UNIVERSITY OF KENTUCKY College of Pharmacy

NIPTE The National Institute for Pharmaceutical Technology & Education

Improving quality and lowering costs of pharmaceuticals

Integrated Approach for Evolving Standards for Analytical Characterization: Case Example – Excipient Variability

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Disclosure

I am a partial owner of Kansas Analytical Services, a company that provides solid-state NMR services to the pharmaceutical industry.

The results presented here are from my academic work at the University of Kansas and the University of Kentucky, and no data from Kansas Analytical Services is presented here.

FDA
Quality Risk Management

"The only difference between an innovator product and a generic product is the formulation" – paraphrase from a comment made at last year's GDUFA meeting

Analyze the Product

Intrinsic – Ingredients and Process
- Formulation – what's in it
- Manufacturing – how's it made

Extrinsic – What is the Product?
- Ingredient variability
- Drug-excipient interactions
- Impact of processing

Analyze the Performance

Functional Properties
- *in vitro* composition, disintegration, dissolution,

Bioequivalence
- *in vivo* clinical performance

FDA
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"The only difference between an innovator product and a generic product is the formulation" – paraphrase from a comment made at last year's GDUFA meeting

Analyze the Product and its Performance

Advanced Analytical Methodology
- Drug Substance
- Excipients
- Drug Product

- Interactions
- Impact on physical properties
- Physical/chemical stability
- Transformations

→

Functional Properties
- *in vitro* composition, disintegration, dissolution,

Bioequivalence
- *in vivo* clinical performance

FDA
Quality Risk Management

Risk Reduction Opportunities: two "very" common causes

- Deficient Facilities and Processes
- **Ingredient Variability – Excipients**

Recalls due to Excipient Variability:

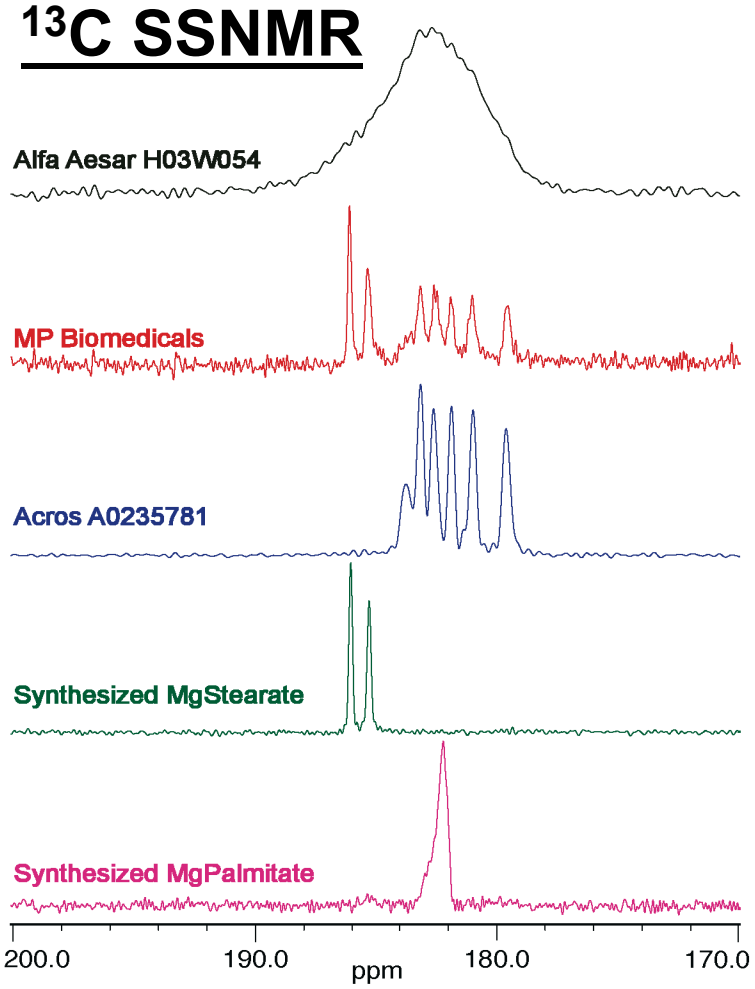
"Oral powder for suspension product **failed dissolution** due to glyceryl behenate acid value"

