



Terahertz Research at FDA

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Terahertz Research at FDA Outline



- FDA PAT Initiative and Terahertz
- Transmission of pharmaceutical samples dispersed in polyethylene.
- Transmission of whole tablets.
- Pulse imaging of a delayed-release dosage form.
- Pulse imaging of a complex dosage form.



FDA PAT Initiative



General Regulatory Needs:

- Identify emerging technologies that may contribute to future process analytical technology.
- Uncover the scientific merits and technical challenges for emerging technologies.
- Share the findings with FDA reviewers, managers, and the scientific community.

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FDA PAT Initiative



Objective & Goals

Use the principles of QbD and PAT to:

- Examine the effects of instrumental and compositional variables on spectral data quality used to characterize pharmaceutical materials and dosage forms.
- Develop quantitative approaches in spectroscopy for pharmaceutical applications.

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FDA PAT Initiative



Identifying PAT compatible technologies

Must haves:

- Non-destructive
- Fast enough to sample meaningfully

Good to haves:

- Non-contact
- Simple
- Process compatible data
- Continuous sampling capability

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Some PAT Technologies ca. 2000



- Physical Values: T, P, Mass, Power
- Physical Properties: Thermal Conductivity & Effusivity, RI, η , ρ , etc.
- Near Infrared – Abs. & Refl.
- Raman
- Infrared – ATR, Diffuse refl.
- Tuned-Diode Laser Absorbance Spect.
- Active & Passive Acoustic Spect.
- ... Many more (including **Terahertz Spectrometry**).

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Terahertz spectrometry



- PAT characteristics: non-contact, non-destructive, comparatively fast.
- Instrumentation:
 - Synchrotron radiation sources.
 - Modified FTIR (DPQR-NIST work).
 - Electro-optical, pulsed NIR light gated Auston solid state switch (DPA – TeraView work).

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Terahertz Spectrometry Configurations



- Transmission
- Pulsed imaging
- Reflectance

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Terahertz Transmission



- Measures the entire volume traversed by the beam.
- Single beam – separate reference spectrum.
- $Abs = -\log_{10} (T_{Sample} / T_{Reference})$.
- Applies to most dry solids.
- Can work with intact samples.
- High optical density - inherently scattering media.

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THz Transmission

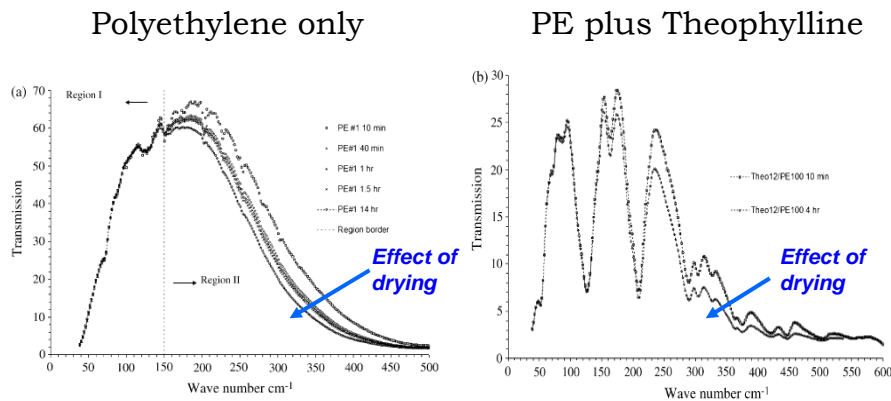


- Huiquan Wu's work on purposely formulated tablets.
- Small scale tablet batches formulated according to typical pharmaceutical practice.
- Resulting tablet milled and diluted (<10%) in a Polyethylene pressed pellet matrix for Terahertz spectra.

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THz Transmission Spectra – the effect of drying



Spectra collected on a conventional FTIR modified for far-infrared
Range: 700-50 cm^{-1} .

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Effects of Instrumental and Compositional Variables



Factors that impact THz spectra:

- Component loading (6 mg per 100 mg PE).
- Component chemistry (crystalline material produces strong peaks).
- **Disk drying time** (wait at least 30 min).

What contributes to disk drying time dependency?

