#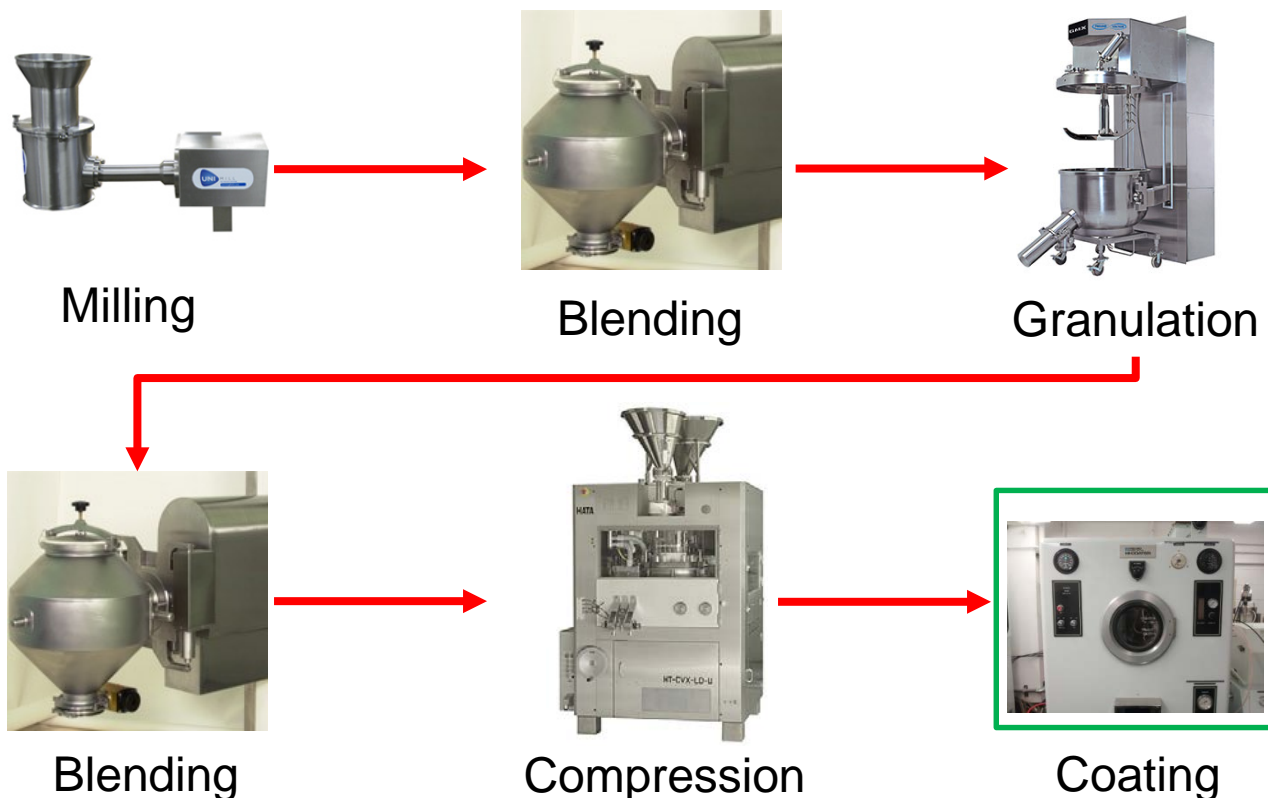 Improving On-line Monitoring of Tablet Coating Process with Terahertz Pulsed Imaging based Near-Infrared Coating Thickness Models
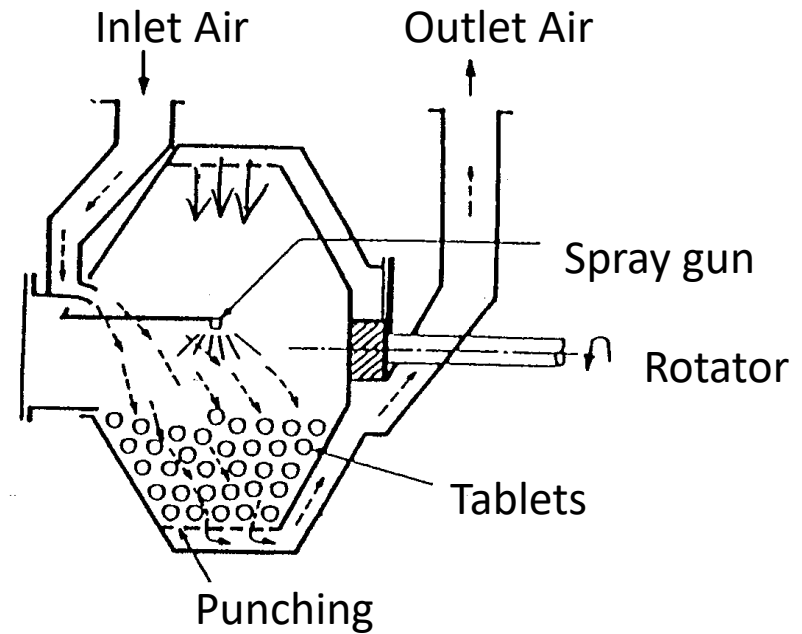
Shikhar Mohan
Noritaka Odani
Hanzhou Feng
James K. Drennen, III
Carl A. Anderson
IDRC 2018

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Solid Oral Dosage Manufacturing Process