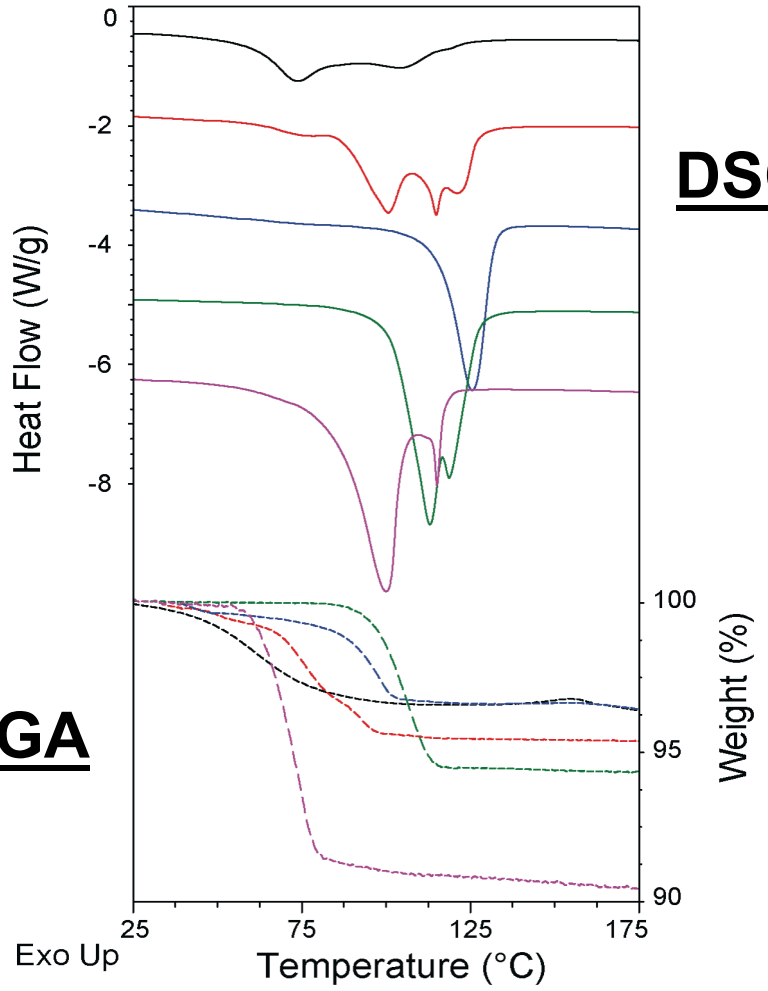
"Extended release tablet **failed dissolution** due to variability of ethyl cellulose excipient"

"Tablet lots had **significant dissolution failures** due to variation in the coating agent, Zein NF…"