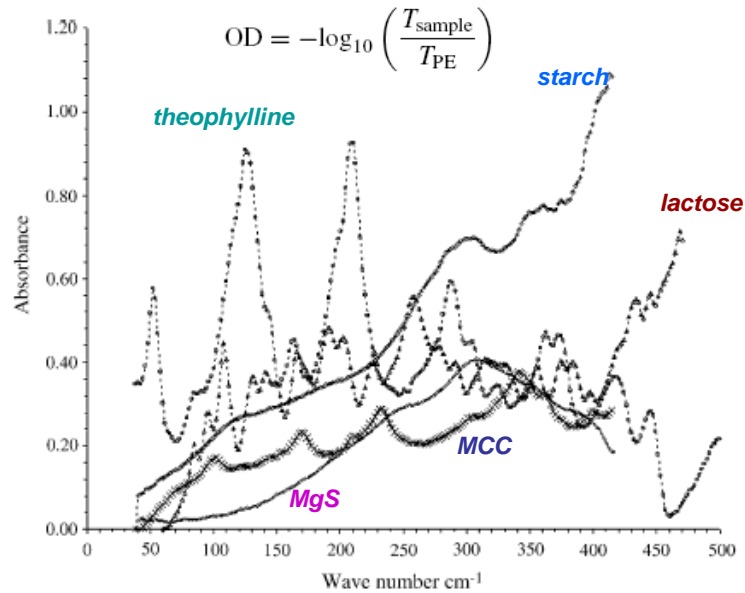
- Quality of the PE (to a large extent).
- Particle scattering (particle size of sample & PE).
- Absorbed moisture.

Wu et al, International Journal of Pharmaceuticals 343(2007)148-158

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THz Absorbance Spectra



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Predicting API & Excipient Concentration



Three Analysis Methods Used:

- Characteristic Peak Univariate Method
- Superposition Method
- Multivariate Data Analysis Method

Univariate Method (linear regression):

Theophylline Peaks:

- 129 cm^{-1} and 210 cm^{-1}
- R^2 ranged from 0.28 to 0.55

Lactose Peaks:

- 141 cm^{-1} and 216 cm^{-1}
- R^2 ranged from 0.18 to 0.49

Wu et al, J. Pharm. Sci. 2007, DOI 10.1002/jps.21004

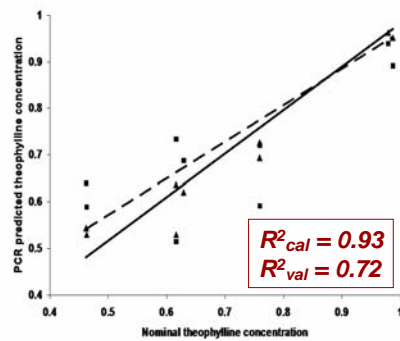
14



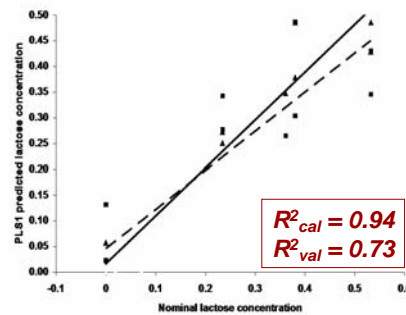
Multivariate Regression Methods – predicting API and Excipient from Terahertz transmission spectra



PCR: Theophylline



PLS: Lactose



————— Calibration
----- Validation

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THz Tablet Transmission

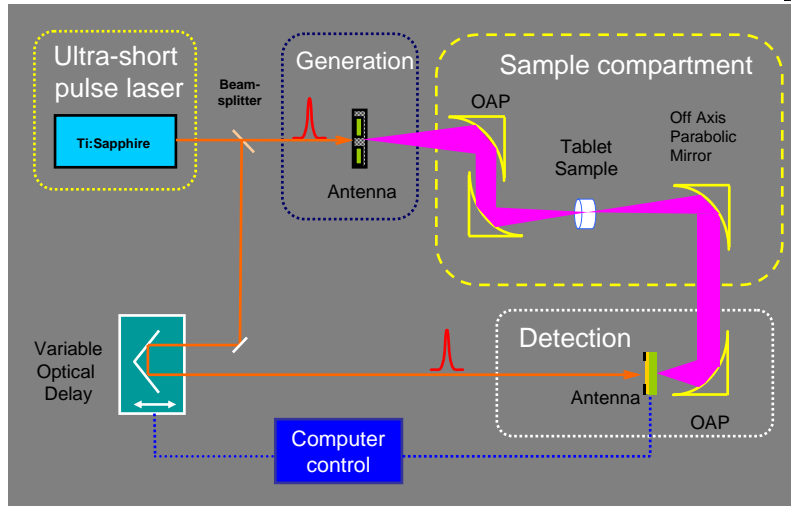


- Pulsed Terahertz spectrometer.
- Whole tablet placed in the beam.
- Highly scattering medium.
- This measurement shares many of the same problems as NIR tablet transmission that result from very low light throughput.