- Example of tablet manufacturing process

Milling → Blending → Granulation → Blending → Compression → Coating

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Film Coating Process

Inlet Air   Outlet Air

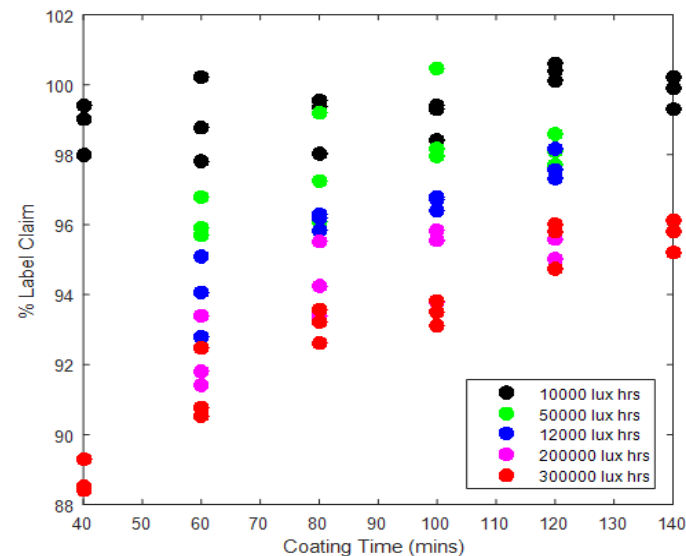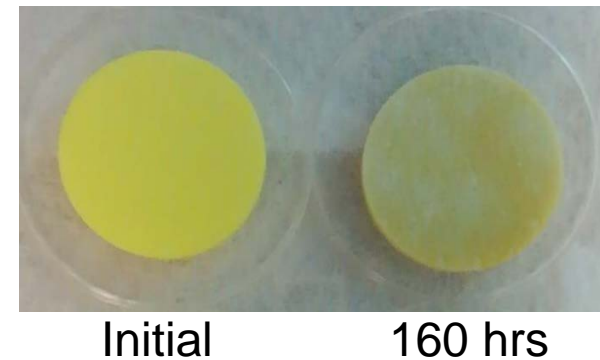Spray gun

Rotator

Tablets

Punching

Pre-heating ⇒ Spraying ⇒ Drying ⇒ Cooling

- Tablet coating is performed for reasons such as taste masking, aesthetics, stability improvement, and modifying drug release
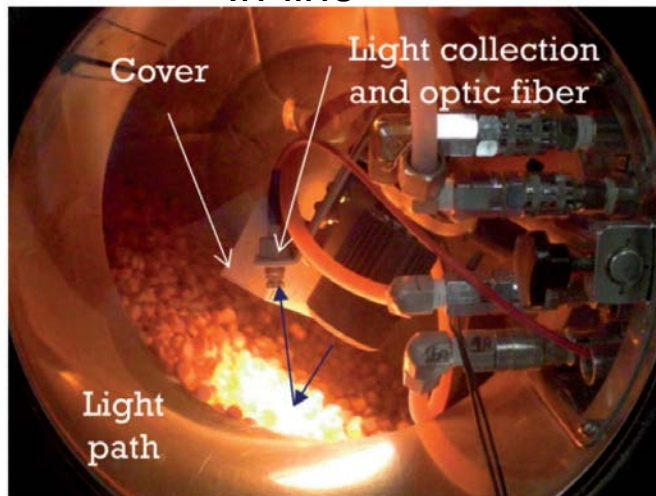
Coating for Photostability

- Film coating nifedipine tablets improves photostability of the product

- Core tablet formulation
  - Nifedipine (10%wt), HPC (70.8%wt), ethylcellulose (18.6%wt), magnesium stearate (0.6%wt)

- Coating Solution
  - HPMC (4%wt), Titanium dioxide (2.4%wt), talc (0.8%wt), PEG (0.8%wt)

- The amount of photo-degradation is related to the film coating thickness.

Initial   160 hrs

Legend:
- 10000 lux hrs (black)
- 50000 lux hrs (green)
- 12000 lux hrs (blue)
- 200000 lux hrs (magenta)
- 300000 lux hrs (red)

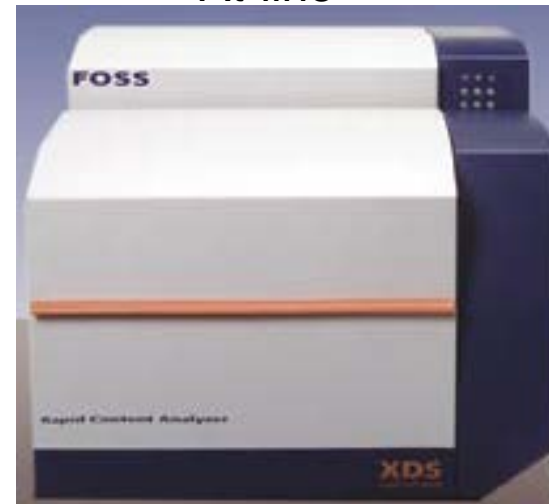x-axis: Coating Time (mins)
y-axis: % Label Claim