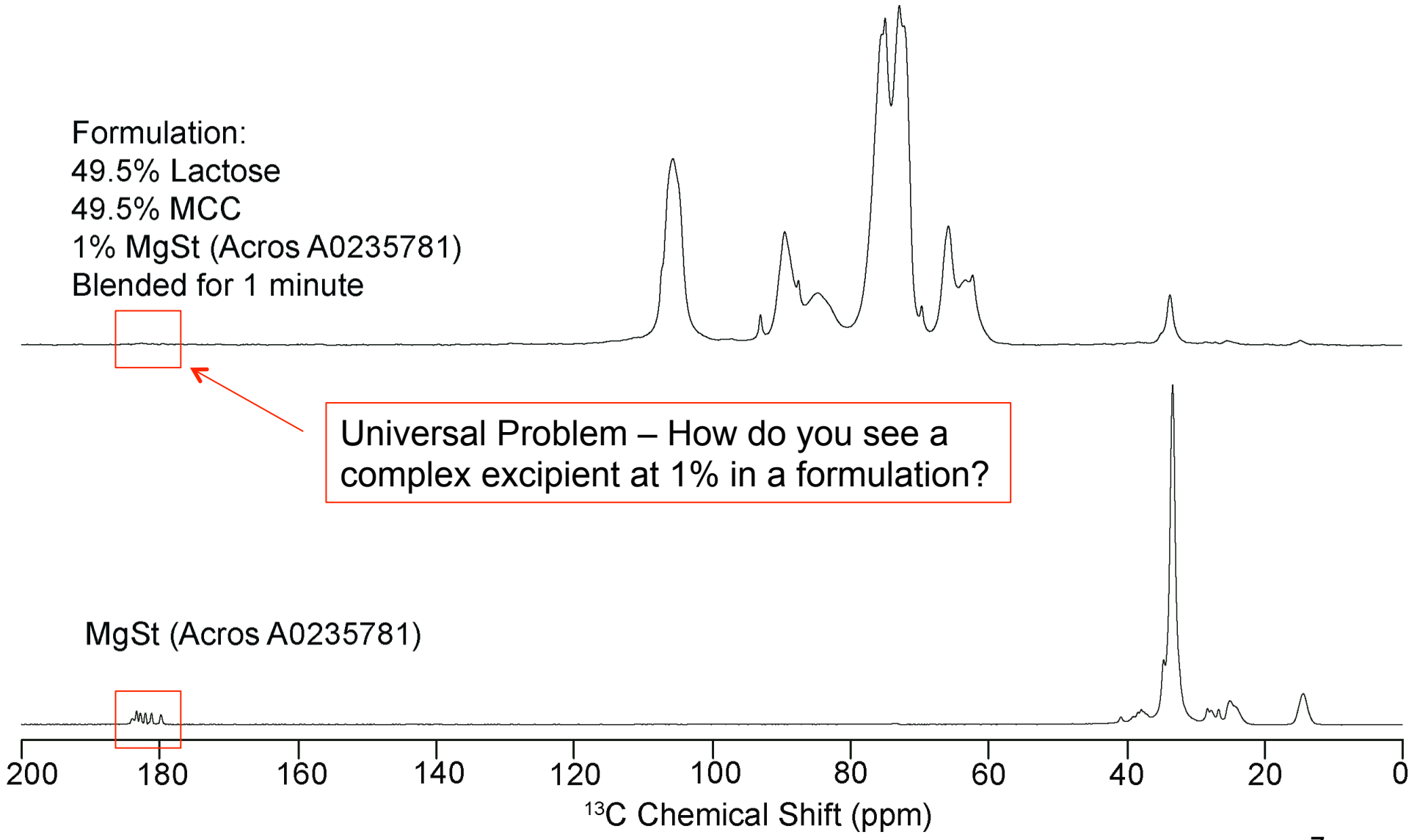
"**Dissolution failure** in soft gel capsules as a result of cross-linking of short chain aldehydes and other liquid components"