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THz – Tablet Trans



TeraView instrument configuration.

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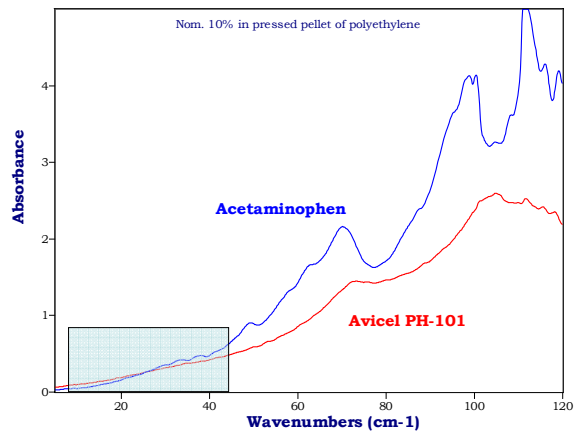


Terahertz Transmission



Components of formulated tablets –
10% in Polyethylene pressed disks.

Terahertz Absorbance Spectra



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Experimental sample set



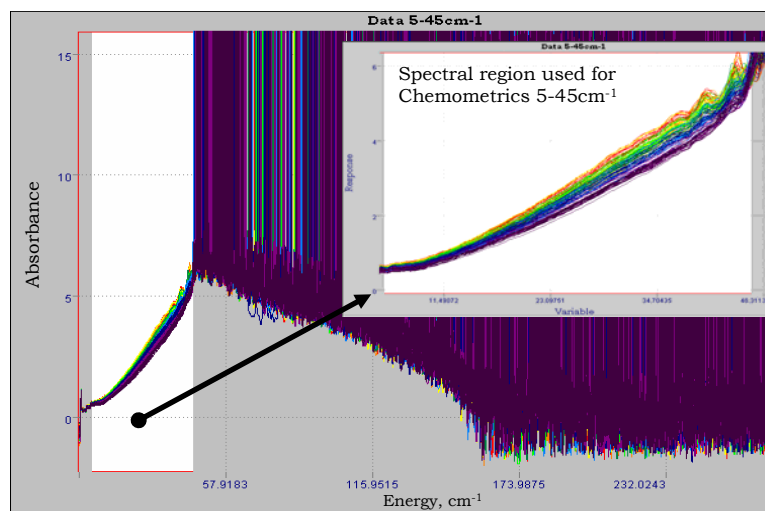
Sample sets	APAP Content(mg) from	
Sample #	Formulation	HPLC
1	59.2	59 ± 3
2	68.3	70 ± 2
3	77.4	78 ± 2
4	81.9	84 ± 3
5	91	90 ± 3
6	100.1	101 ± 2
7	104.7	103 ± 3
8	113.8	114 ± 2
9	122.9	120 ± 2

5 tablets of each content pressed at three different compaction forces – 5.9, 8.8 and 11.8 kN
5 X 9 X 3 = 135 samples scanned

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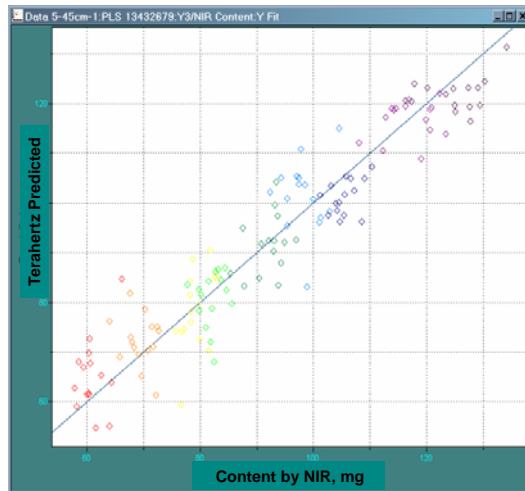
Full tablet THz Trans



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THz Trans - Chemometrics



9 content values
3 compressions
5 tablets each
135 THz Transmission

Content from NIR
Calibration.