Estimated Coating Thickness with NIR

- One of the most common PAT techniques for monitoring coating thickness is NIR

- Disappearance of core and appearance of film layer with increase in coating time information in NIR can be associated with film thickness
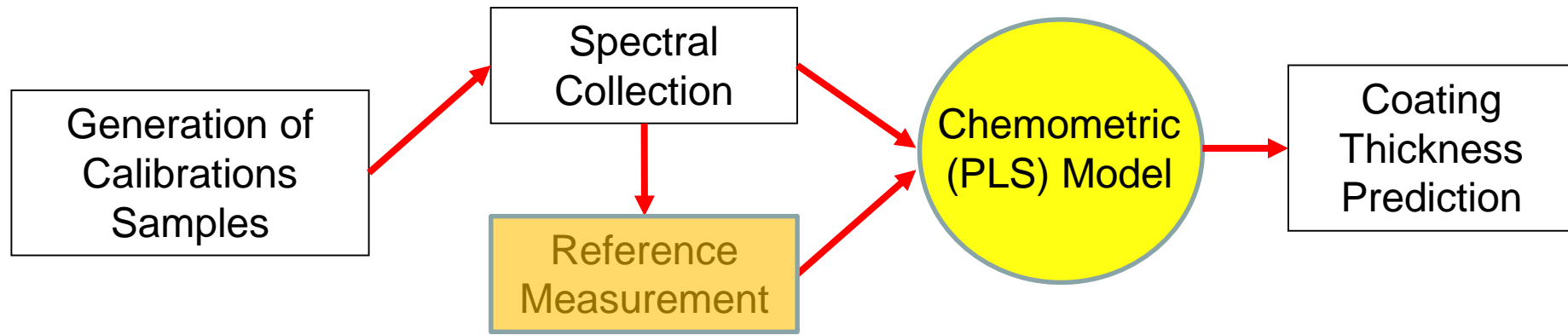
In-line

At-line

Igne, Benoît, et al. "Effect of Sampling Frequency for Real-Time Tablet Coating Monitoring Using Near Infrared Spectroscopy." *Applied spectroscopy* 70.9 (2016): 1476-1488.
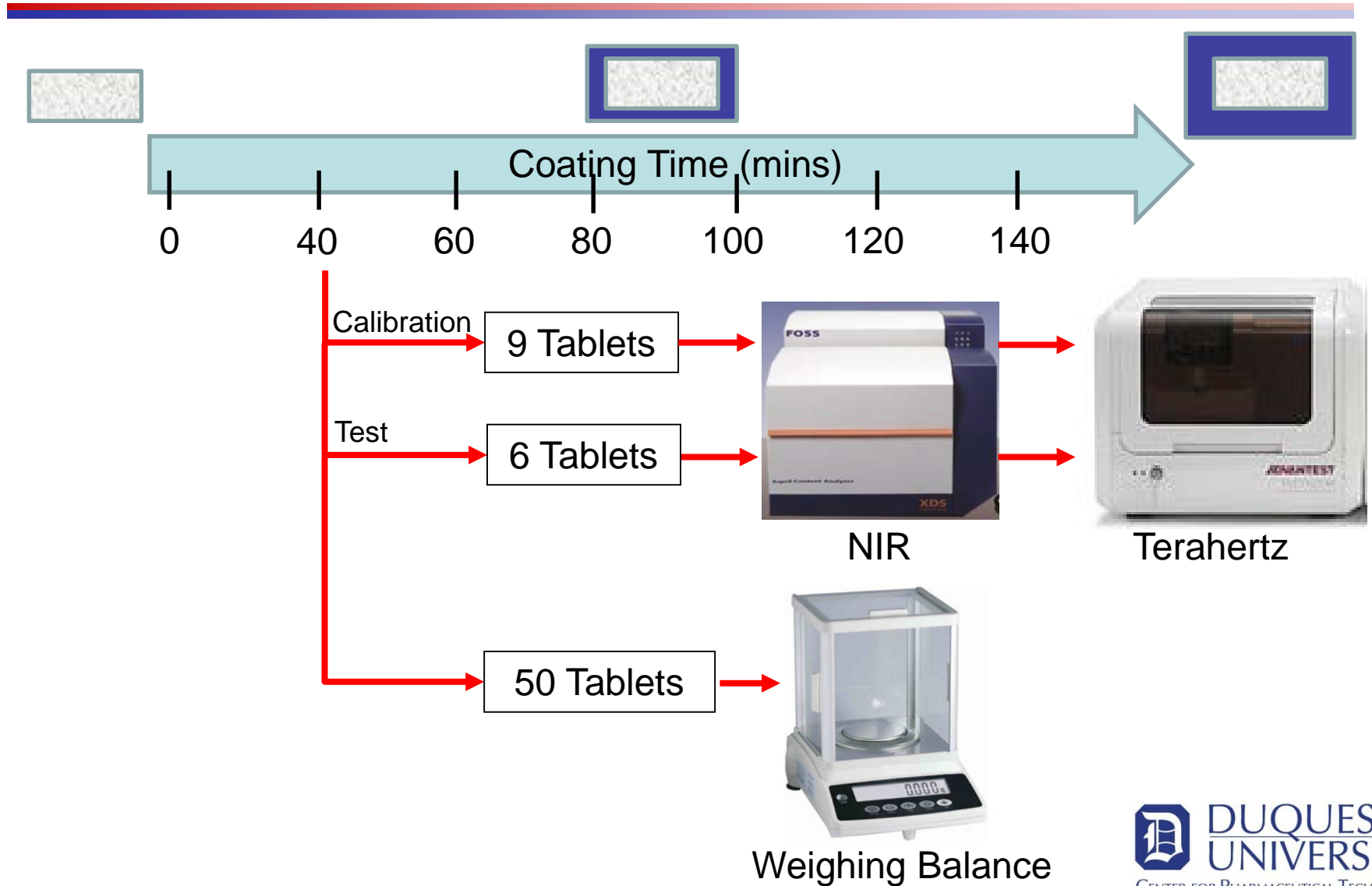
NIR Method Development

- Reference coating thickness includes:
  - Weight-gain based coating thickness
  - Micrometer based coating thickness
  - Cutting tablets and taking images
  - X-ray microtomography
  - Terahertz spectroscopy
- This study investigated the affect off two different reference method on NIR prediction performance of coating thickness

