The Utility of Level C IVIVC for Setting Clinically Relevant Specifications: Case Studies and Implications

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Dissolution and Translational Modeling Strategies
Enabling Patient-Centric Product Development

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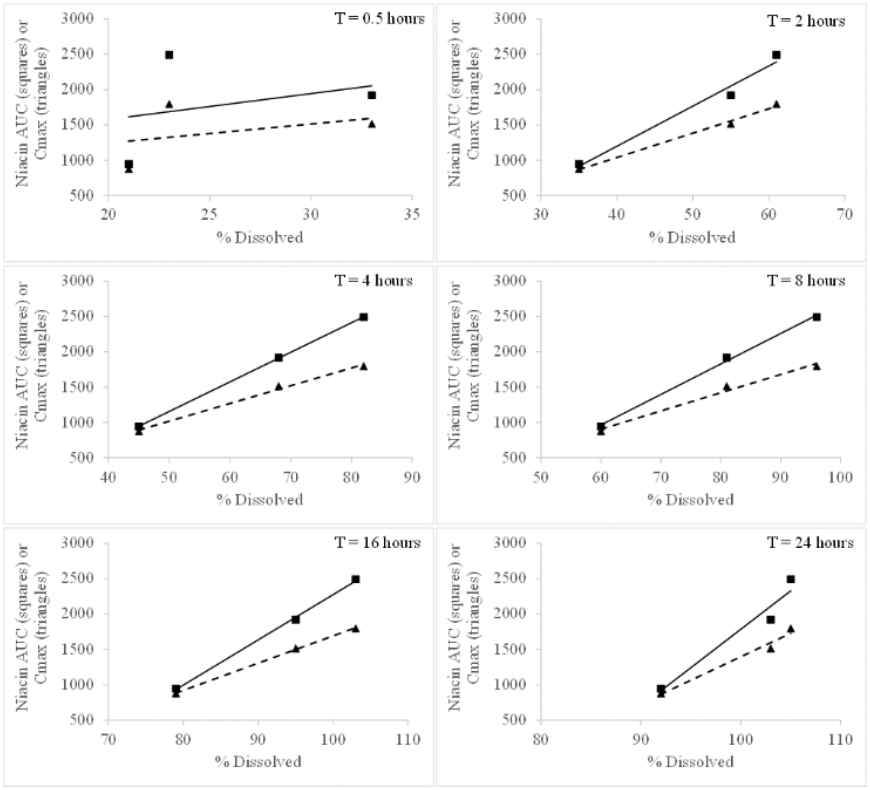
Outline

- Level C and Level A IVIVC
- Case study 1 – Impact of polymer on MR product
- Case study 2 – Impact of API PSD on IR product
- Case study 3 – Impact of tablet hardness of IR product
- Level C vs Level A IVIVC – A theoretical exercise (PQRI project)
- Conclusions

Multiple Level C IVIVC



IVIVC guidance: If such a multiple Level C correlation is achievable, then the development of a Level A correlation is likely

Is this statement always true? Is it accurate for IR products? And is the Level A model always needed?

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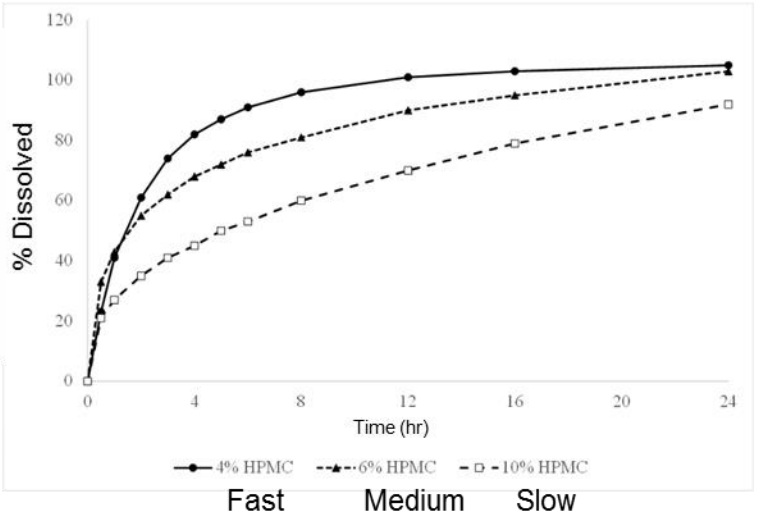
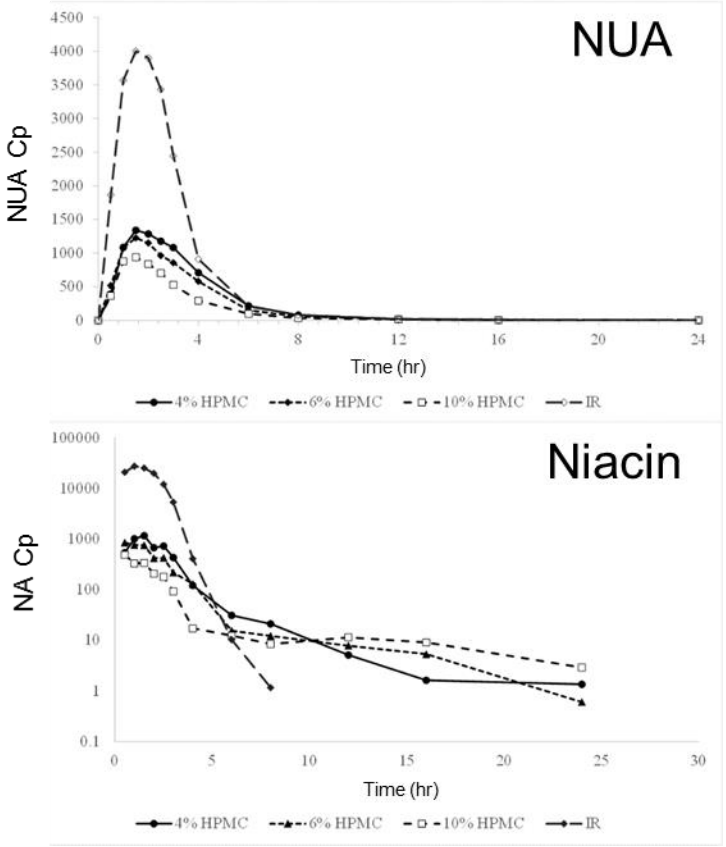
Case Study 1 - IVIVC for Niacin ER