Magnesium Stearate: SSNMR, DSC,and TGA correlations

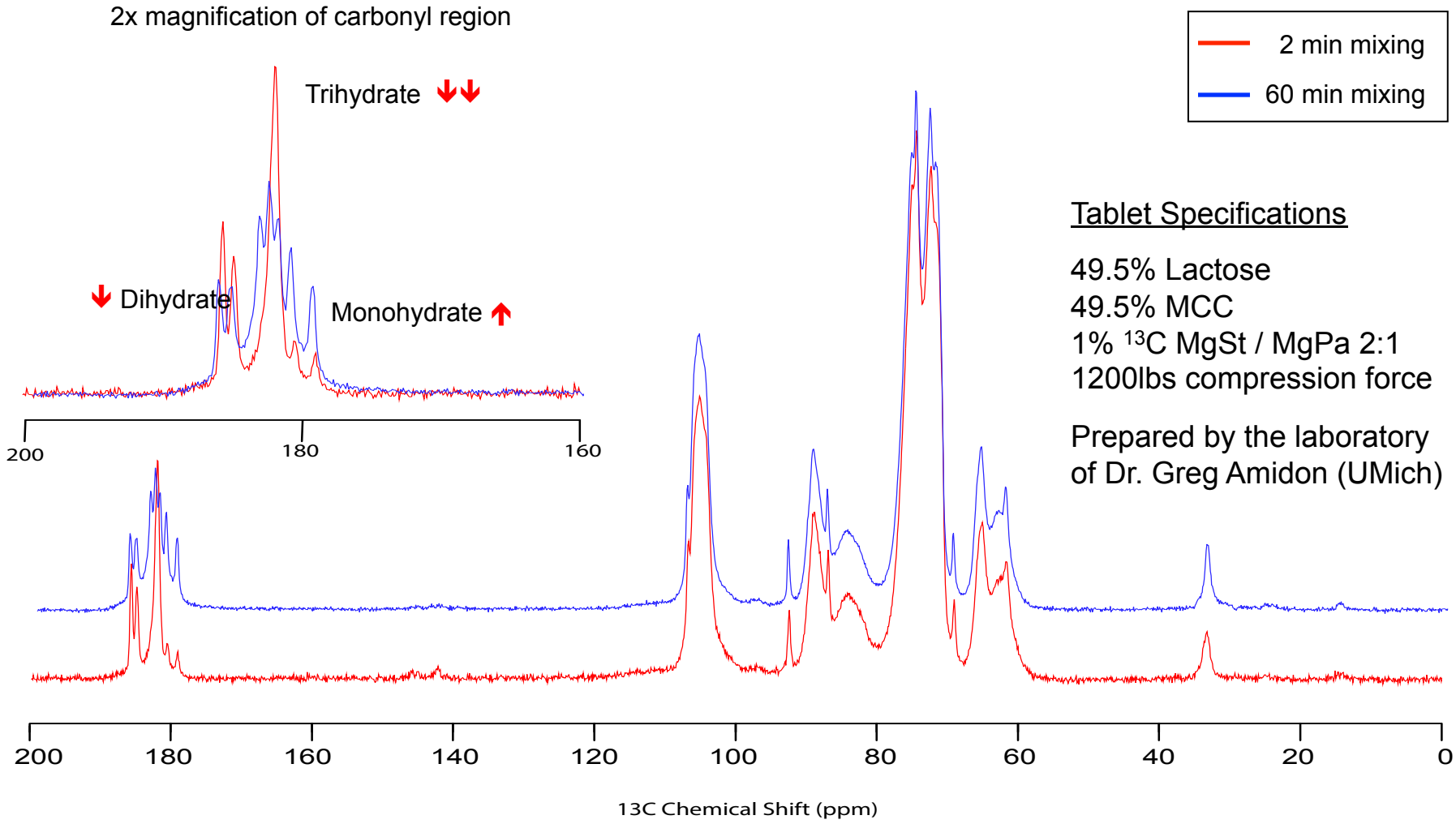




SSNMR Spectroscopy of Formulations Containing MgSt