Partial Least Squares

No transforms
Mean centered data
5 Factors

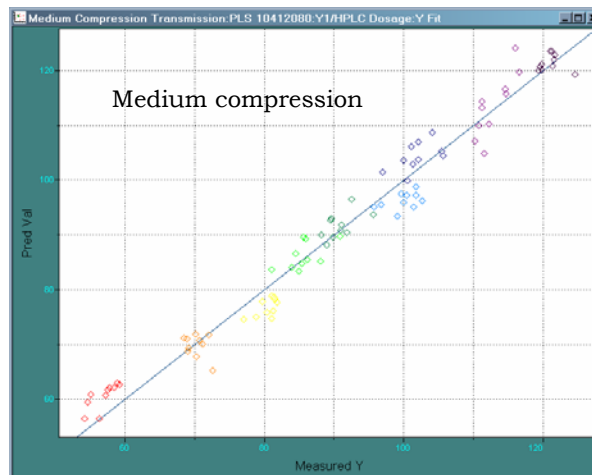
Assessments:

Y-fit plots and simple
statistics

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NIR Trans - PLS Fit

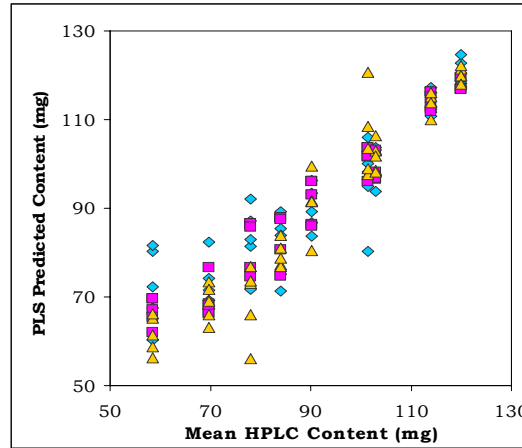


PLS Model of NIR spectra using HPLC content values gives RMSECV = 3.6%

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THz Trans – PLS Fit



Y-Fit results for PLS model of terahertz spectra using mean content values from HPLC analysis.

Compaction force:

◆ 5.9 kN

■ 8.8 kN

▲ 11.8 kN.

PLS Content Model	Factors	Percent	Cumulative	RMSECV
Est. content	6	0.120	98.860	6.675
Mean HPLC	6	0.128	98.856	6.622

Spencer, et. al., J. Pharm. Innov. (in press).

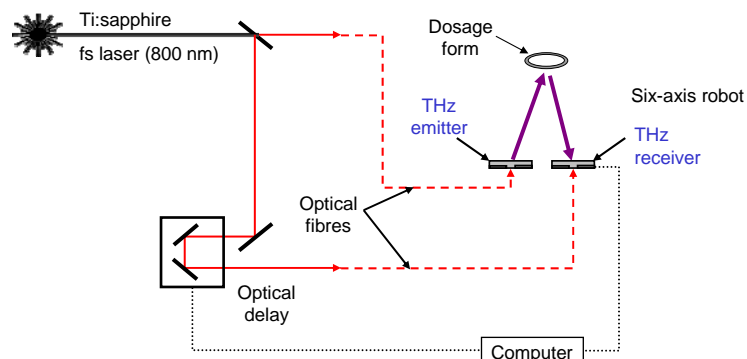
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Terahertz Pulsed Imaging 'TPI' - Optics



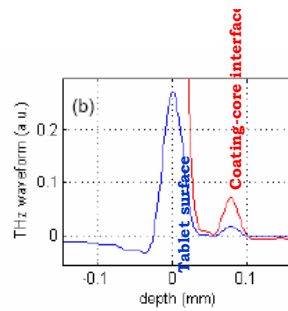
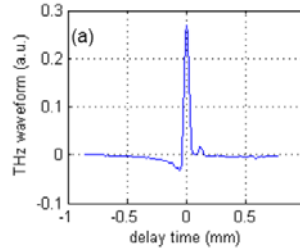
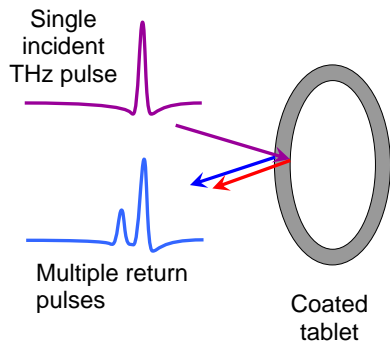
Interferometric configuration



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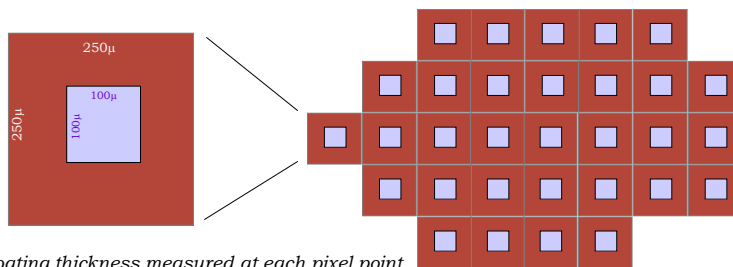
Coating Measurement



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3D Terahertz pulsed imaging Step size and spot size



