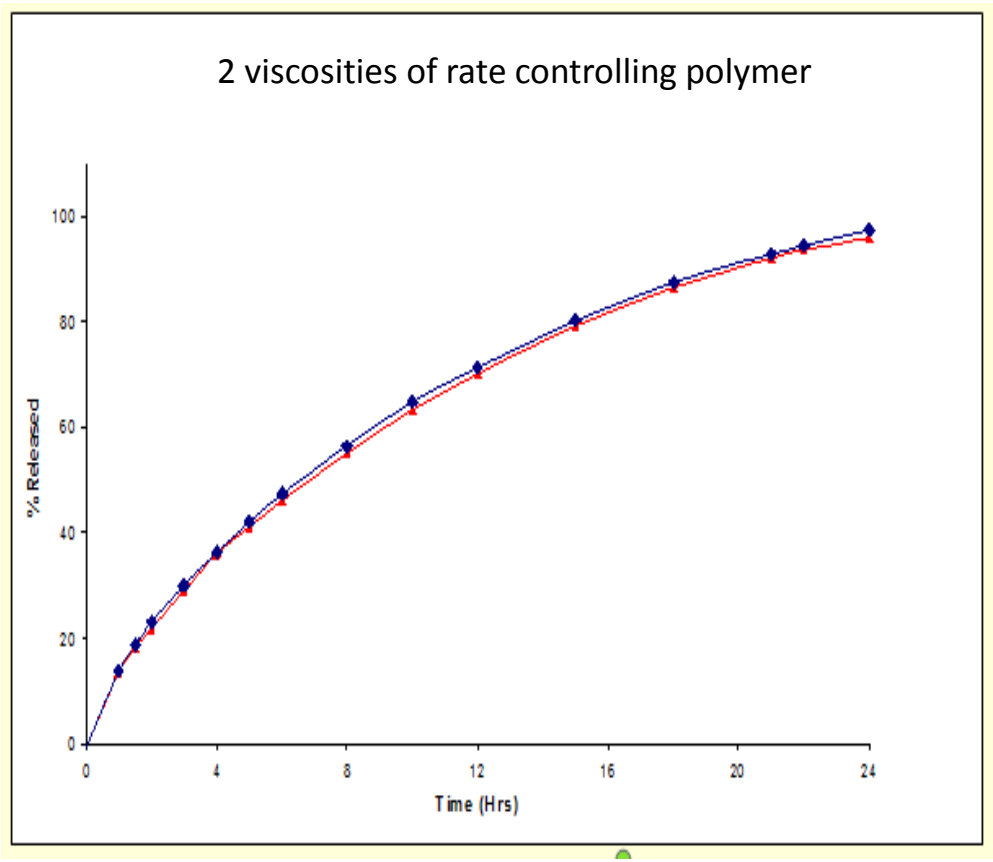
Evaluation of Typical CMAs

- **Dissolution independent of API particle size and polymer viscosity**

API particle size

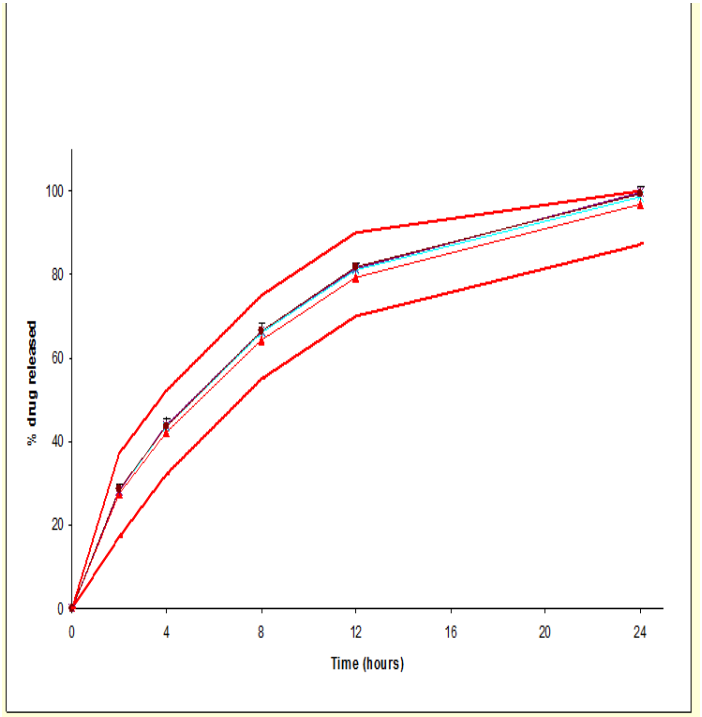


2 viscosities of rate controlling polymer

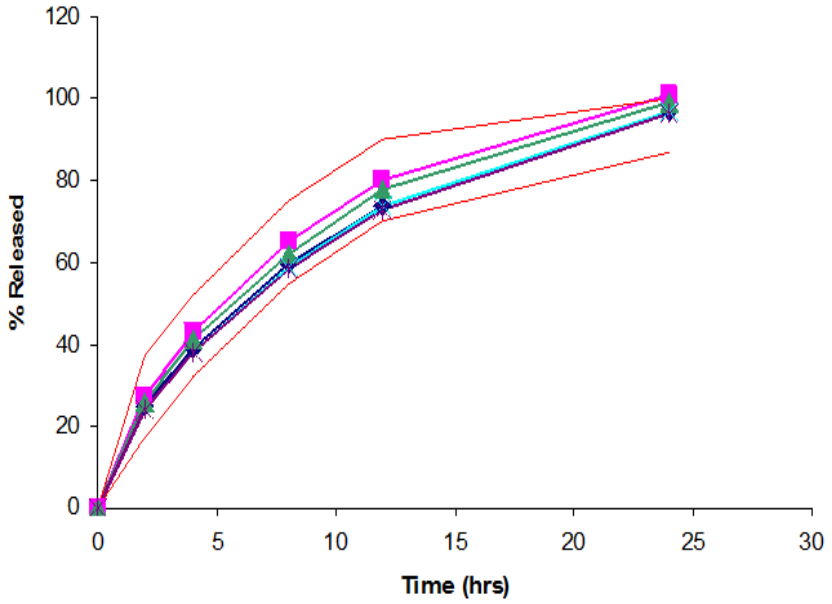


Evaluation of typical tableting process parameters

- **Dissolution independent of tablet hardness and small variations in polymer content**