SSNMR Spectroscopy of Tablets Containing MgSt

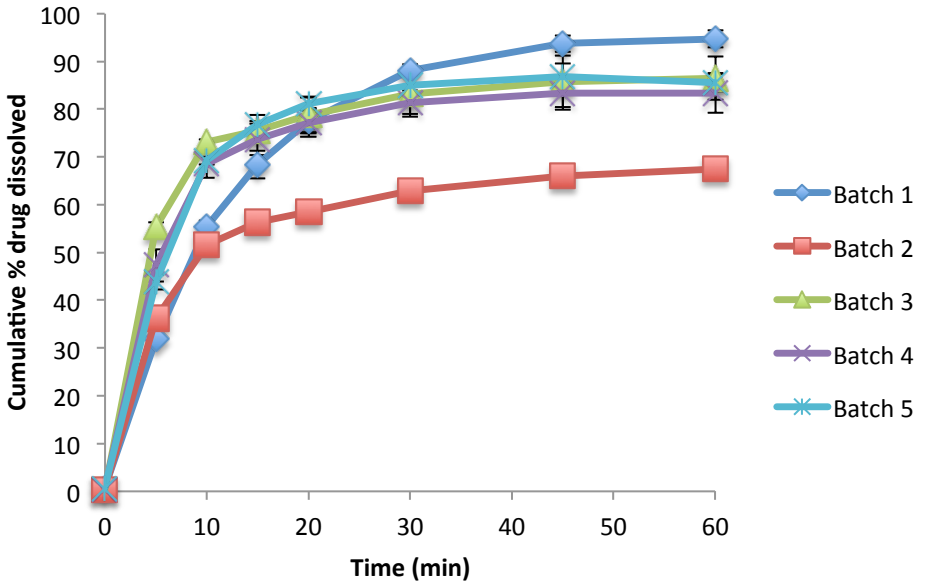


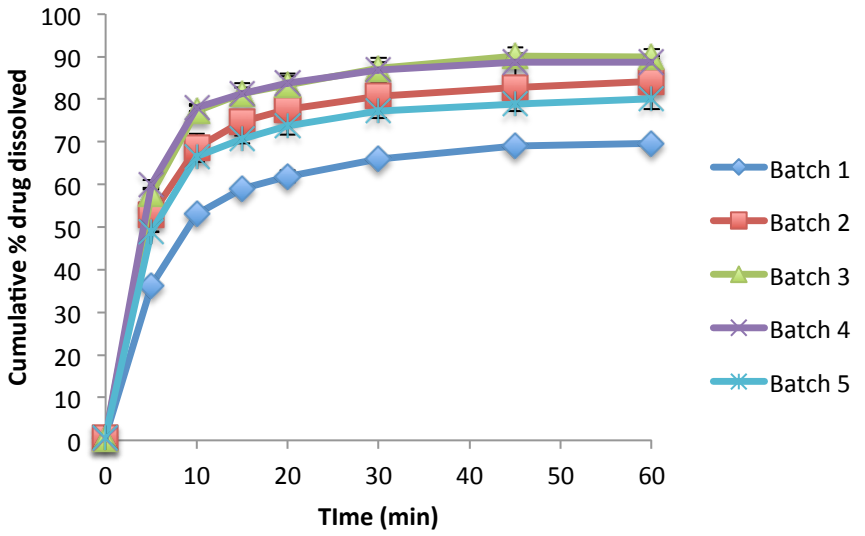
Tablet Specifications

49.5% Lactose