Layer thickness	>30µm
Thickness resolution	± 2 µm
Penetration depth, typical	3 mm
Sample dimensions	5-20 mm
Acquisition rate	~20 minutes
<i>(for 5-mm diameter round dosage with 250 µm pixel spacing)</i>	

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Using Terahertz Pulsed Imaging



Coated tablet attributes:

- **Coating thickness**
- Material characterization
- Cracks
- Delamination
- Dislocations
- Layer uniformity
- Chemical distribution

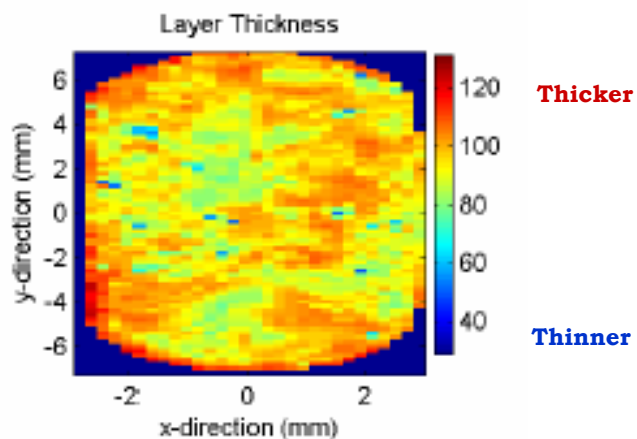
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TPI Coating Maps



Convex Tablet Face



The same false color scale is used in all thickness maps.

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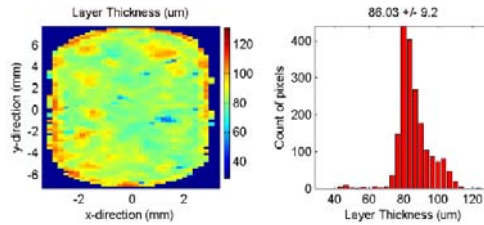


TPI Reproducibility

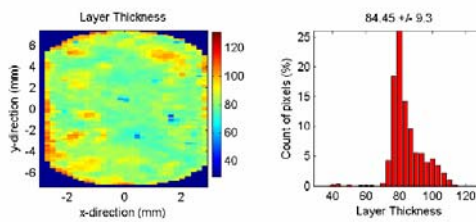


Scans of same tablet face performed
~6 months apart.

Lot: 423422S2
Tablet: 6
Weight: 0.55090 g



Lot: 423422S2
Tablet: 6
Lower face



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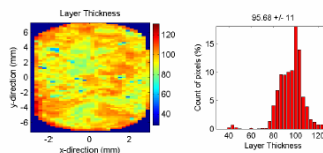
Complete mapping of all tablet surfaces



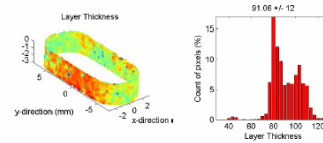
Mesalamine Tablets
- Enteric coating



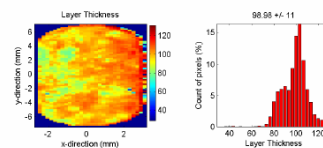
Lot: 423153S3
Tablet: 1
Upper face



Lot: 423153S3
Tablet: 1
Center-band



Lot: 423153S3
Tablet: 1
Lower face



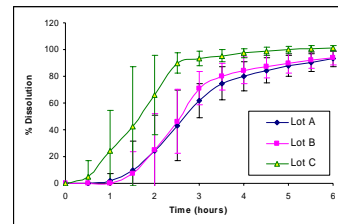
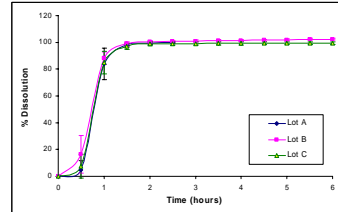
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Mesalamine Dissolution



- USP monograph pH 7.2
 - Acid stage - 0.1N HCl, 2 hours, 100 rpm.
 - Buffer stage 1 - pH 6.0 phosphate buffer, 1 hour, 50 rpm.
 - Buffer stage 2 - pH 7.2 buffer, 6 hours, 50 rpm.
- Modified method pH 6.8
 - Acid stage and Buffer stage 1 - same as USP.
 - Buffer stage 2 - pH 6.8 buffer, 6 hours, 50 rpm.