- Extremely complex metabolism, dependent on rate of absorption





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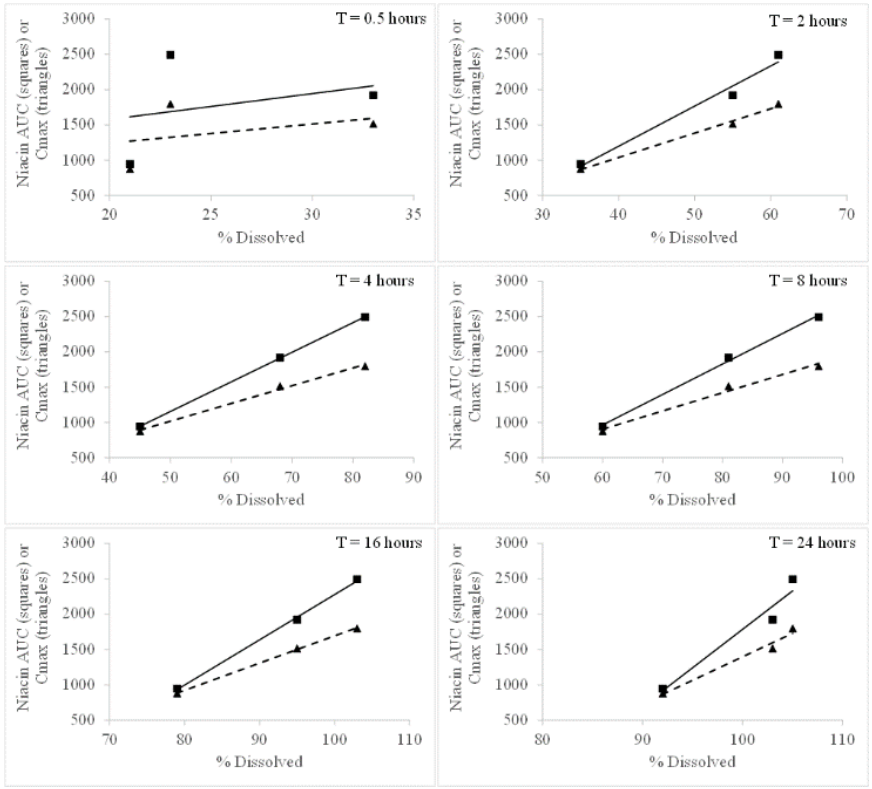
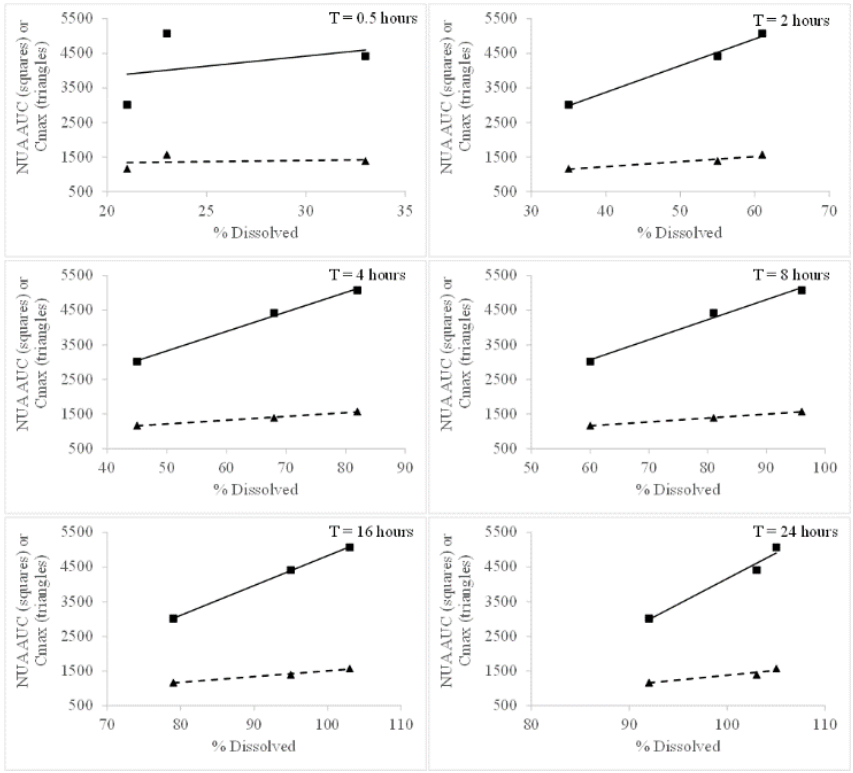
Multiple Level C IVIVC Models

Niacin



NUA



With the exception of first timepoint (0.5 hrs), P.E. < 5%
Similar correlation seen for total urinary excretion

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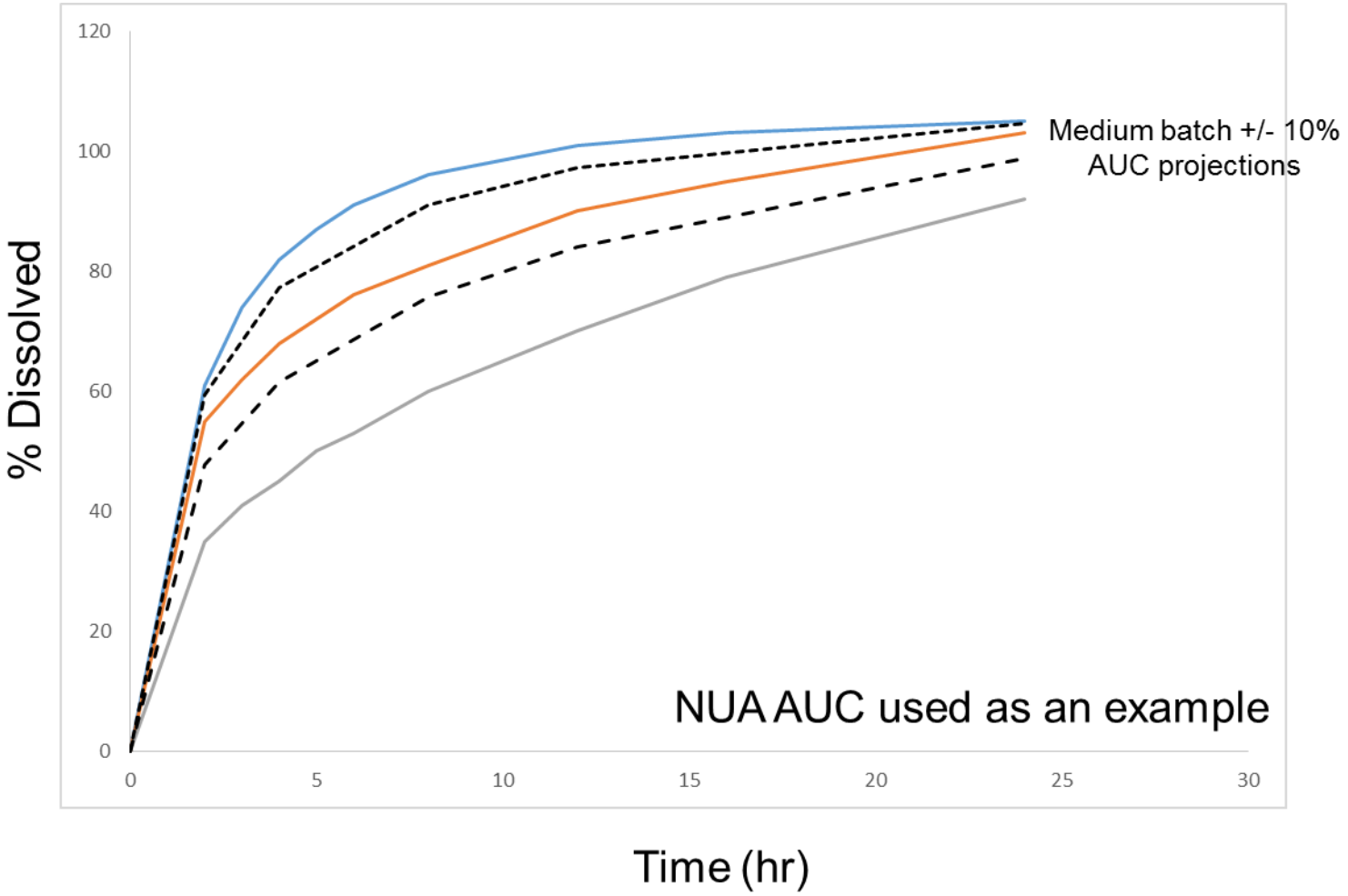
Level A Model