49.5% MCC
1% ^{13}C MgSt / MgPa 2:1
1200lbs compression force

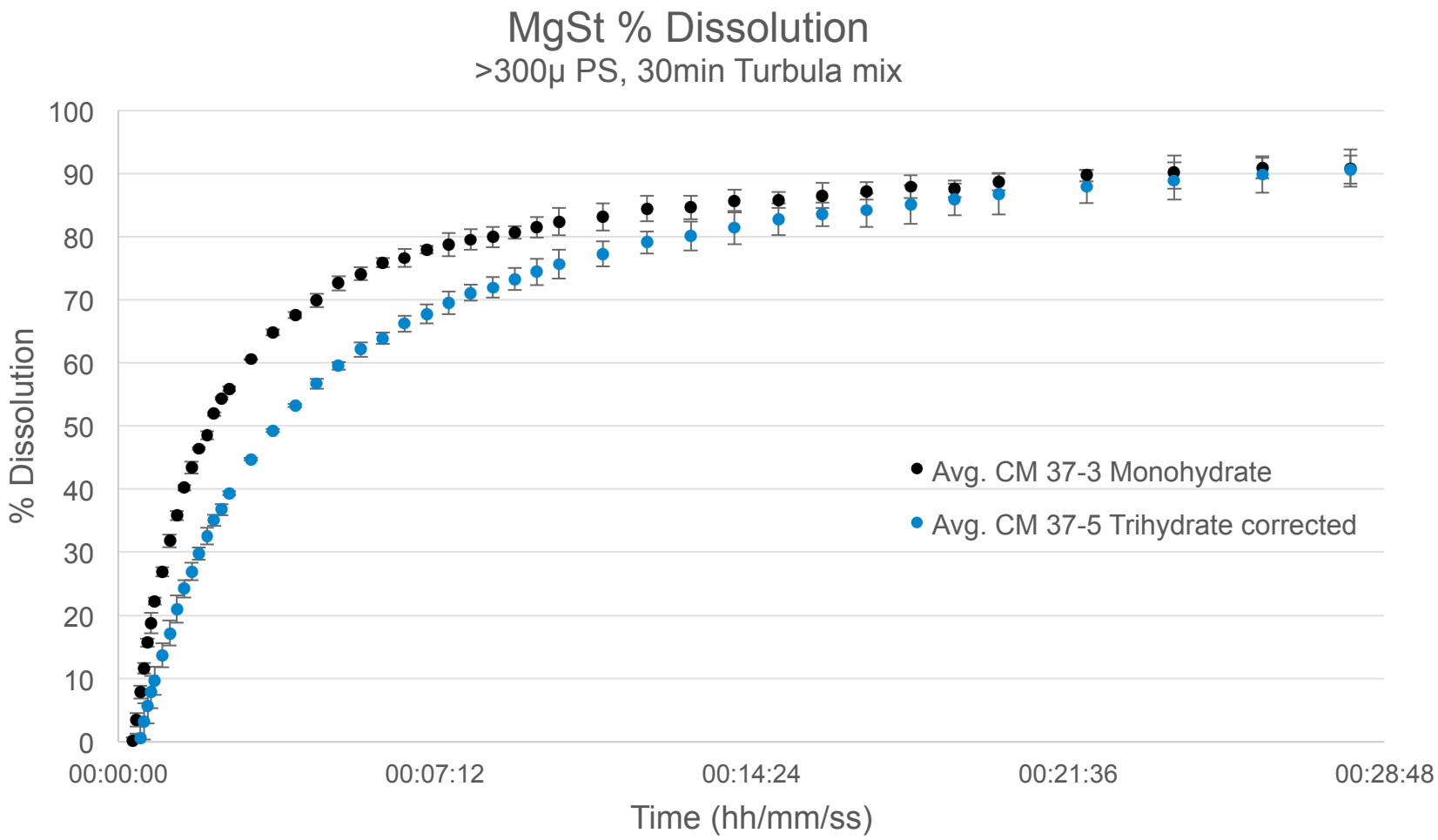
Prepared by the laboratory of Dr. Greg Amidon (UMich)