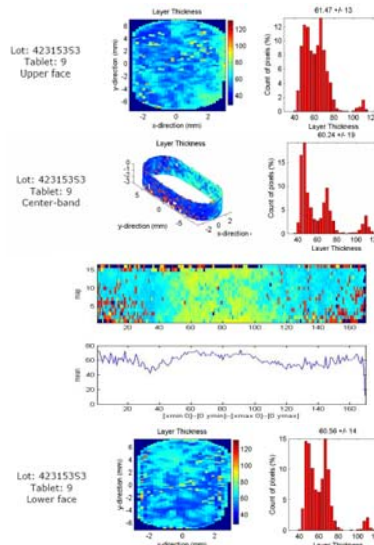
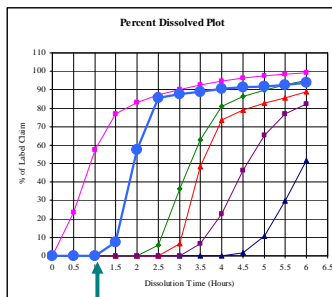
Dissolution at pH 6.8 discriminates between individual tablets.

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FASTER - Vessel 6 - S3_9 - 72 minutes

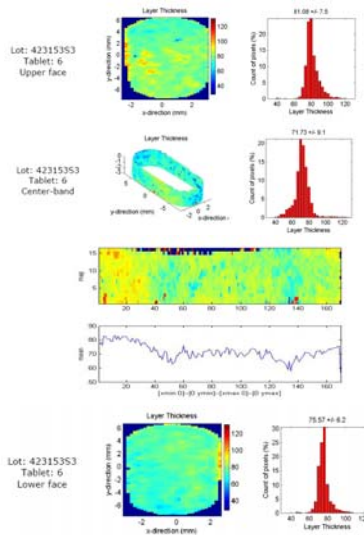
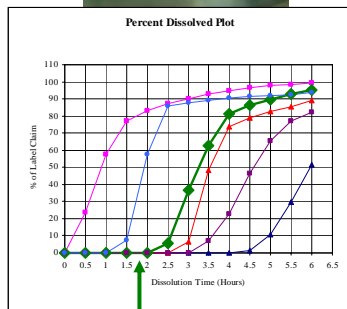
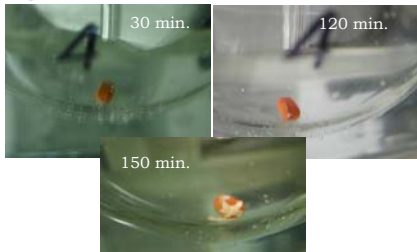
61 / 60 / 60 Microns



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MEDIUM - Vessel 4 - S3_6 - 150 minutes

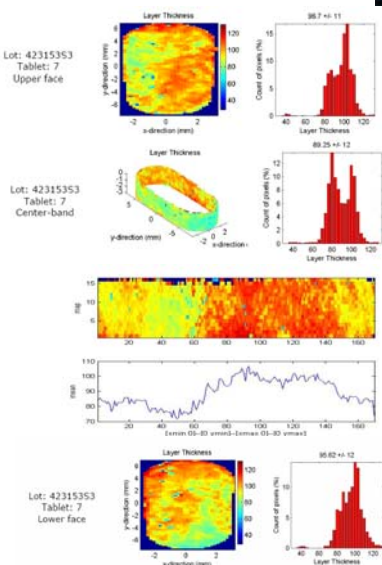
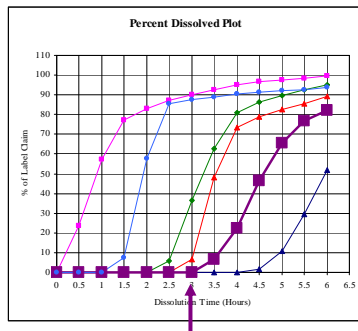
81 / 72 / 76 Microns



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SLOWER - Vessel 5 - S3_7 - 180 minutes

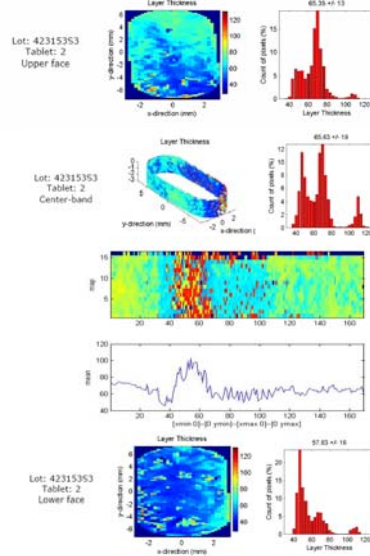
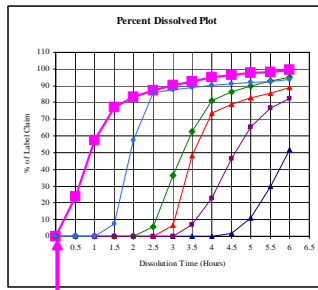
97 / 89 / 96 Microns