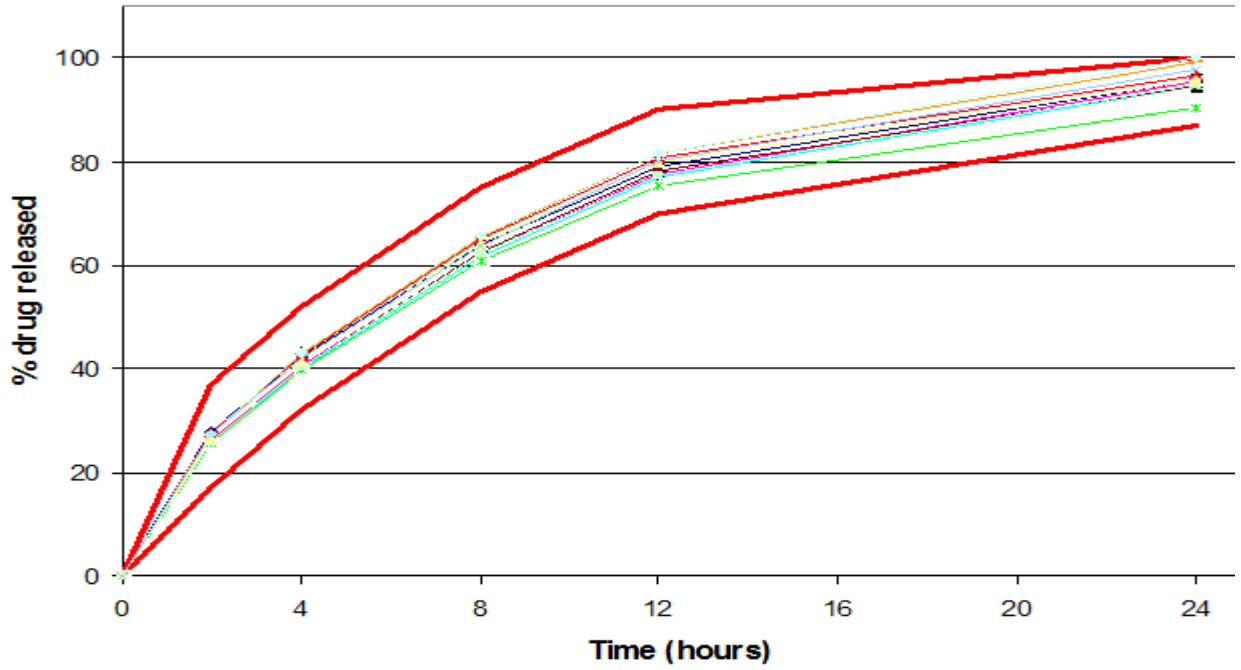
% dissolved v. time for different hardnesses



% dissolved v. time for a range of polymer levels

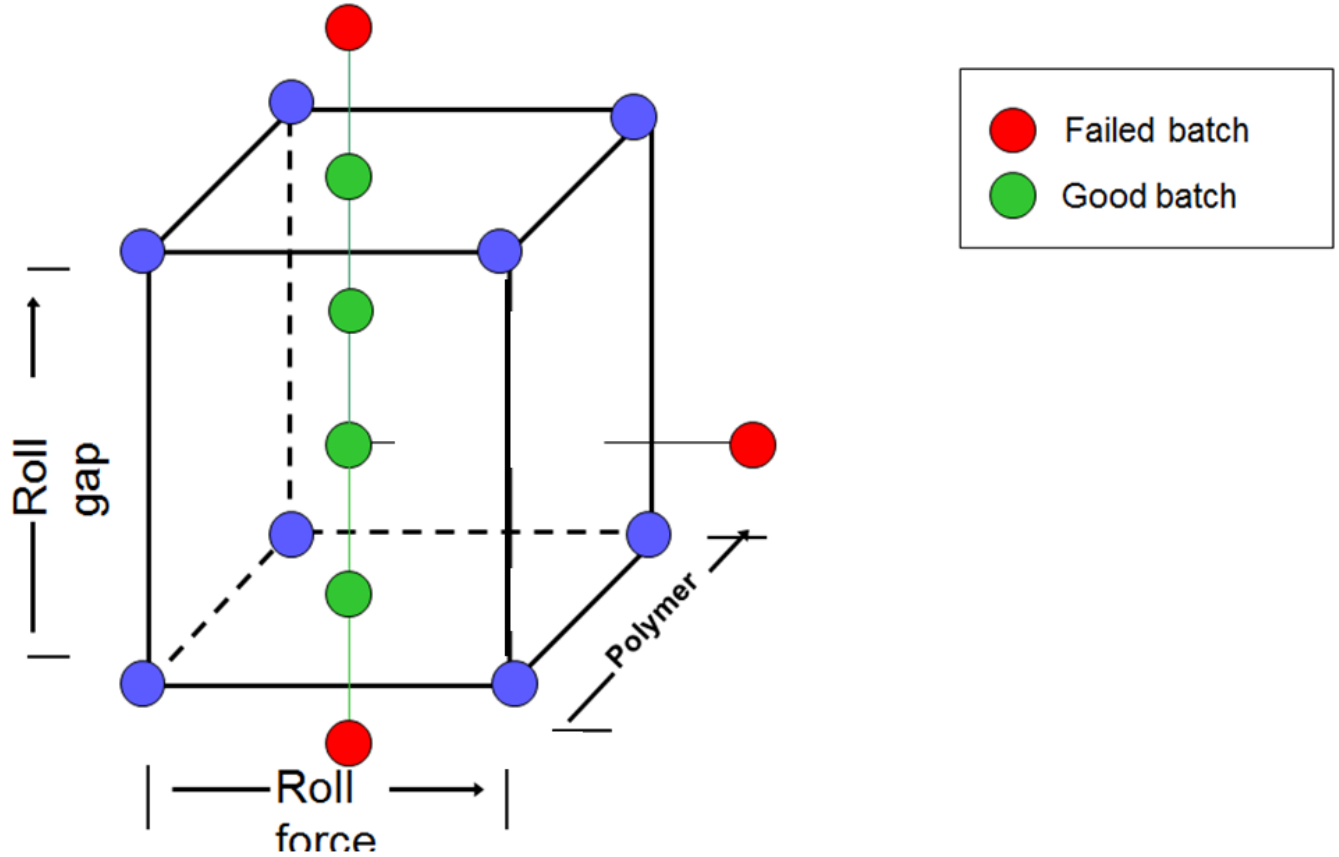
QbD DoE Results

- **Dissolution evaluated for roller pressure, roller gap and polymer level**



QbD DoE Results

- **Batches manufactured outside of the roll compaction design space fail tablet compression, not dissolution**