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Experimental Design

Coating Time (mins)

0   40   60   80   100   120   140

Calibration → 9 Tablets → NIR → Terahertz

Test → 6 Tablets → NIR → Terahertz

NIR

Terahertz

50 Tablets → Weighing Balance

Weighing Balance

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Weight Gain Based Coating Thickness

- One of the most commonly used reference methods is weight gain based coating thickness estimates

- Weight gain measurements are obtained by subtracting average coated tablet weight and average core tablet weight

- Weight gain is converting to coating thickness by measuring film density

$$Solid\ Weight = Tablet\ Weight - (Tablet\ Weight * \frac{LOD}{100})$$

$$Film\ Amount = Solid\ Weight_{Sample} - Solid\ Weight_{Core}$$

$$Coating\ Thickness(\mu m) = \frac{\frac{Film\ Amount\ (mg)}{Surface\ Area_{Core}\ (mm^2)}}{Film\ Density\ (\frac{mg}{mm^3})} * 1000$$
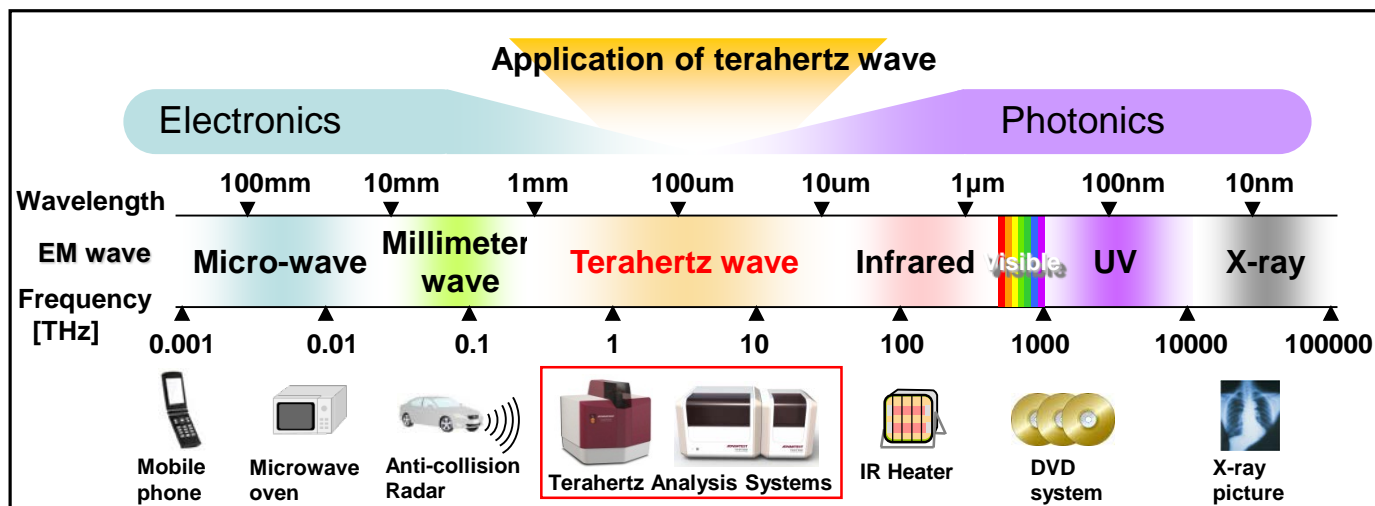

Film Casting

Weight Gain Based Coating Thickness Cont.

- Disadvantages
  - Assumes narrow core tablet weight distribution
  - Doesn't account for attrition during the process
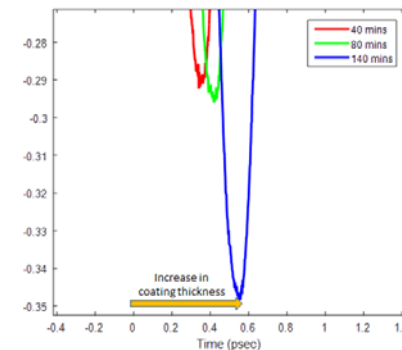 - Unaccounted moisture variation leads to error in measurement

Relative error of each model (RMSEP/ AVG of predicted value of calibration set)

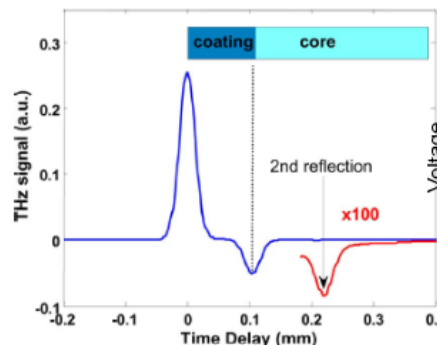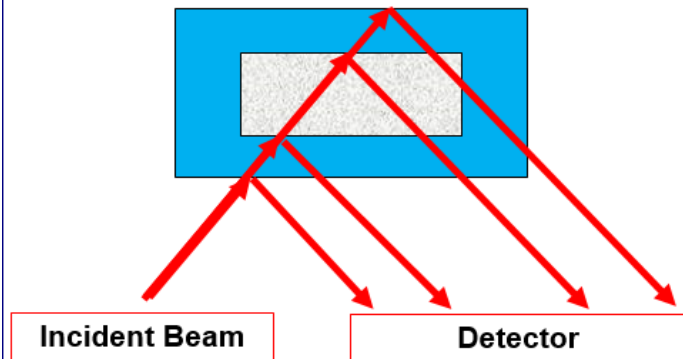| Model	Relative Error
film amount model 100T	9.2
film amount model 50T	9.2
film amount model 10T	12.1
film amount model 5T	15.5