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OOPS! - Vessel 2 - S3_2 - 4 minutes (premature) 65 / 66 / 58 Microns



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TPI Coating Thickness and Mean Dissolution Time (MDT)

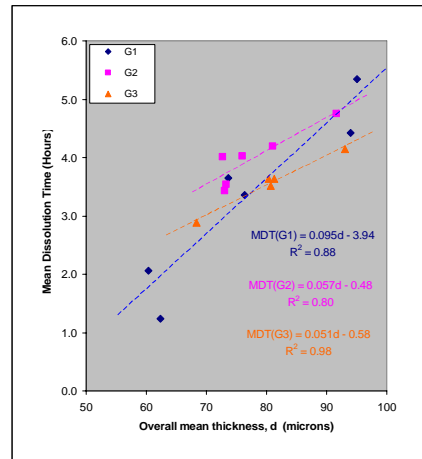


Run	Sample	Thickness (Microns)				Mean	± Std. Dev.	MDT (Hours)	Onset time (Obs.,Hours)
		Upper face	Centerband	Lower face	Mean				
G1	1 3S3_1*	95	91	99	95	4	5.3	4.20	
	2 3S3_2	65	65	57	62	5	1.2	0.07	
	3 3S3_4	82	68	71	74	7	3.6	2.72	
	4 3S3_6	81	72	76	76	5	3.4	2.50	
	5 3S3_7	97	89	96	94	4	4.4	3.00	
	6 3S3_9	61	60	60	60	1	2.1	1.20	
G2	1 2S2_2	83	72	73	76	6	4.0	3.00	
	2 2S2_3	70	69	79	73	6	4.0	3.50	
	3 2S2_5	95	87	93	92	4	4.8	4.00	
	4 2S2_6	82	77	84	81	4	4.2	4.00	
	5 2S2_8	80	68	72	73	6	3.5	2.50	
	6 2S2_9	80	69	70	73	6	3.4	2.75	
G3	1 2S2_1n	73	66	66	68	4	2.9	2.50	
	2 2S2_2n	96	86	97	93	6	4.1	3.00	
	3 2S2_3n	75	75	91	80	9	3.6	2.75	
	4 2S2_4n**	82	75	82	80	4	0.5	0.00	
	5 2S2_5n	94	79	71	81	12	3.6	2.25	
	6 2S2_6n	81	75	86	81	6	3.5	2.40	

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Mean Overall Thickness and Mean Dissolution Time



All faces averaged.

Spencer, et.al., *J.Pharm.Sci.* 2007 DOI 10.1002/jps.21051

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Some conclusions about TPI as an adjunct to Dissolution learned from studying Mesalamine



- Mean coating thickness generally correlates with onset of dissolution.
- Single face scans are unreliable predictors of dissolution behavior.
- Instances of premature onset are observed. One tablet in 36 studied failed while in the acid stage. There was no predictive evidence in the map.
- Tablet faces and centerband tend to be about the same thickness.

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Using TPI



Non-destructive
characterization of
complex dosage forms.

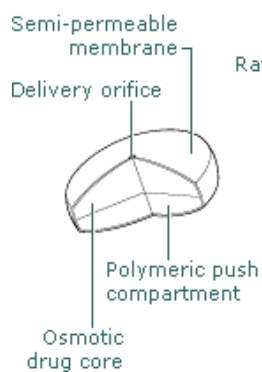


Concerta[®]

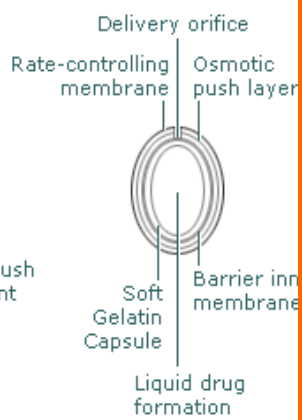


OROS[®] (ALZA) Tri-Layer dosage form

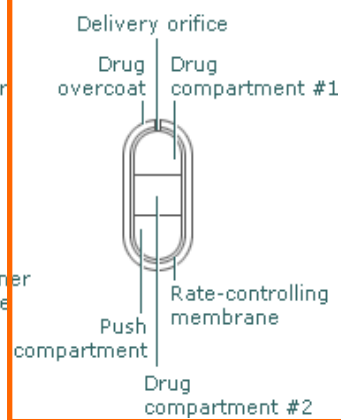
OROS[®] Push-Pull[™]