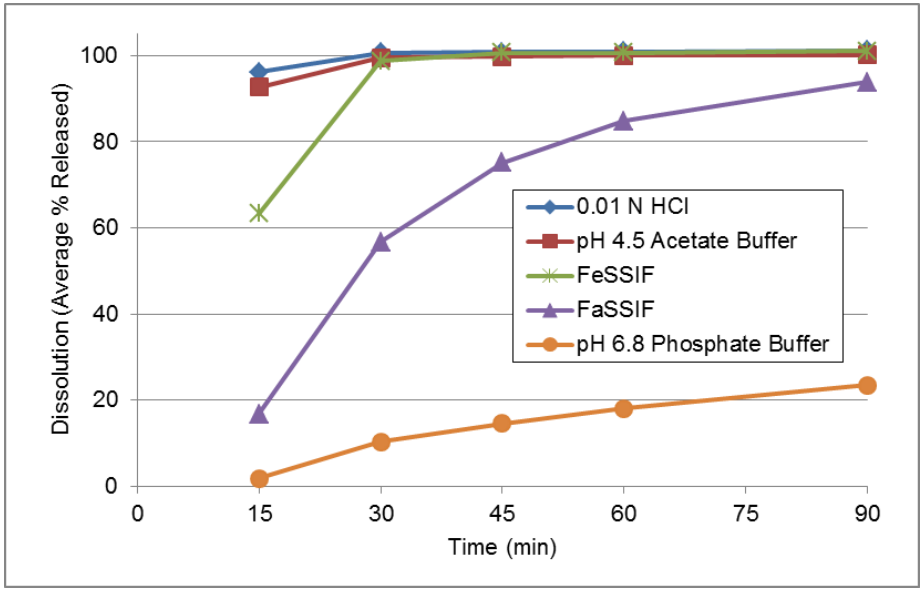
Case Study 1 Conclusion

- **Well behaved compound and formulation lent themselves to the development of a Level A IVIVC**
  - **formulation design (i.e., controlled release) meant that dissolution was the rate limiting step for absorption, therefore a Level A IVIVC would be expected**
- **Clinically relevant dissolution test with Level A IVIVC is an excellent surrogate for in vivo studies to evaluate material attributes, processing parameters and CPPs**

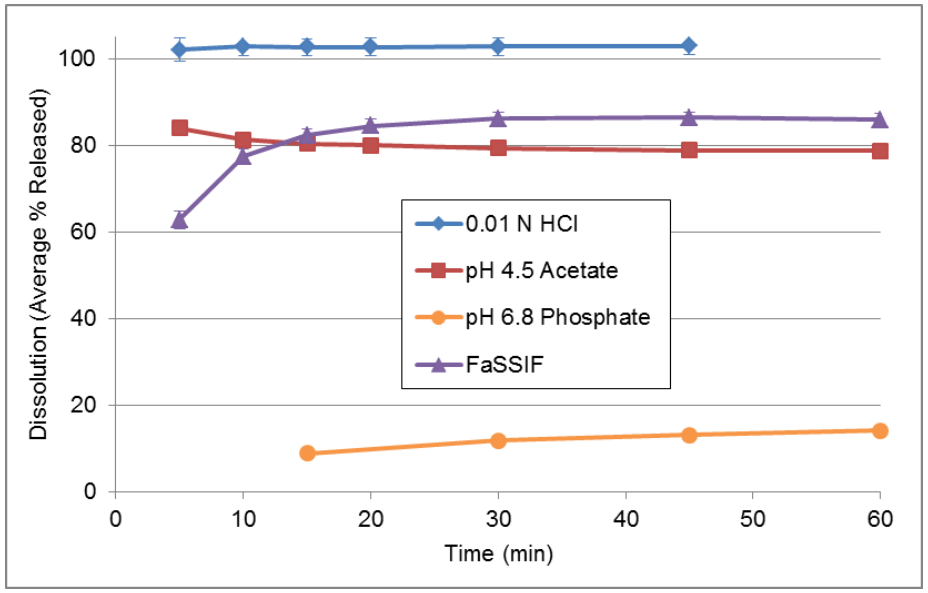
Case Study 2

- **QTPP: Immediate release tablet, with release comparable to or faster than previous formulations used in clinical trials.**
- **Molecule properties:**
  - **Highly soluble across physiological pH range.**
  - **Dissolution kinetics slower at higher pH, but faster in FeSSIF/FaSSIF.**
  - **Excipient-drug binding at higher pH, but broken up in presence of bile salts (FaSSIF).**