- Impossible to obtain for Niacin (multiple methodologies attempted)
- Traditional (time scale/shift/cutoff) or compartmental based for NUA was successful for AUC but ~33% P.E. on Medium formulation C_{max}
- Level A model obtained for NUA using a correlation between dissolution in vitro fit parameter (Makoid-Banakar TMAX) and in vivo absorption parameter (Hill function Finf and MDT)

Multiple Level C Model Application



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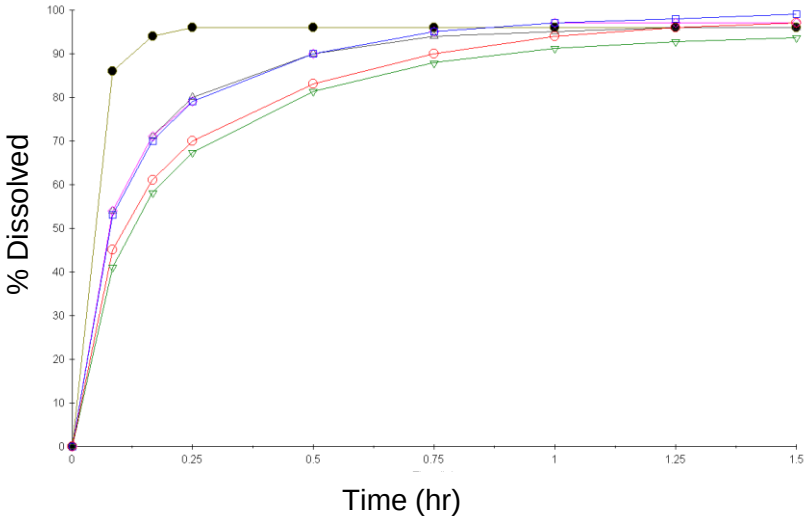
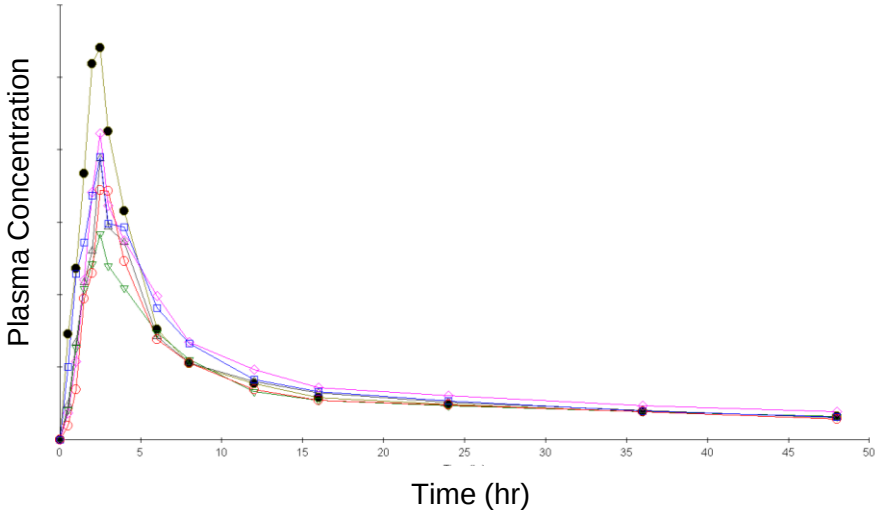
Case Study 2 - Impact of API PSD on IR Product

- BCS II
- IR formulation (crystalline API)
- Dissolution sensitive to API PSD



Dissolution for experimental batches of varying API



Relative Bioavailability Study

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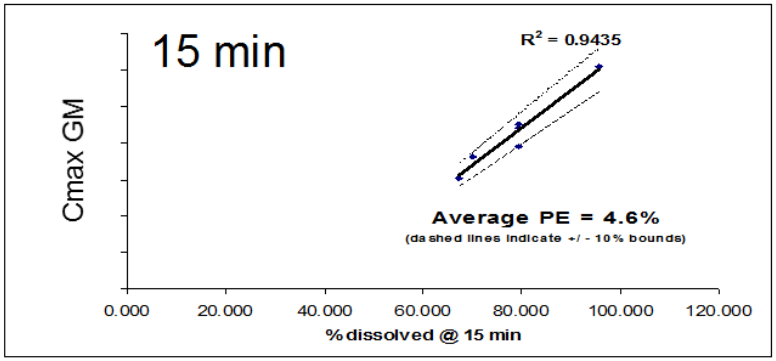
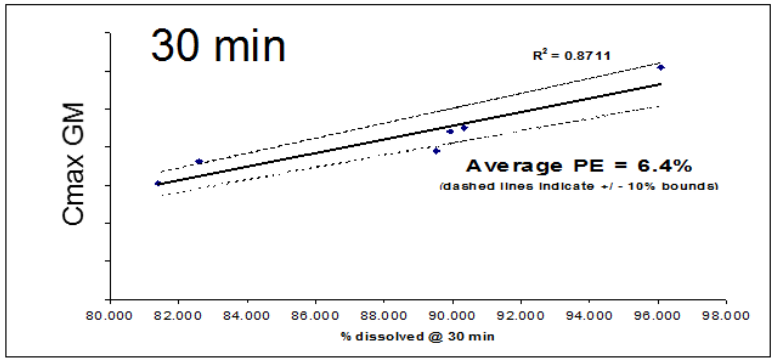
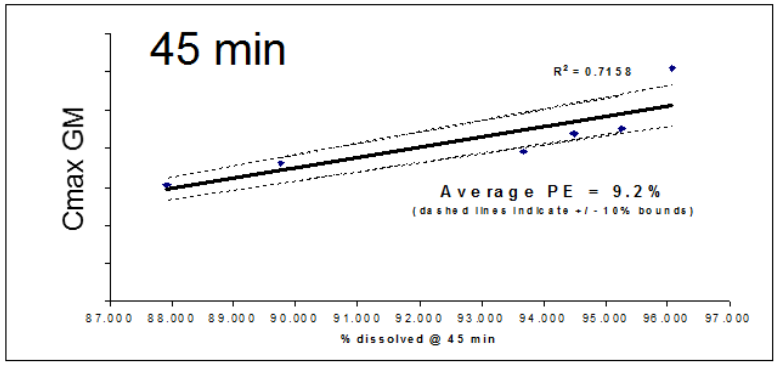
Multiple Level C IVIVC







Dissolution correlated with C_{max}

Linear regressions against C_{max} explained observed data

As expected, later dissolution time points show somewhat lower R^2 values (formulations close to complete release)