Terahertz Spectroscopy

- Terahertz radiation is in the far-infrared region of the electromagnetic spectrum (0.5-7 THz)
- The low frequency radiation induces:
  - intermolecular bond vibrations (hydrogen-bonding)
  - Crystalline phonon vibrations
  - Torsion vibrations
- Application
  - Coating Thickness
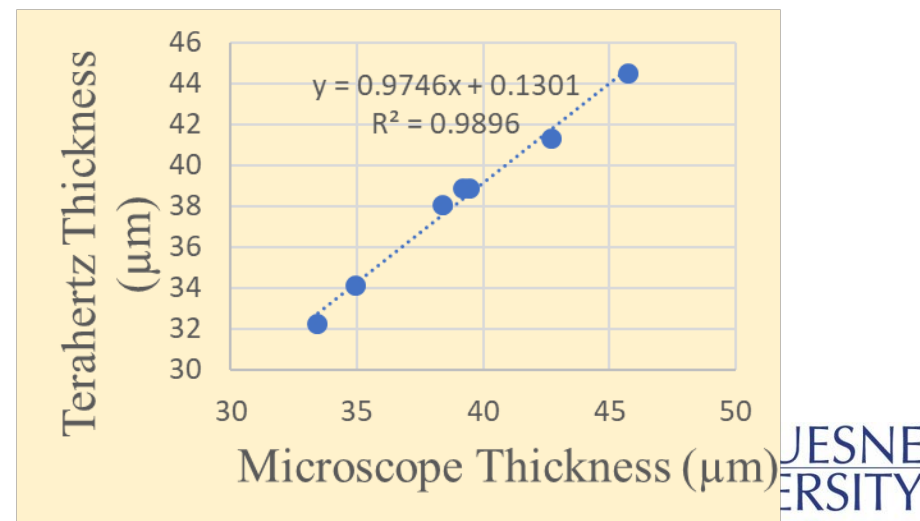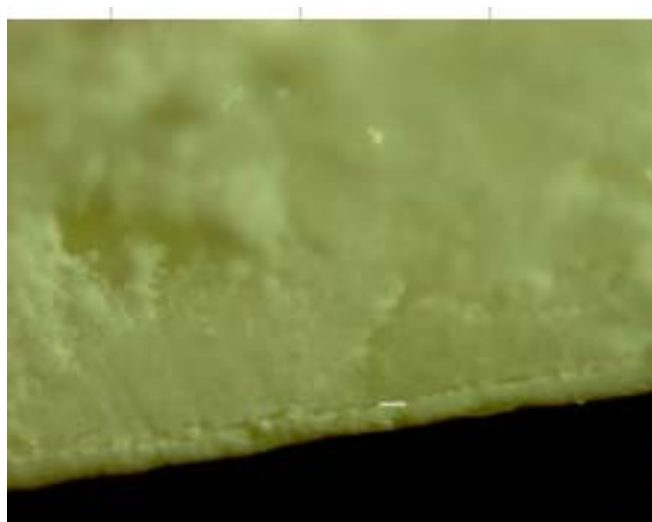 - Crystallinity/polymorphism

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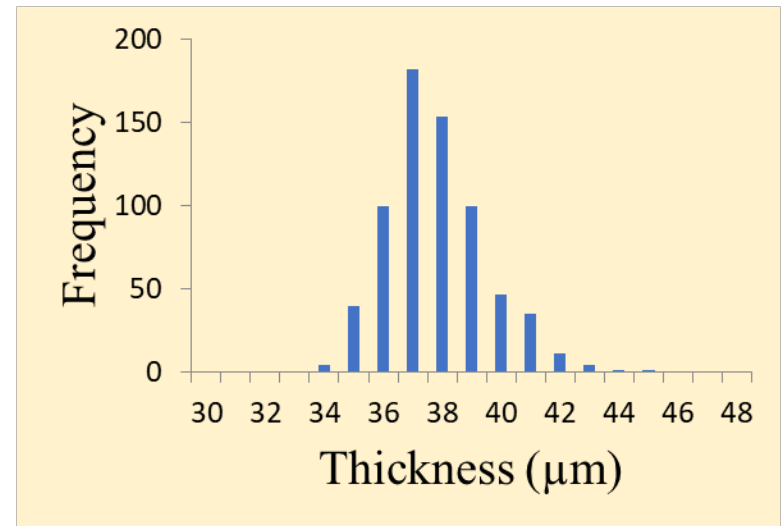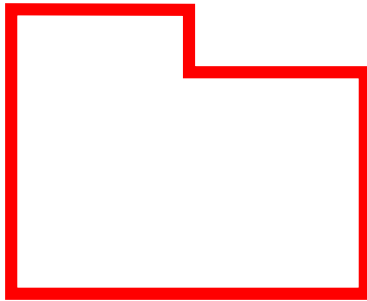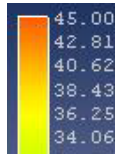
Terahertz Based Coating Thickness

- Terahertz radiation is in the far-infrared region of the electromagnetic spectrum (0.5-7 THz)