Clinical formulation C

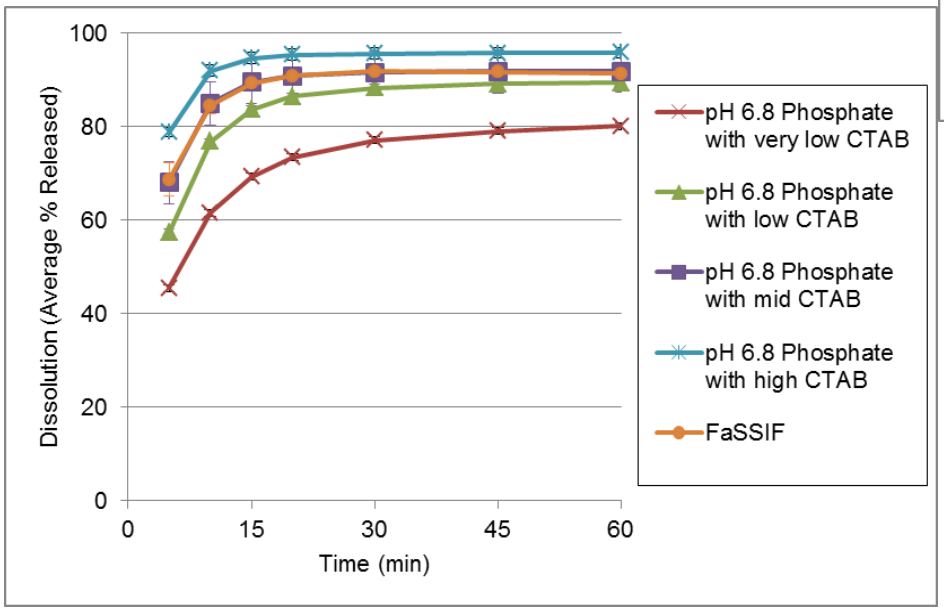


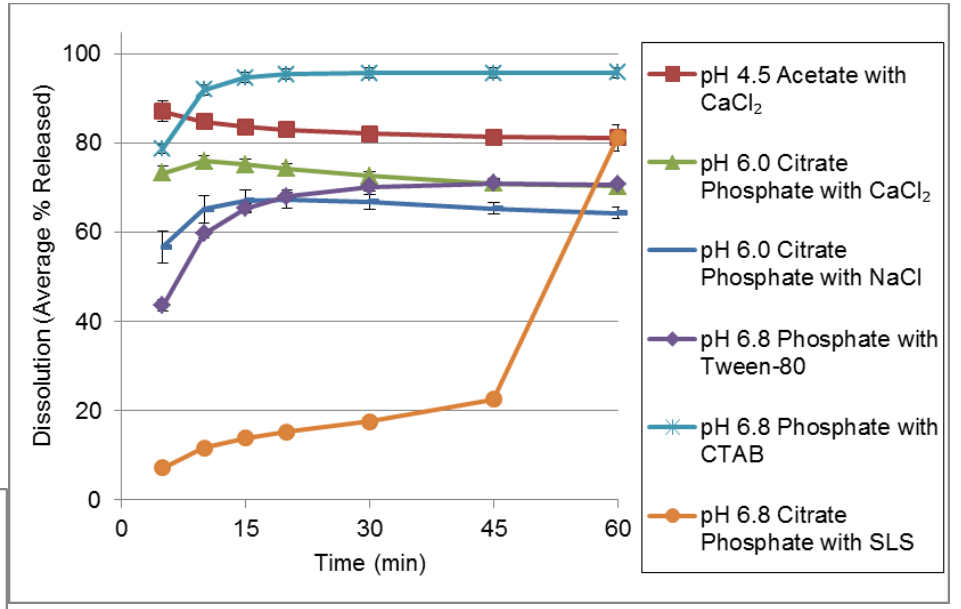
Tablet formulation



Media Selection

- Screening focused on pH range 4.5-6.8.
- Surfactants and salts were added to break up drug-excipient binding.
- CTAB was selected as it resulted in a profile comparable to FaSSIF.
- At CTAB levels that gave complete drug recovery, release was very rapid and lacked discriminatory potential.

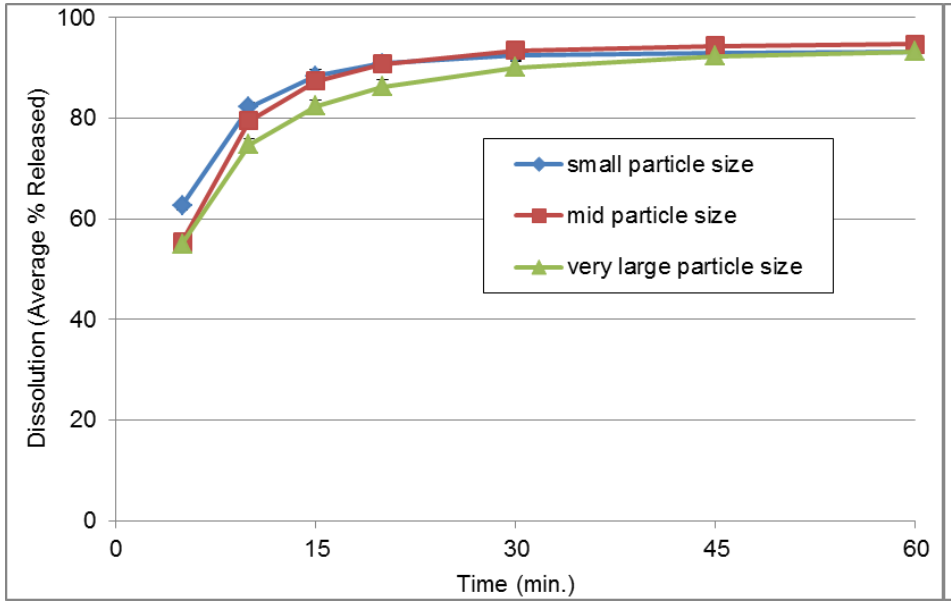


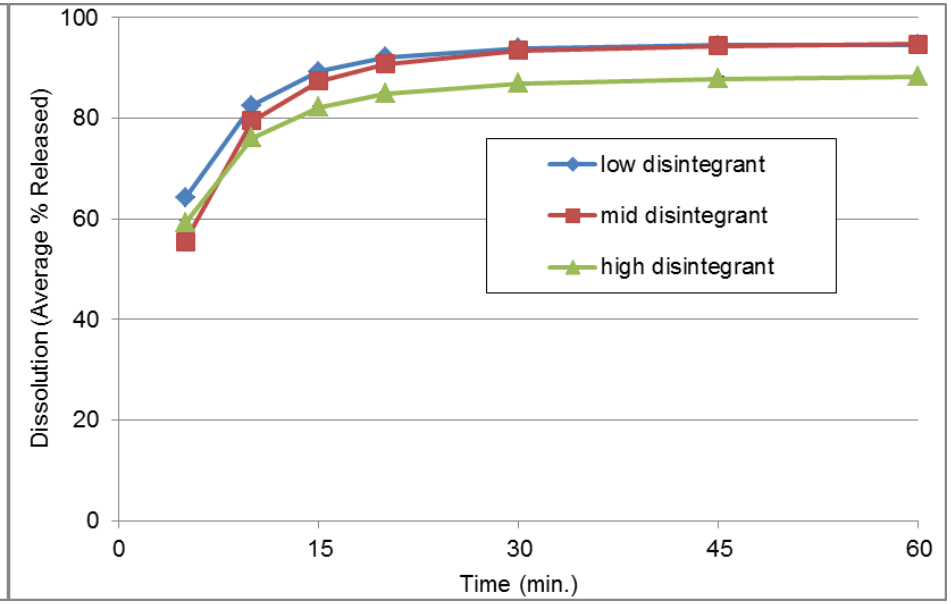


- Control medium (QC) of 0.01 N HCl was selected consistent with FDA draft guideline for highly soluble drugs.
- The CTAB medium with dissolution similar to FaSSIF was selected for use in development to assess robustness of design space.