Dashed lines indicate +/- 10% prediction error bounds around regression line

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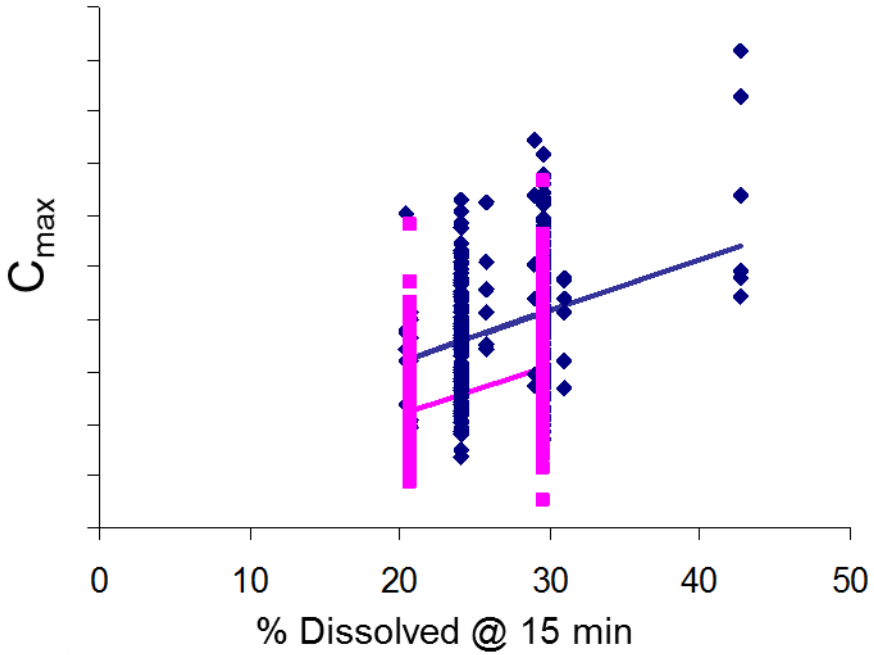
Cross-study Multiple Level C IVIVC



C_{max} = intercept (θ1) + slope (θ2) x D15 + θ3 x ind + θ4 x D15 x ind

•where D15 = % Dissolution after 15 minutes.

Blue diamonds: observed data with ind = 0. Blue line: linear regression for data with ind = 0.

•Purple squares: observed data with ind = 1. Purple line: linear regression for data with ind = 1.

•ind = 1 for the data from Part I in Study P06328 and ind = 0 for the rest of the data.

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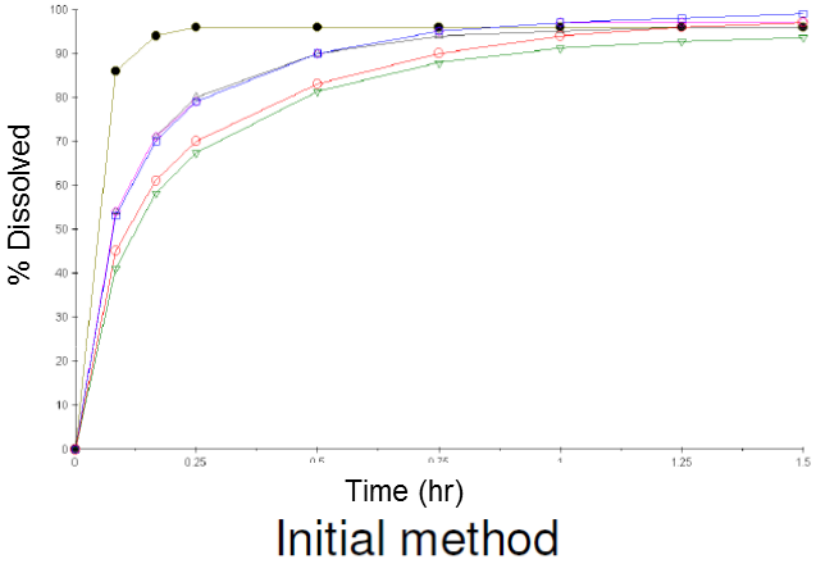
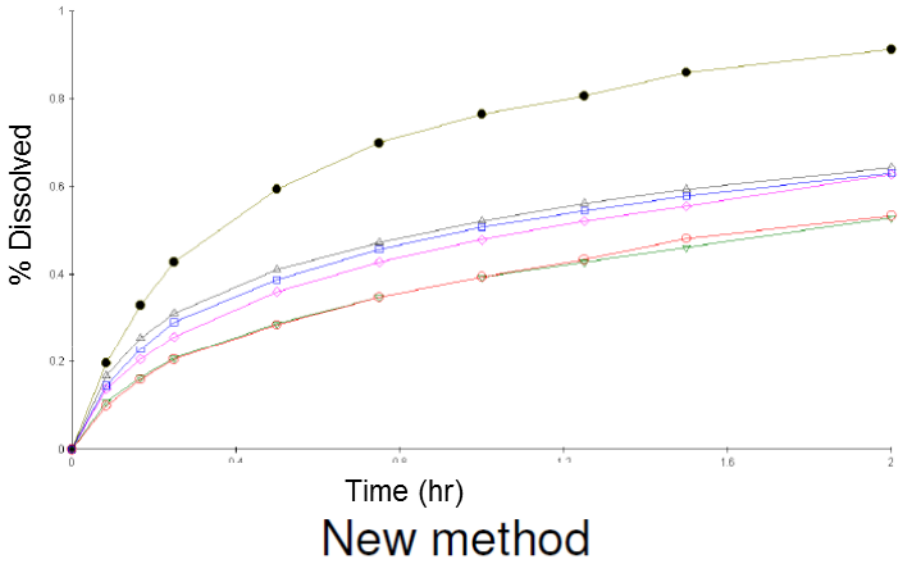
Level A IVIVC via Traditional Deconvolution / Convolution Methodology



Initial method



New method

Traditional Level A model with original method narrowly failed external validation
A slower dissolution method to reduce time-scaling resulted in successful IVIVC model