- The time a reflected Thz beam reaches detector after encountering an interface is used to determine thickness
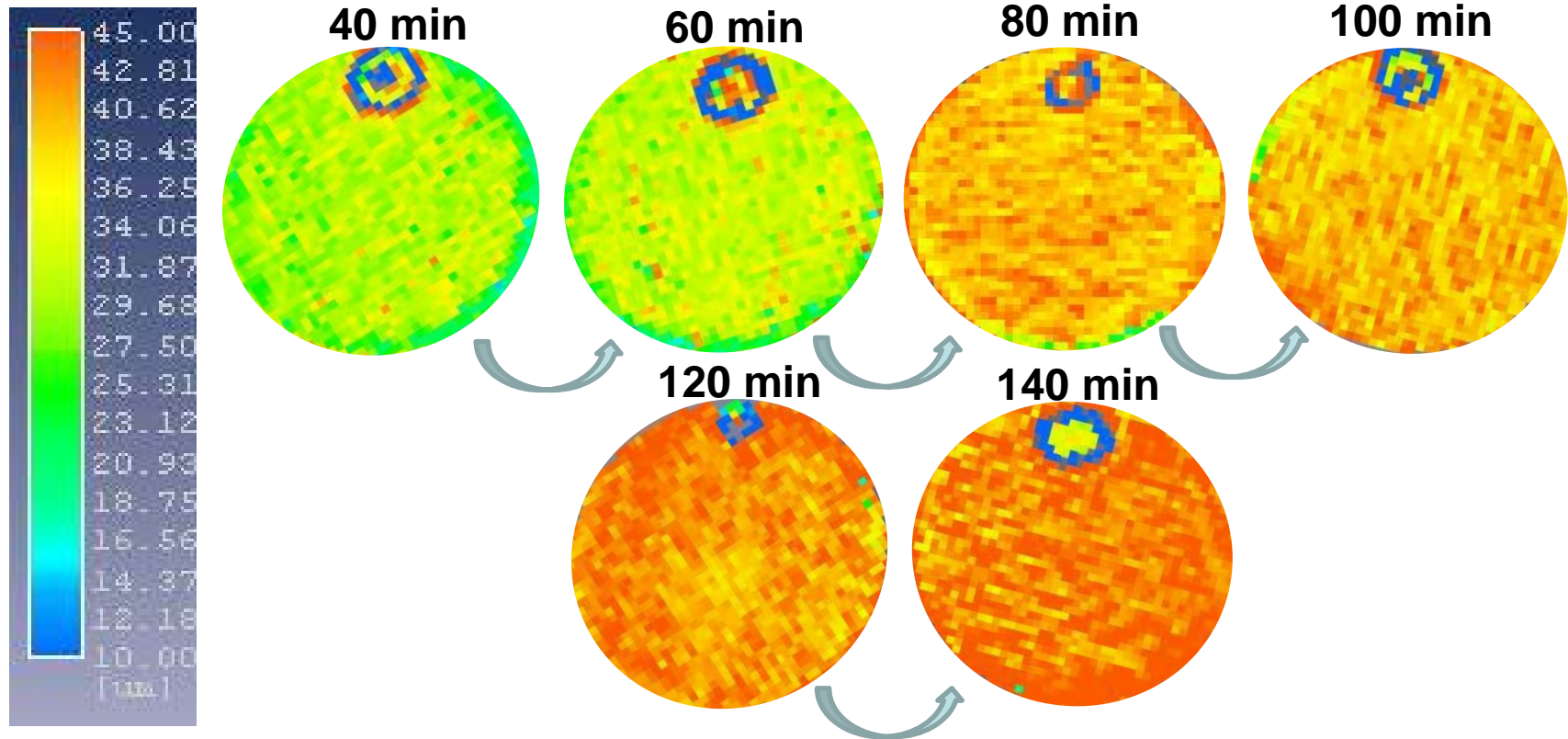
$$CT = \frac{c\Delta t}{2n}$$

Shen, Yao-Chun, and Philip F. Taday. "Development and application of terahertz pulsed imaging for nondestructive inspection of pharmaceutical tablet." *IEEE Journal of Selected Topics in Quantum Electronics* 14.2 (2008): 407-415.