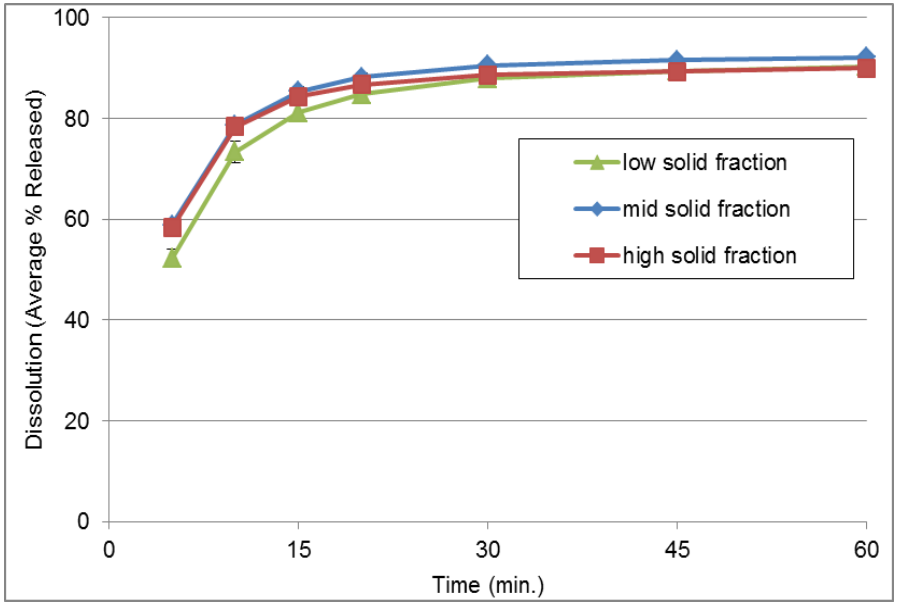
Design Space Verification

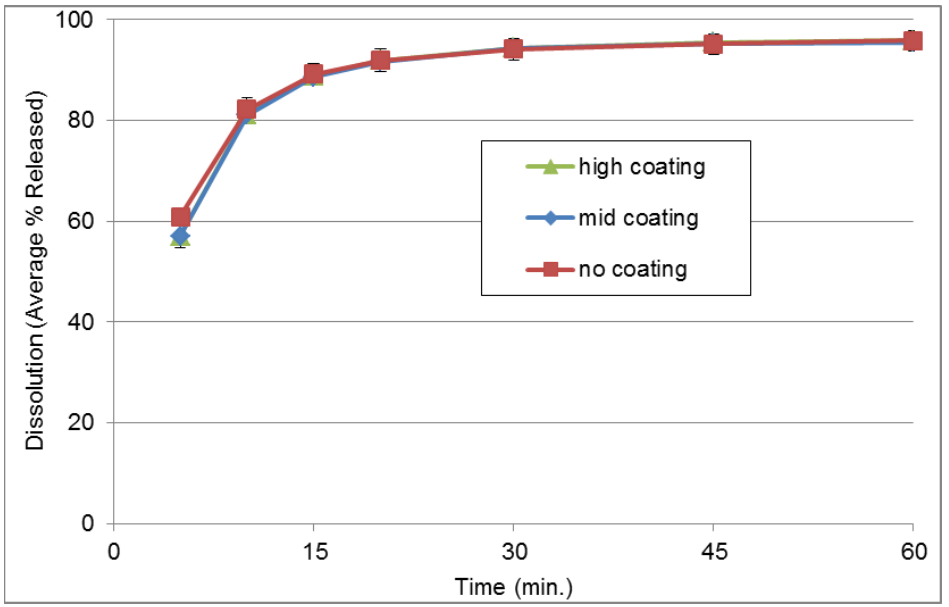
- **Risk assessment identified the following parameters for evaluation:**
  - **Drug substance particle size**
  - **Disintegrant level**
  - **Tablet solid fraction**
  - **Coating level**





Design Space Verification



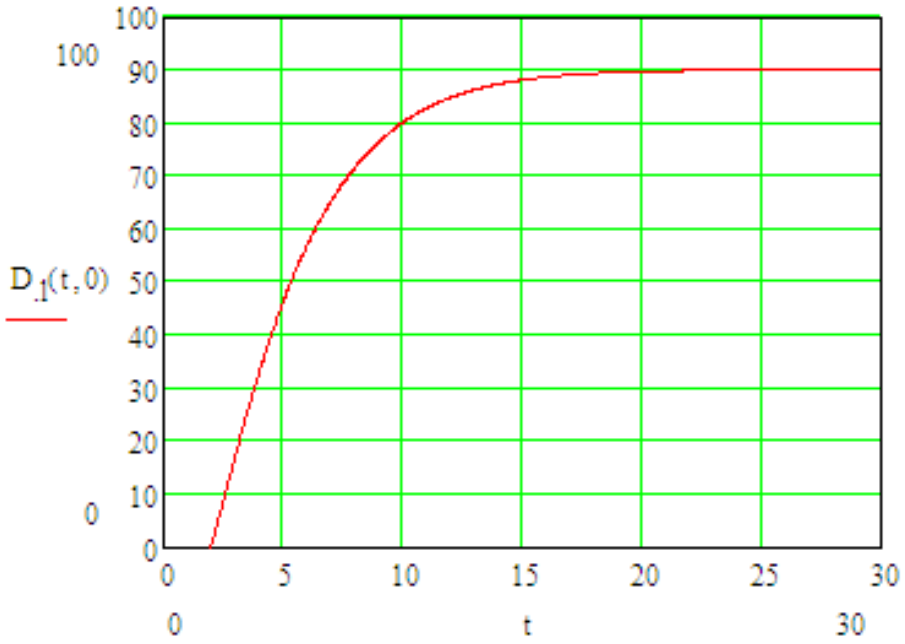


- **Biggest impact to dissolution profile is observed as a function of disintegrant level and dose strength (both related to the drug-excipient binding).**
- **In addition a partial least squares (PLS) model was used to evaluate >100 dissolution results from a range of formulation optimization, process optimization, and tech transfer studies (>20 factors).**
  - **Dissolution profiles were fit to a Weibull distribution.**
  - **Data included some materials well outside the planned control space (very large DS, missing excipients, etc.)**