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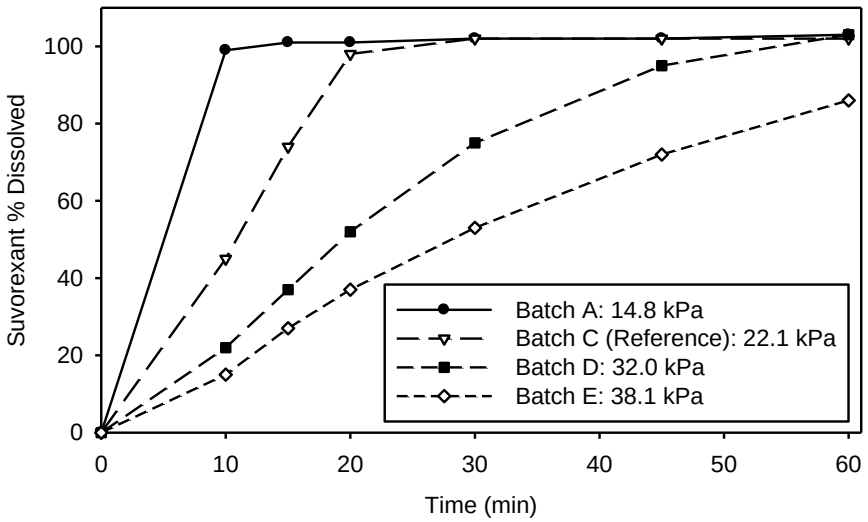
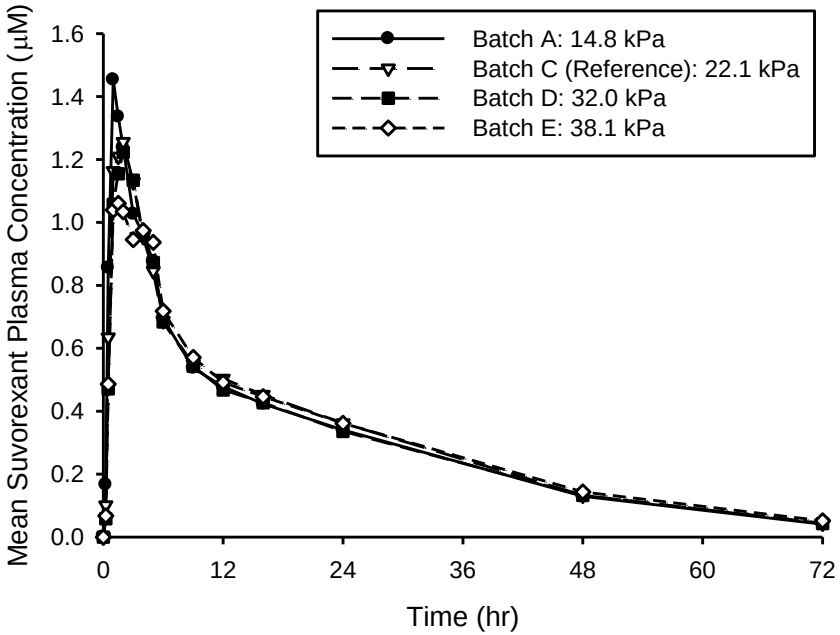
Level C vs Level A BE Prediction

- Predictions of independent relative BA study

	Observed C_{max} GMR	Level A predicted C_{max} GMR	Level C (D15) predicted C_{max} GMR
Batch A vs Batch B	1.12	1.14	1.07
Batch A vs Batch C	1.38	1.35	1.51

Case study 3 – IR Solid Dispersion Tablets Multiple Level C IVIVC





- Formulations (manufactured by varying compression force) selected to cover a wide dissolution range
- All dissolution curves outside F2 bounds
- No meaningful differences in AUC observed – Some Cmax differences seen

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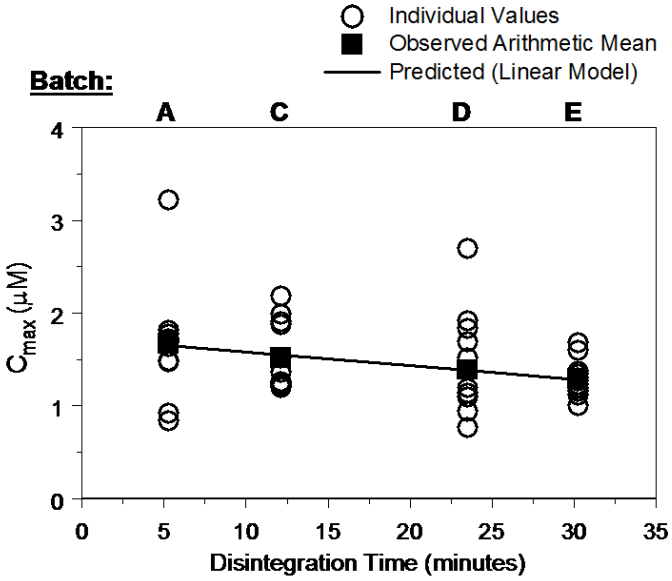
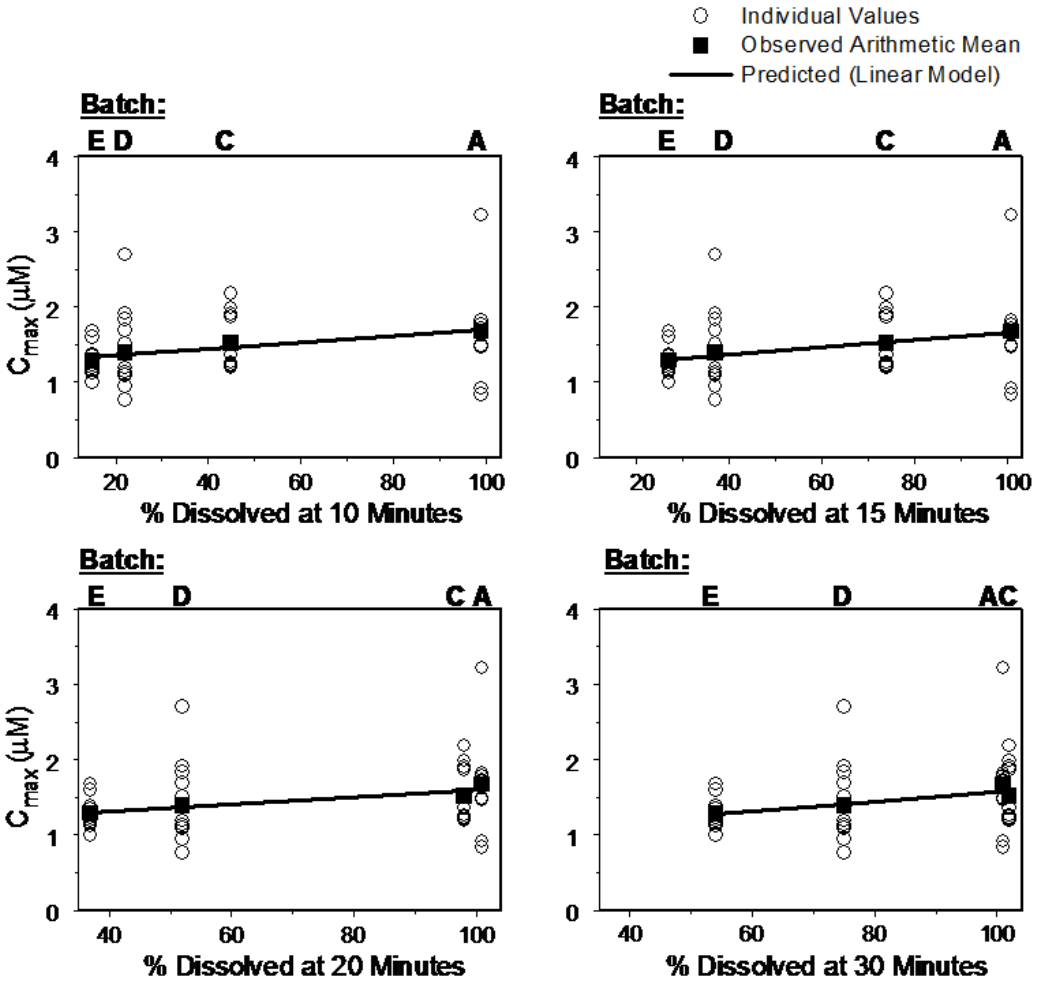
Develop Correlations (IVIVC) Disintegration and Dissolution