Impact of MgSt on Dissolution – Mixing Variability



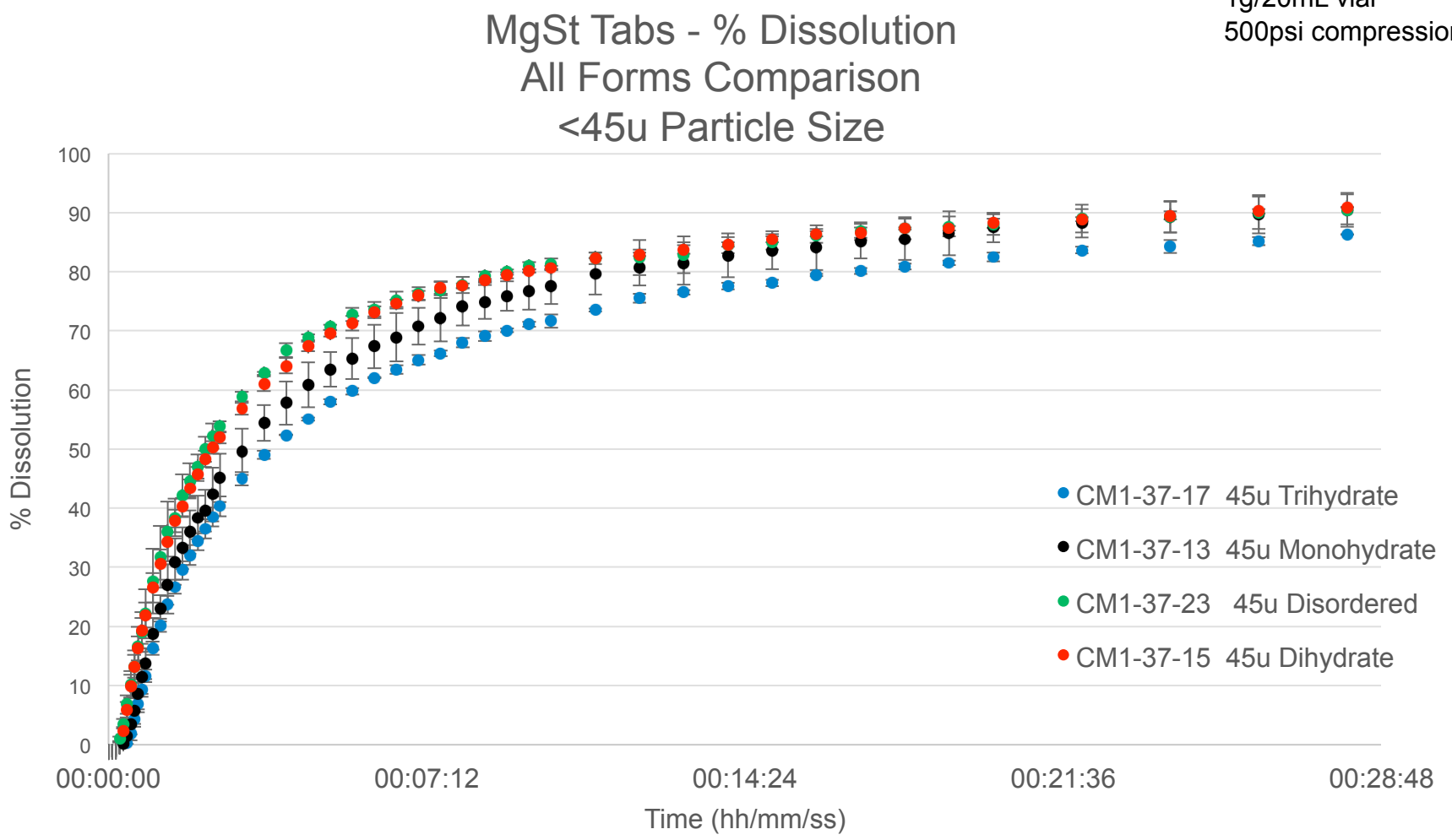


Impact of MgSt Form on Dissolution – Consistent Mild Mixing



Impact of MgSt Form/Particle Size on Dissolution

Other parameters
60 min Turbula mix
1g/20mL vial
500psi compression



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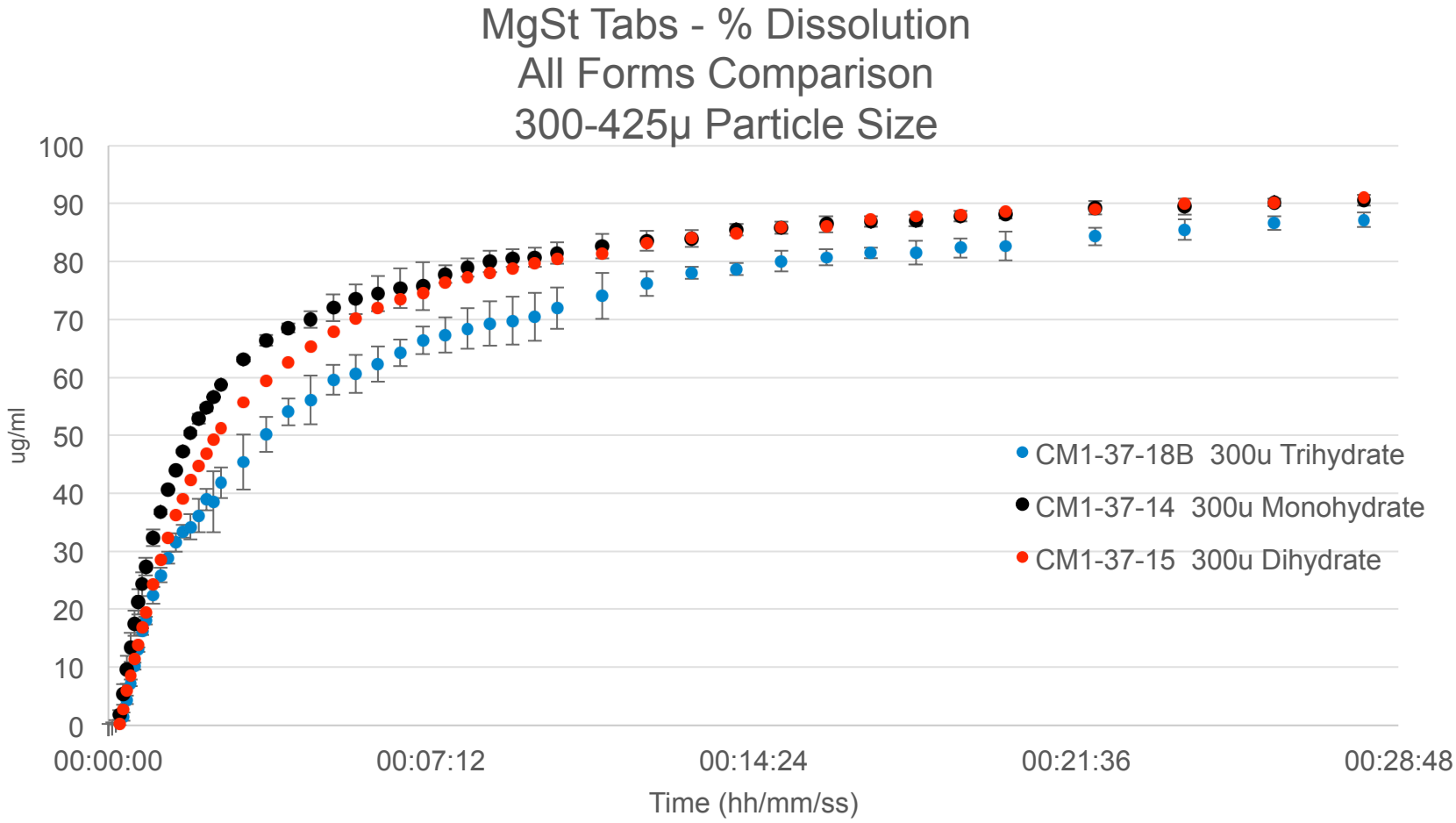

Summary

FDA Quality Risk Management

Analyze the Product and its Performance –
Advanced Analytical Characterization of Dosage Forms

Integrated approach to understand complex dosage forms, convert it to a knowledge base that is accessible, and translate that to reviewers through education

Recommendations for FDA Support – Establish Research Priorities for Generic Drug Product Characterization

- What is the optimum portfolio of orthogonal analytics that are needed for product characterization?
- How should these be integrated in design/development space?
- What should be the validation criteria for R&D analytics?
- What is the utility across dosage forms for these analytics?
- What is the relationship between R&D analytics, QC testing, and effective methods for root cause investigations?