Weibull Fit

- **Each dissolution profile is empirically fit to a Weibull distribution:**

$$D(t) = P\left(1 - e^{-\frac{(t-\tau)^b}{A}}\right)$$



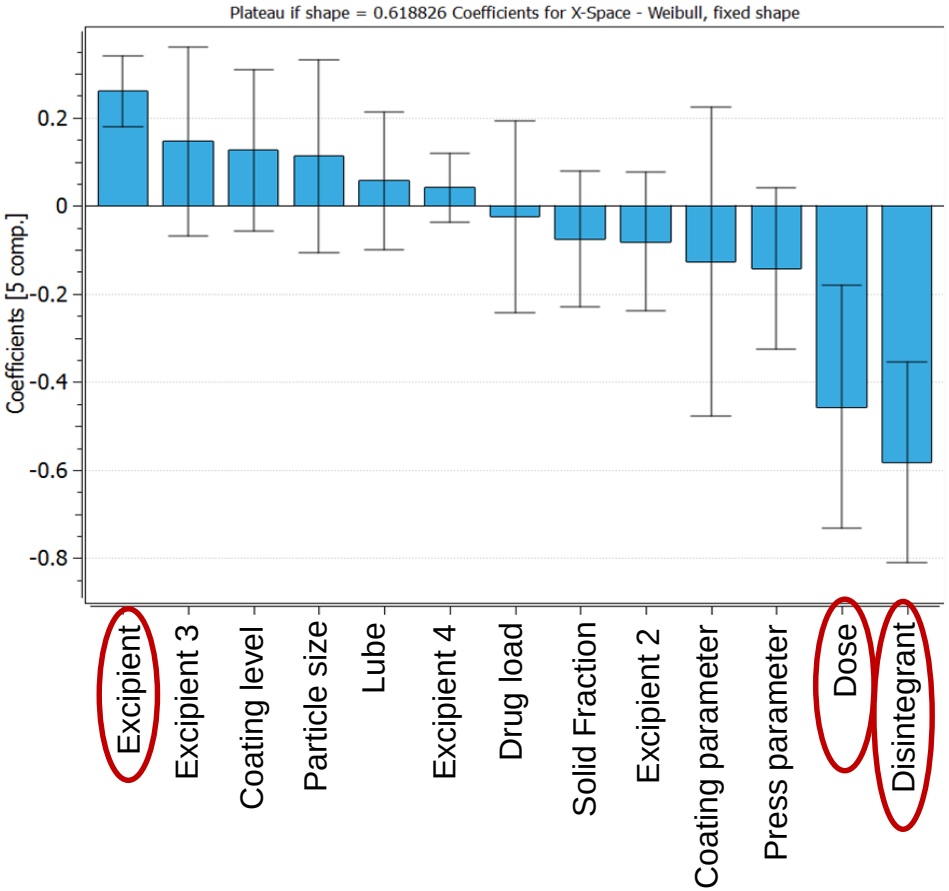
Where D is the dissolution as a function of time, t. P is a plateau value corresponding to the maximum extent of release observed.

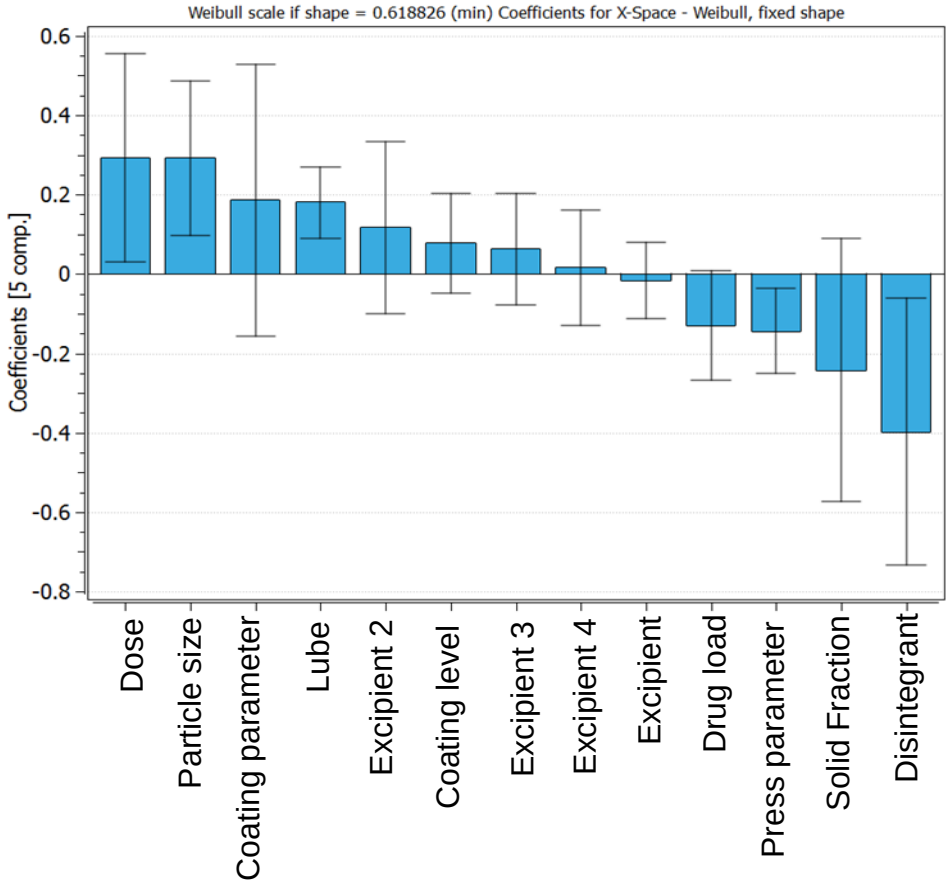
τ is a delay factor for the lag time prior to the start of dissolution.

b is a shape factor, and was determined by fitting to dissolution profiles. A value of 0.62 was used for remaining curve fits.

A is a scale parameter, which together with the shape factor b describes the rising portion of the dissolution profile.