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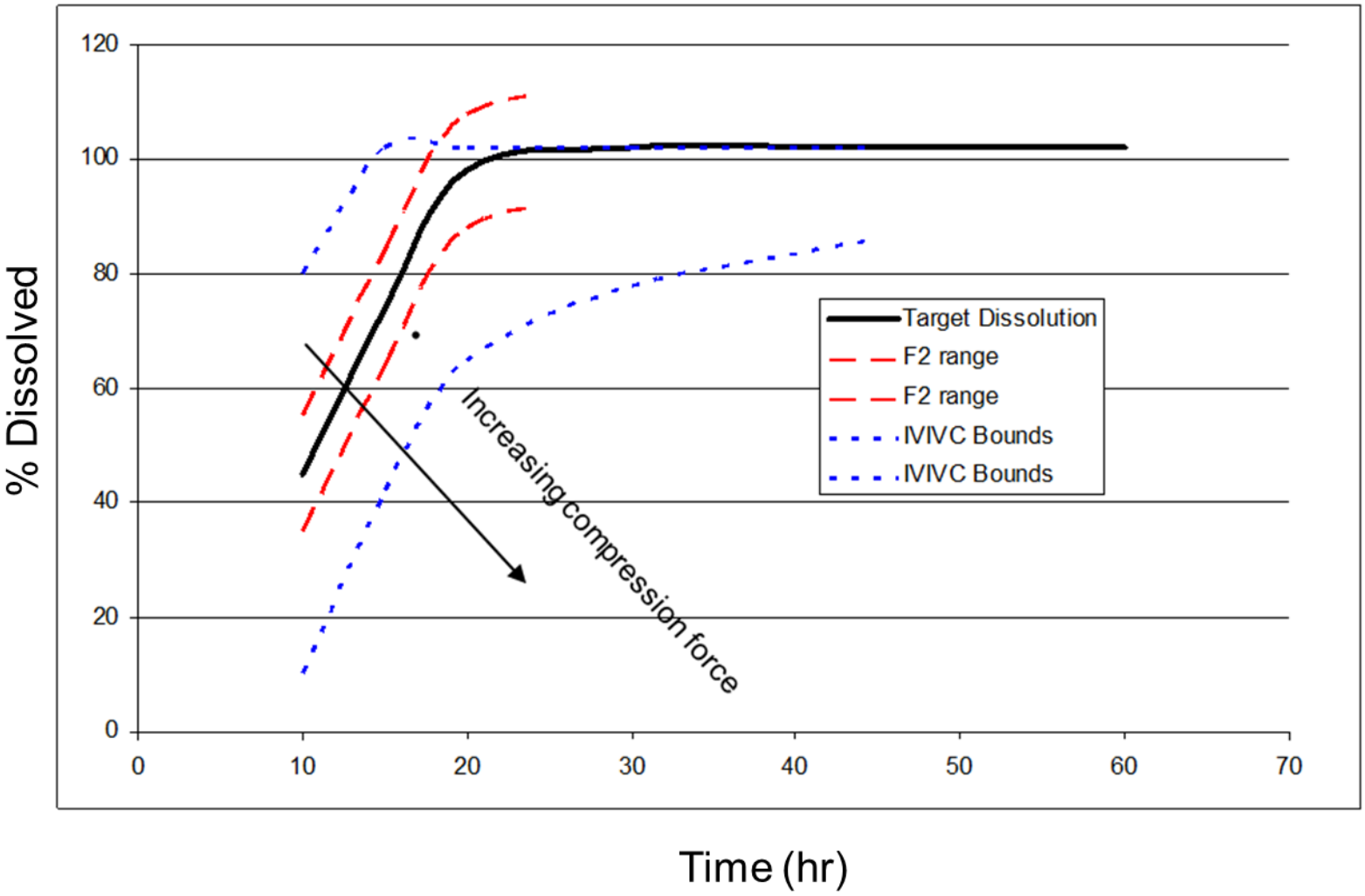
Use IVIVC to Estimate Dissolution Bounds



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Can Multiple Level C be used to predict BE?

- Bioequivalence study between strengths to support interchangeability (much faster dissolution for 15 vs 30 mg and 20 vs 40 mg tablets)
- IVIVC used to inform POS and power study (maximum 9.5% difference predicted based on 20 min dissolution)

	AUC0-t	AUC0-inf	Cmax	Cmax IVIVC prediction
2x20 (n=59) vs 1x40 mg (n=60)	102.52% (99.09-106.07%)	102.33% (98.80-105.99%)	96.58% (90.96%-102.55%)	105.3%
2x15 (n=60) vs 1x30 mg (n=59)	99.71% (96.66%-102.85%)	99.66% (96.52%-102.91%)	108.74% (101.10%-116.95%)	109.5%

Supplementing Level C IVIVC with Additional Modeling

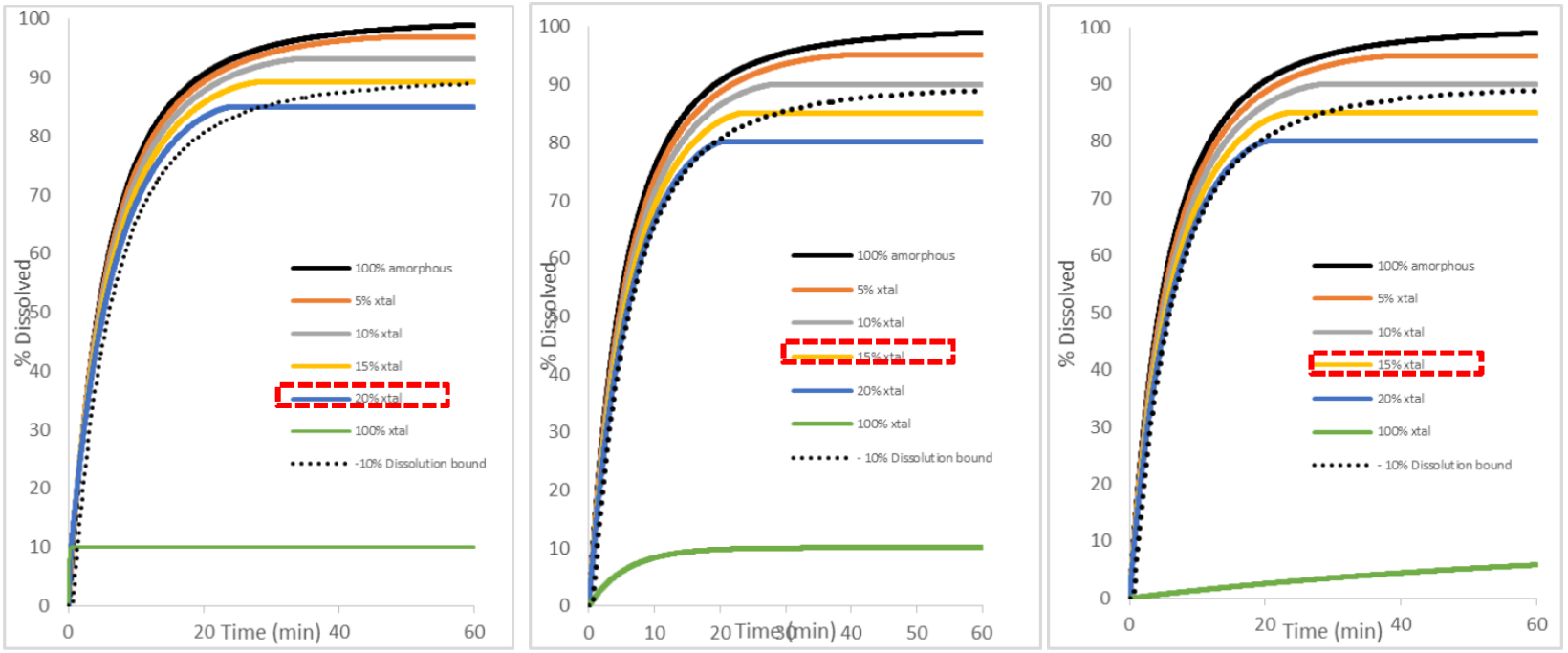
Question: IVIVC study focused on tablet hardness. How about other CQAs (eg. crystallinity)?