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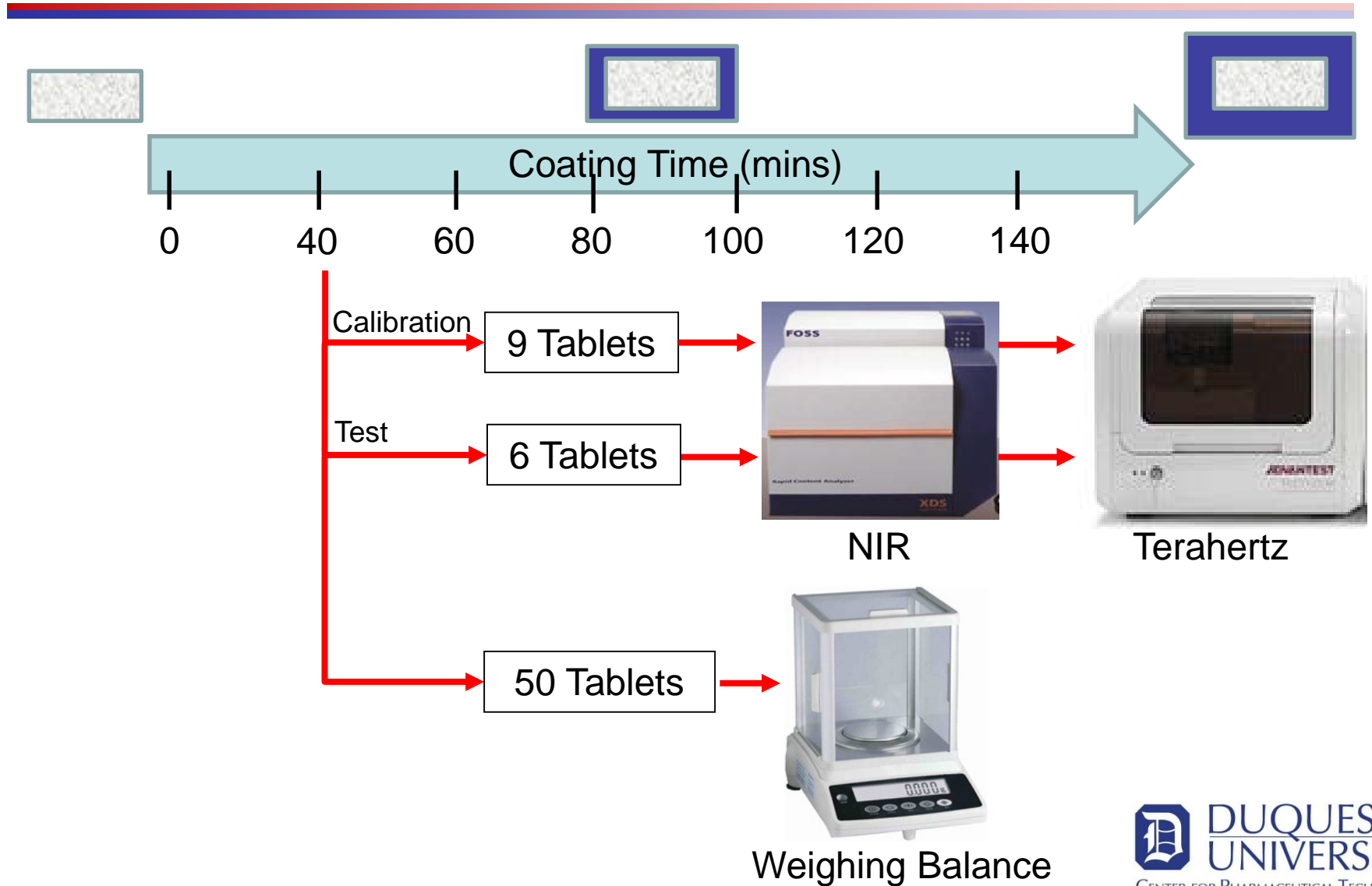
Validation of Terahertz Thickness Measurments

Terahertz Images

- The terahertz images show increasing coating thickness versus time.

Experimental Design

Coating Time (mins)

0   40   60   80   100   120   140

Calibration → 9 Tablets → NIR → Terahertz

Test → 6 Tablets → NIR → Terahertz

50 Tablets → Weighing Balance

NIR

Terahertz

Weighing Balance

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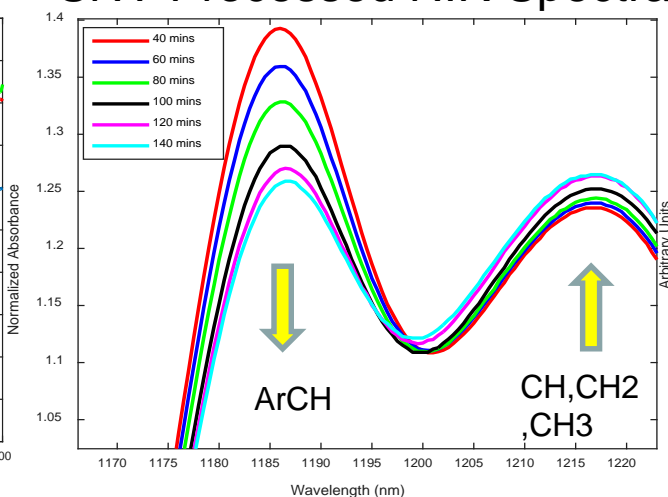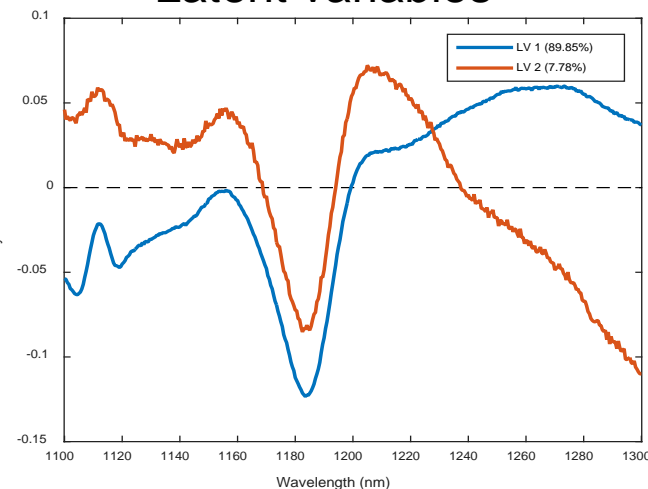CENTER FOR PHARMACEUTICAL TECHNOLOGY