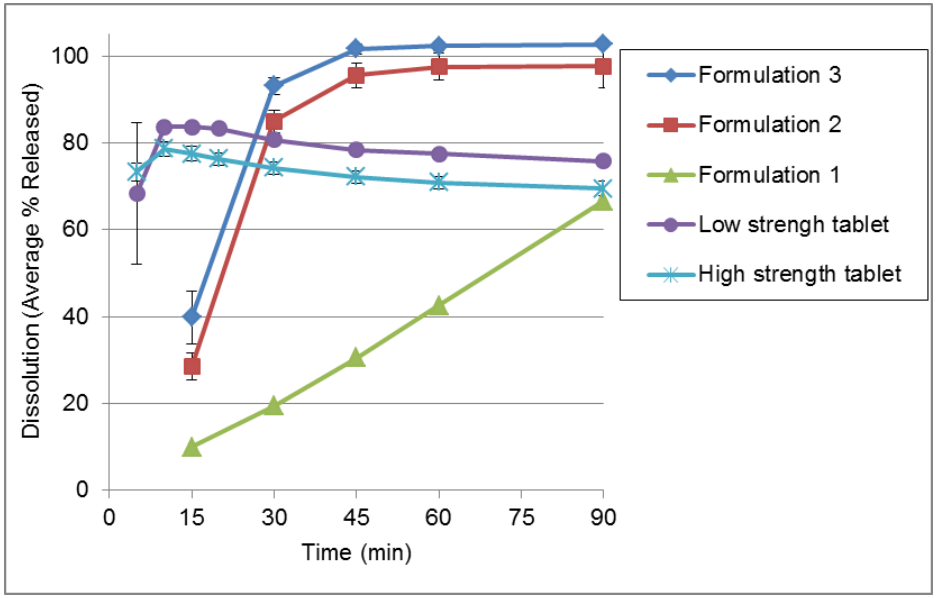
PLS Model



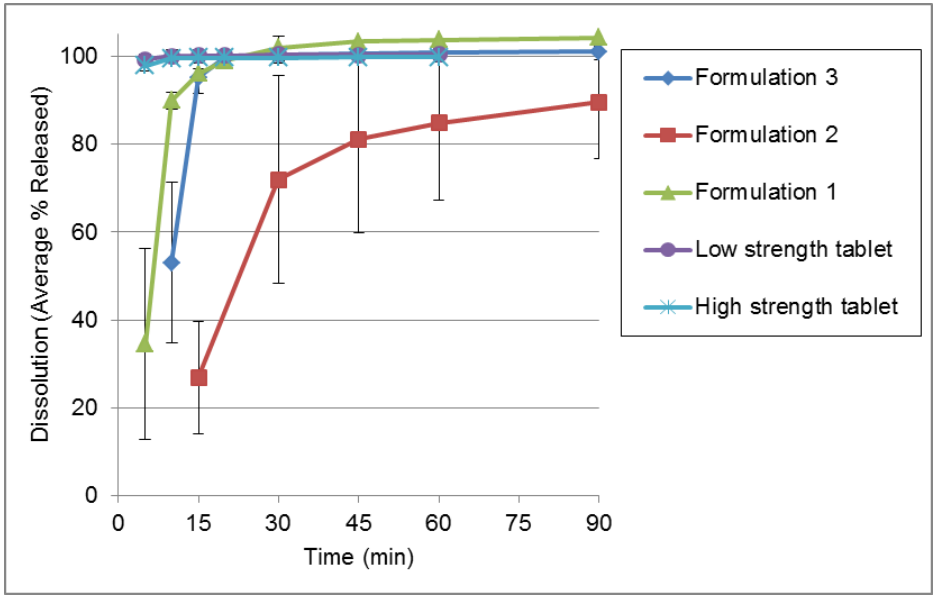


- **Again, the biggest impact to dissolution profile is observed are related to drug-excipient binding.**
- **All other factors have little significant impact, mostly due to experimental conditions well outside of the design space.**

Case Study 2 Conclusions



Formulation 3 Control Method



Tablet Control Method

- **CTAB method is used to demonstrate robustness of design space.**
- **Control method proposed consistent with FDA guideline for highly soluble products.**
- **BE study shows formulation 3 is equivalent to tablet. This is consistent with PBPK models (not discussed here) that suggest exposure is insensitive to dissolution rate.**

Case Study 2 Conclusions, cont'd

- **A challenging case wherein it was not possible to achieve method conditions that met the needs of both a quality control method (robust, validatable) and potentially discriminating for properties that may impact in-vivo performance**
- **A dual method approach was used:**
  - **a potentially discriminating method with a slower dissolution profile to confirm the process and formulation design space, and,**
  - **a control method based on the default conditions of the draft FDA guideline for highly soluble drugs**

Points to Consider

- All along the continuum of clinical relevance, dissolution is a valuable tool for confirming manufacturing consistency
- Dissolution methodology needs to be tailored for the specific use
- Level A IVIVC is considered the gold standard for clinically relevant dissolution
  - When achievable it gives a good prediction of in-vivo performance, minimizing the need for additional in-vivo studies
  - Level A IVIVC may not be achievable, depending on drug and formulation (i.e., IR vs. MR) characteristics
- Alternate approaches may be needed, depending on the specific situation
  - For BCS 1/3 with rapid or very rapid dissolution, a profile may not be necessary
  - A discriminating method linked to in-vivo performance via a clinical safe space
  - A discriminating method without additional in vivo data may be used, with acceptable specifications set in association to pivotal clinical batches
  - Others?

Acknowledgements

- **Case Study 1 – Pfizer, Inc.**
  - **Mike Cohen**
  - **Dorys Diaz**
  - **Roger Nosal**
  - **Ron Ogilvie**
  - **Loren Wrisley**

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  - **Pete Shi**
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  - **Mark Polizzi**
  - **John Kreuzman**
  - **Lancaster PSS**