10 um particles for amorphous
1 um particles for crystalline

10 um particles for amorphous
10 um particles for crystal

10 um particles for amorphous
35 um particles for crystal

General model not specific to suvorexant; 1x sink over amorphous solubility assumed



The dissolution curves can be linked to an absorption/PK model to predict impact on PK

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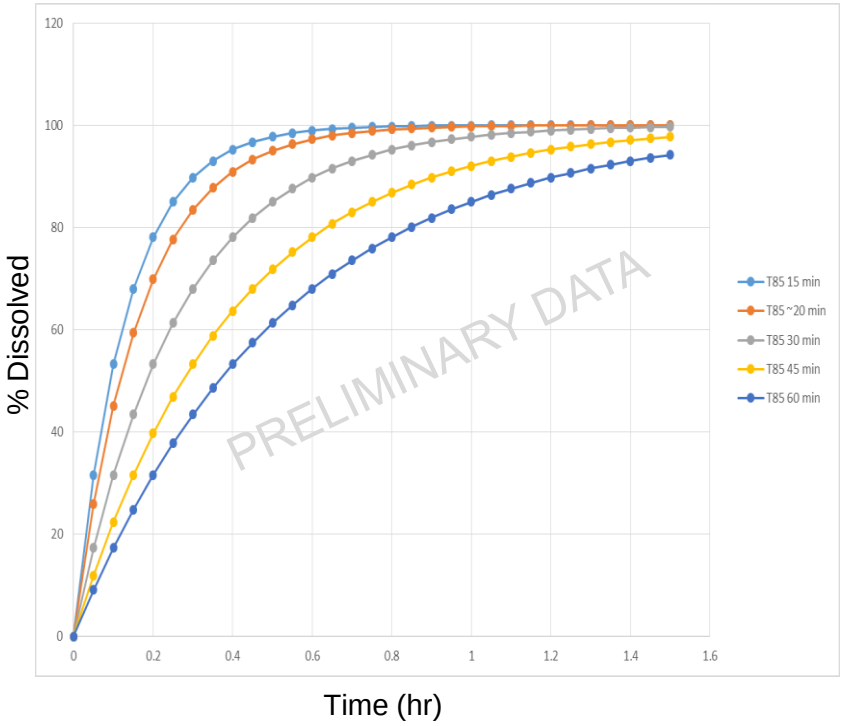
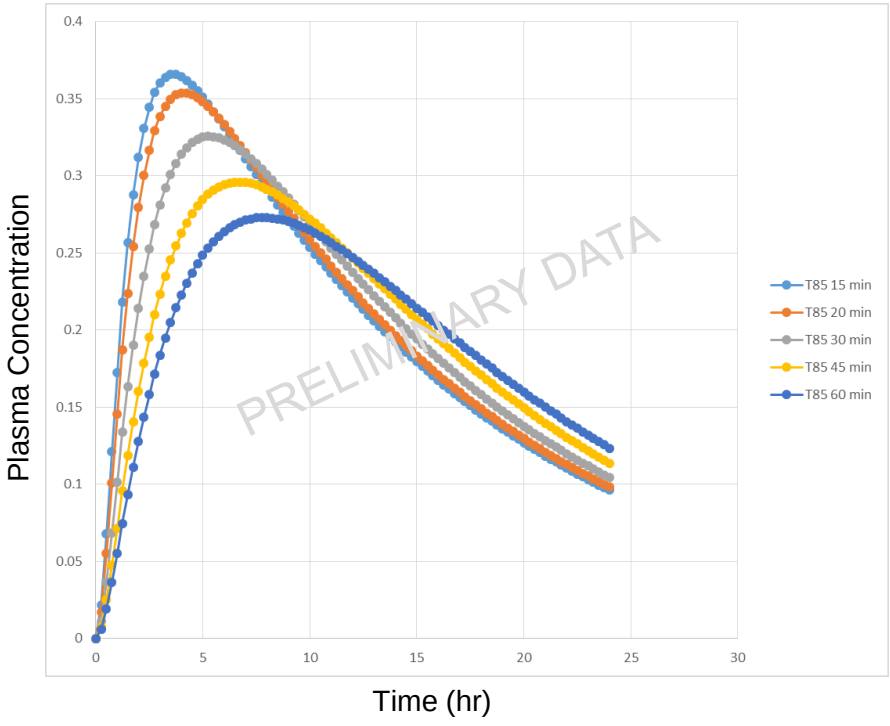
Assessment of Level C vs Level A for an IR product– a theoretical exercise (PQRI project)

Simplified dissolution + absorption model used
Dclumen/Dt = - Dissolution function; Dabs/Dt = ka*Clumen





Clinical PK profiles generated via convolution assuming an underlying IVIVC relationship (DISvivo=DISvitro(Timescale*Tvivo)