NIR Spectra

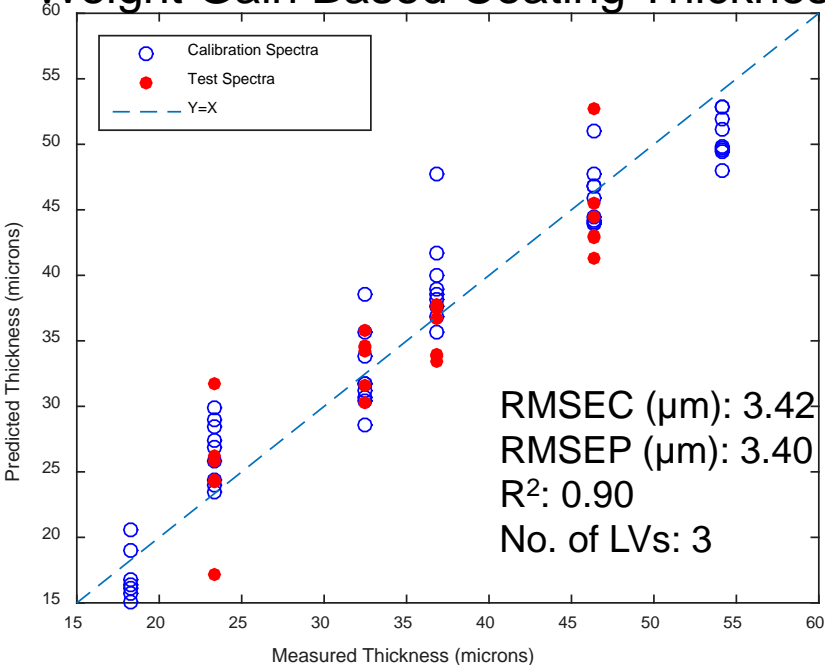NIR Pure Components

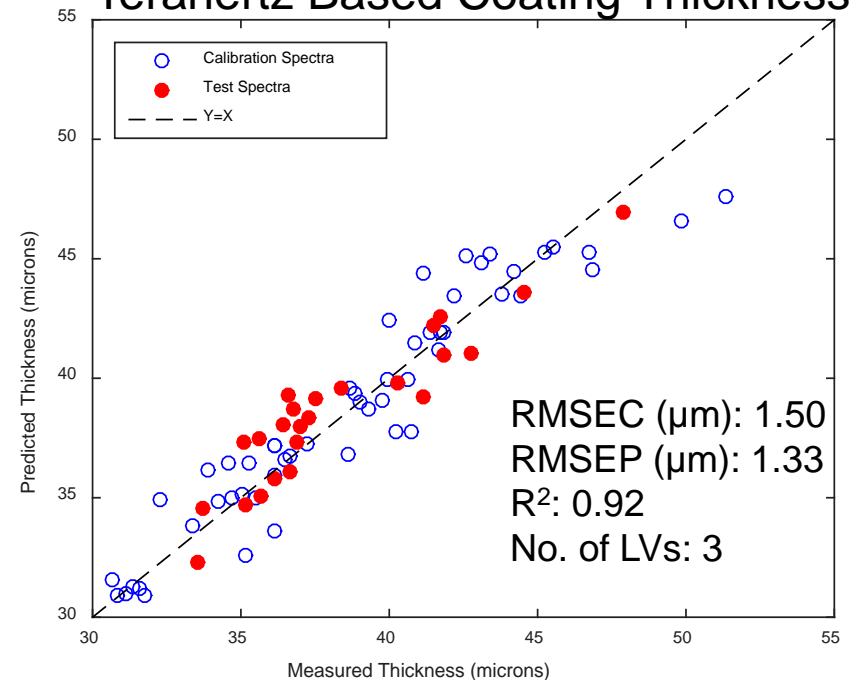SNV Processed NIR Spectra

Latent variables

- The wavelength region of approximately 1100 to 1300 nm was used for model development because this region provided polymer and drug information

NIR Model Comparison
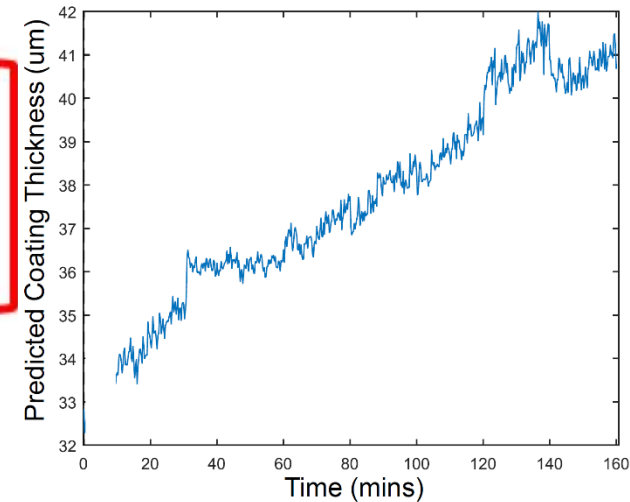

Weight Gain Based Coating Thickness

RMSEC (µm): 3.42
RMSEP (µm): 3.40
R²: 0.90
No. of LVs: 3

Terahertz Based Coating Thickness

RMSEC (µm): 1.50
RMSEP (µm): 1.33
R²: 0.92
No. of LVs: 3
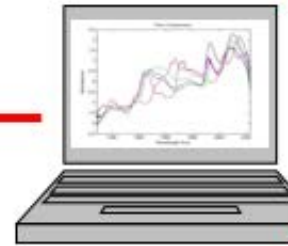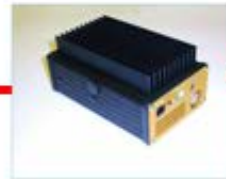
- The prediction performance of the NIR model using terahertz based coating thickness as reference showed better prediction performance compared to when weight gain reference method was used.

Real Time Monitoring of Placebo Batch

- NIR can be placed on-line to monitor coating thickness using reference terahertz measurements

Igne, Benoît, et al. "Effect of Sampling Frequency for Real-Time Tablet Coating Monitoring Using Near Infrared Spectroscopy." *Applied spectroscopy* 70.9 (2016): 1476-1488.

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Summary

- NIR coating thickness model was more accurate when terahertz was used as reference method instead of weight gain based coating thickness

- Terahertz coating thickness measurements can be used as reference technique for on-line NIR models

Acknowledgements

- Advantest; Advantest Advantest America, Inc., San Jose, CA

- Duquesne University Center for Pharmaceutical Technology (DCPT); Duquesne University, Pittsburgh, PA

Thank You