Q&A/Discussion

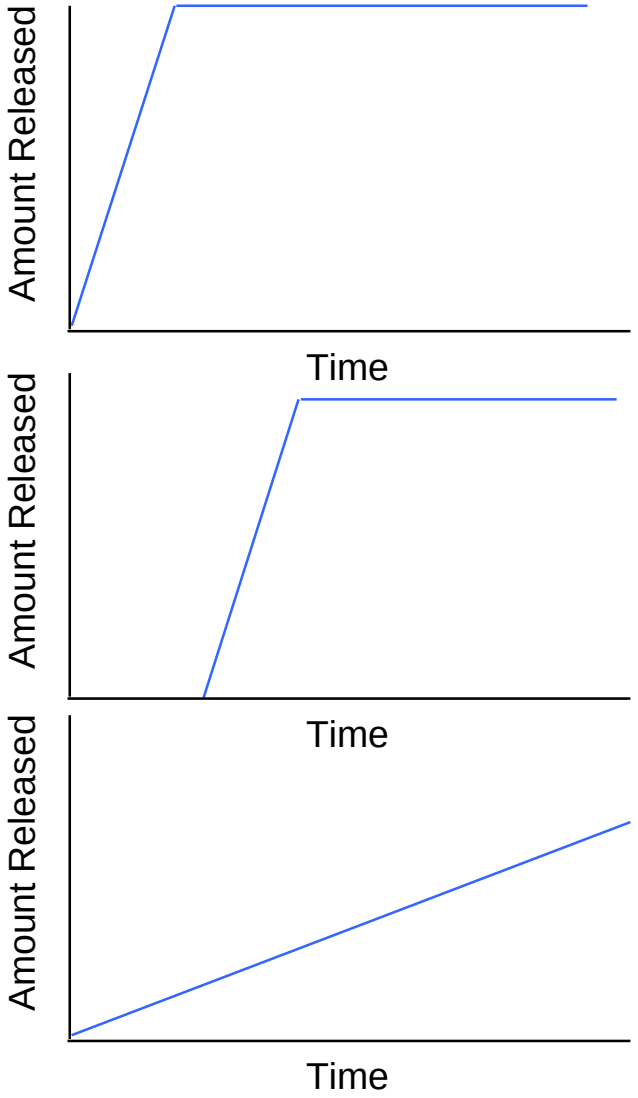
Back-ups

Quality By Design Overview

ICH Q8R2

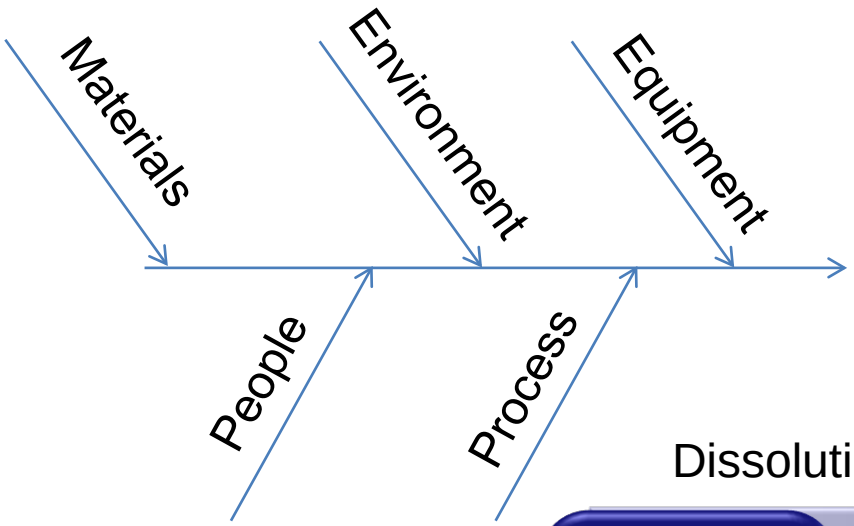
Drug Release CQA

- In vitro dissolution
  - is used as a surrogate for in vivo performance.
  - to determine the rate at which drug is released and dissolved (available for absorption).
- Dissolution testing is utilized to ensure appropriate release of drug from the dose form.
  - Formulation design
    - Immediate release
    - Delayed release
    - Controlled release
  - Clinical Trials
  - Routine Production
  - Formulation changes
  - Process changes



Risk Assessment

Ishikawa Diagram



Dissolution Risk Assessment

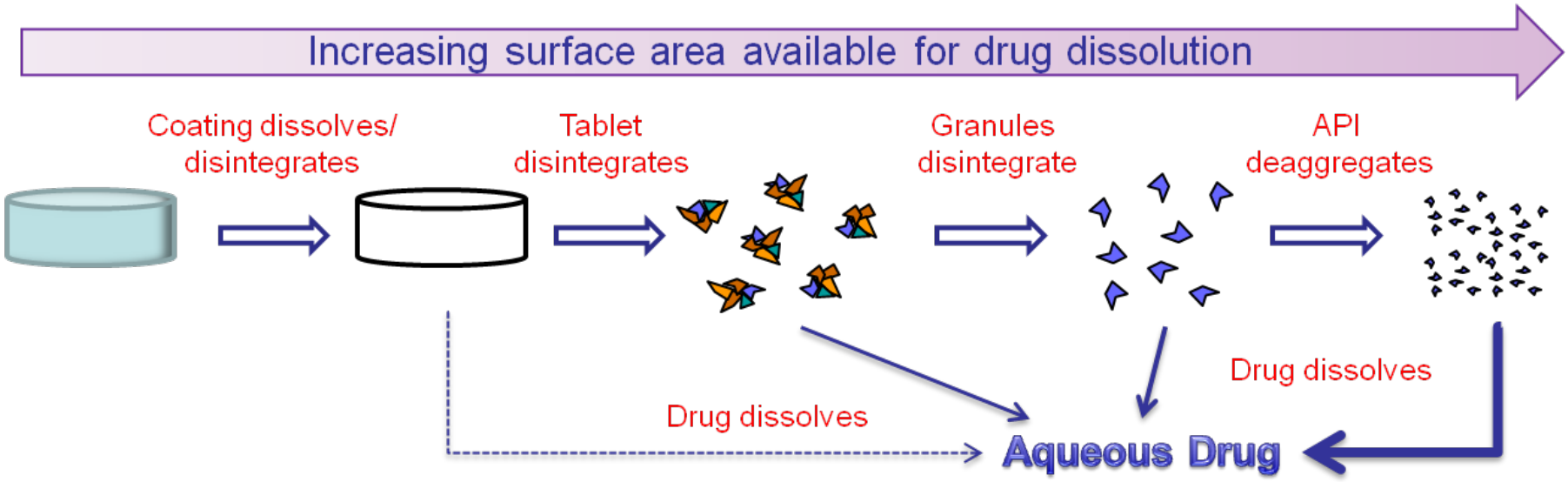
Low
- BCS Class I/III, highly soluble for all dose strengths
- Simple IR formulation
- May be able to use disintegration rather than dissolution as a control.

Medium
- BCS Class IIa-b/IV, but good solubility in some part of the physiological range (pH 1.2-6.8)
- Simple IR formulation

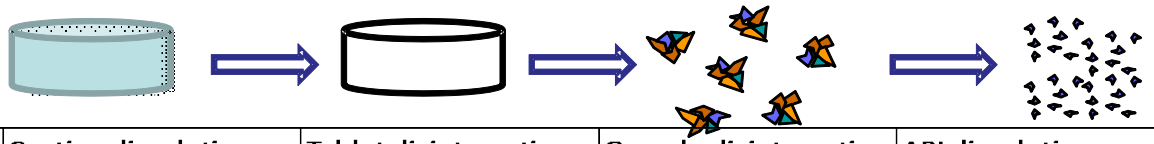
High
- BCS Class II-c/IV, not soluble across the pH range w/o surfactants
- Simple IR formulation

Very High
- Complex or enabled formulation (MR, ER, SDD, etc)

General Dissolution Mechanism



Dissolution Risk Grid



	Coating dissolution	Tablet disintegration	Granule disintegration	API dissolution
API Properties				
Solubility				
Particle size distribution				
Agglomeration				
Salt form conversion				
Crystal form conversion				
Formulation Properties				
Disintegrant				
Binder				
Diluent				
Lubricant				
Surfactant				
Coating (non functional)				
Process Properties				
Blending				
Granulation				
Compression				
Coating				
Stability				

	likely impact
	possible impact
	low probability of impact

Method Discrimination

In vivo performance

Quality Control

The product performance methods need to identify any changes that have the potential impact to BA.

Potential to impact
- Particle size
- Aggregation
- Disintegration
- Solid form change

Not likely to have an impact
- Coning
- Sticking to vessel walls
- Specific buffer or surfactant interactions

Understanding the dissolution mechanism provides insight into process and material impact to dissolution, and improves the ability to determine whether observed changes may impact bio-performance of the product.

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