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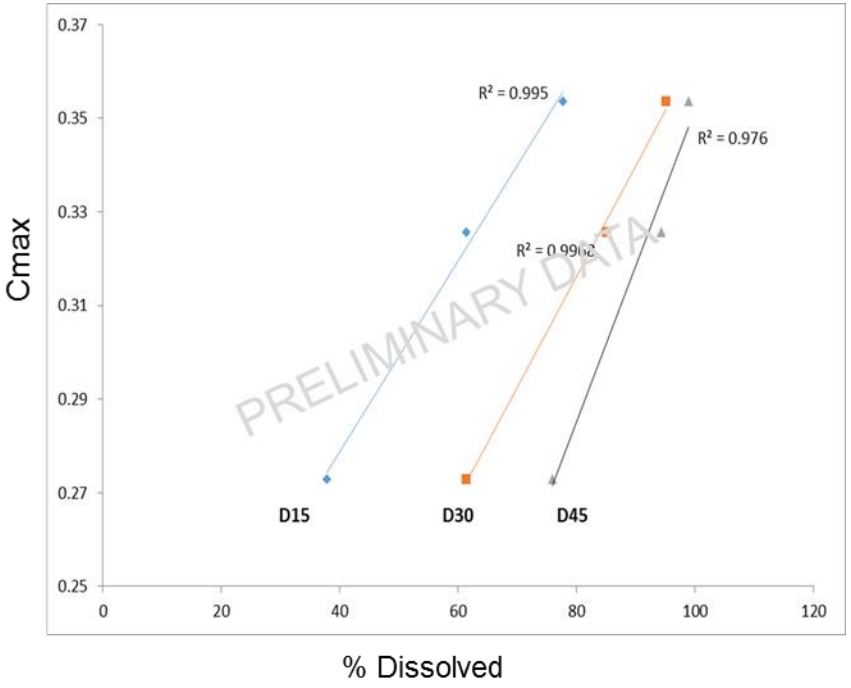
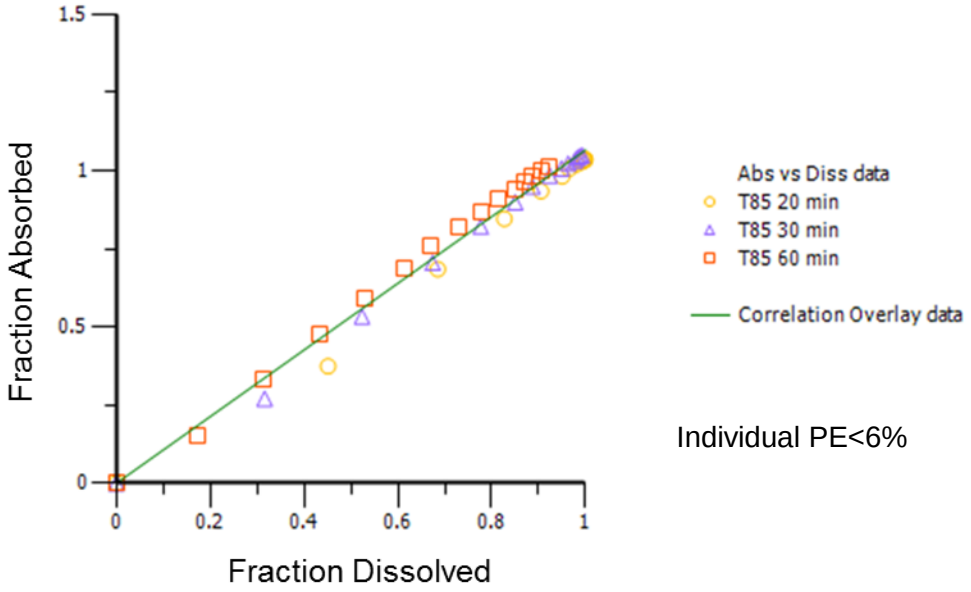
Multilple Level C and Level A IVIVC





Individual PE<6%

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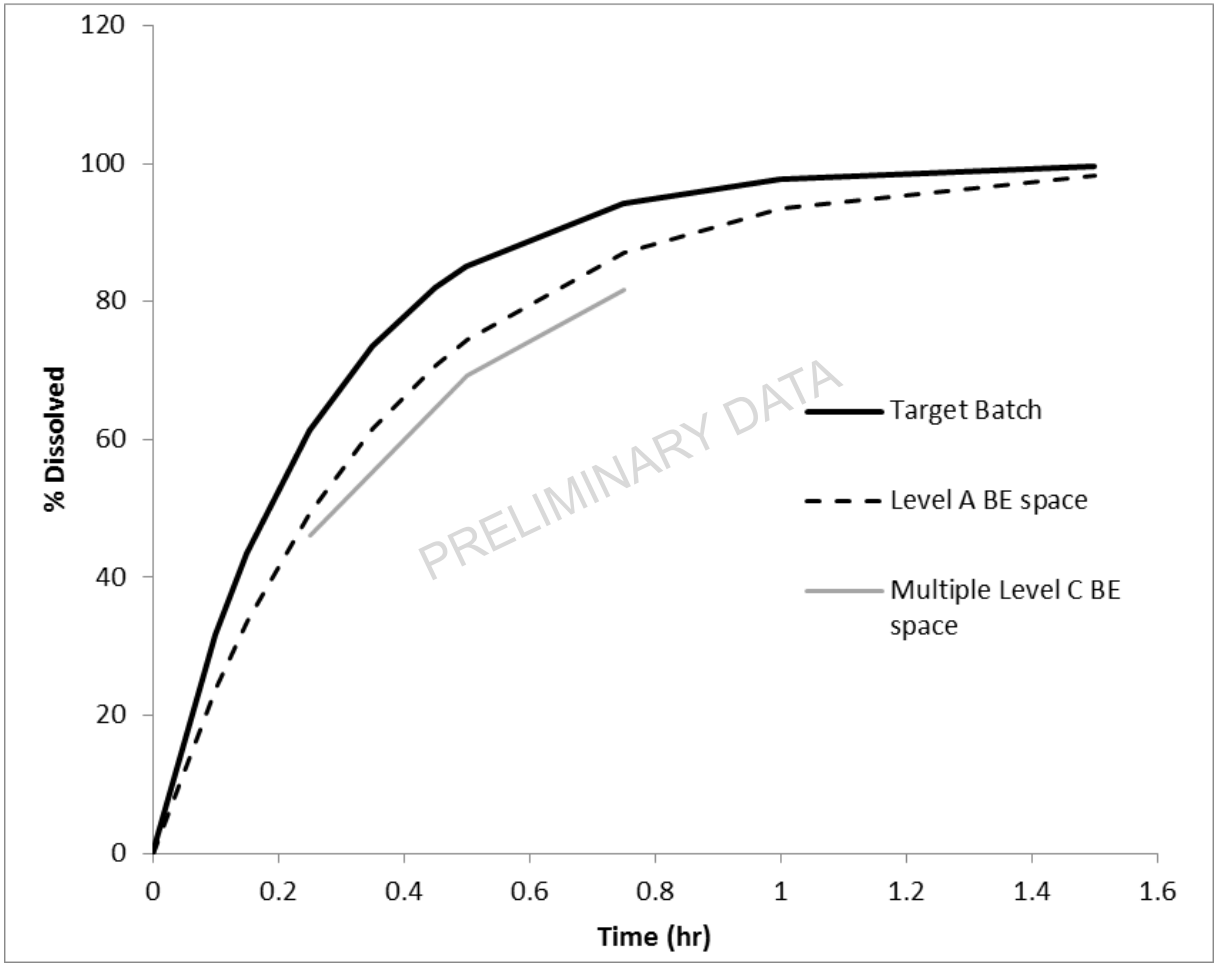
BE Predictions



Small differences in prediction of BE space between Multiple Level C and Level A

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Conclusions

- Multiple Level C IVIVCs
  - may be more readily established than Level A models for complex PK and for IR formulations
  - have been successfully used to project bioequivalence outcomes
  - can be used to set clinically relevant specifications by estimating the bioequivalent dissolution space
- Especially for IR products, information gained from a Multiple Level C vs. a Level A model may not be that different
  - Especially for BCS II compounds, dissolution variability impact, <u>if any</u>, may be just on C_{max} rather than AUC
- Additional modeling tools can be used to supplement the IVIVC model as needed (e.g. to assess impact of a CQA not included in the IVIVC study).

Acknowledgements

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- D. Good, D. Sperry, X. Zhang, A. Narang, A. Abend and PQRI BTC