L-OROS[™]

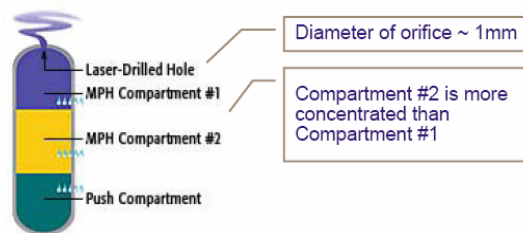


OROS[®] Tri-Layer





Concerta Structure



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Concerta – TPI Work (Collaboration of FDA with TeraView and KLA-Tencor)



Objectives:

- Measure the thickness of coating layers.
- Study homogeneity of the coating layers.
- Image the interior structure, esp. interfaces
- Estimate the volume of the interior chambers.

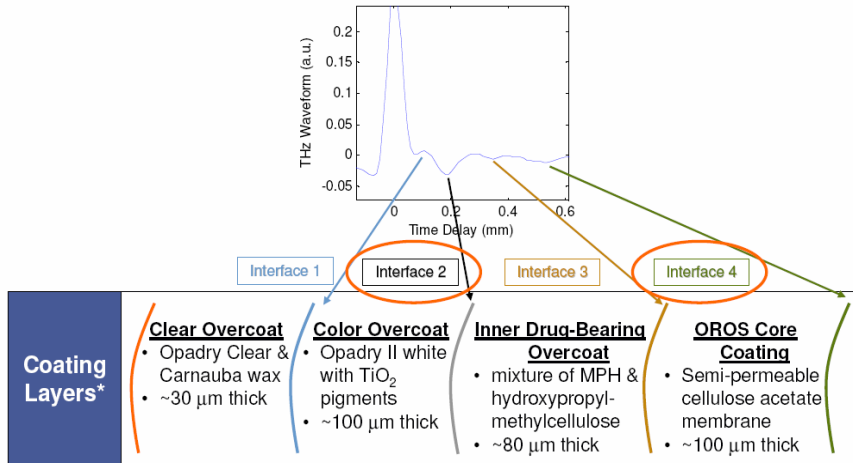
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TPI Coating Measurements



THz Waveform Reflected from Side of Tablet



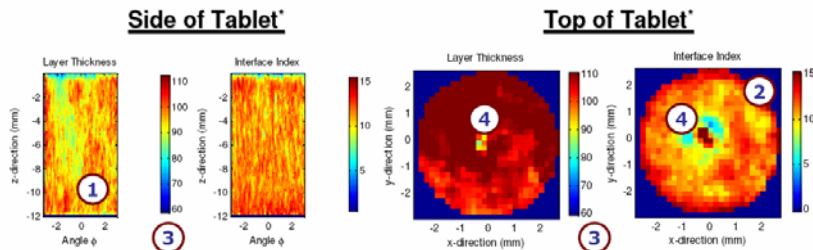
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Immediate release MPH layer



Observations at Interface 2



Key Observations

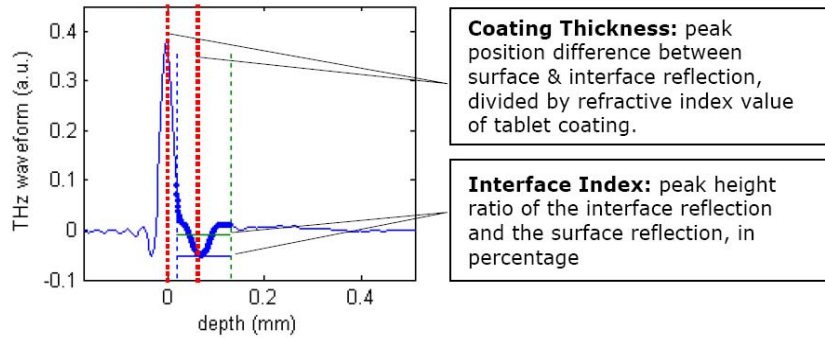
1. Streak distribution in Interface 2 thickness on side of tablet
2. Ring-shaped distribution in interface index around rim of tablet top
3. Interface 2 thicker on top of tablet than on side
4. Laser-drilled hole impacted spatial distribution of thickness & interface index

*Data is from Tablet 3 of Lot 0122224.

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Interface Index



The interface index can be mapped just the same as the coating thickness.

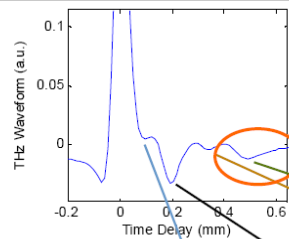
47



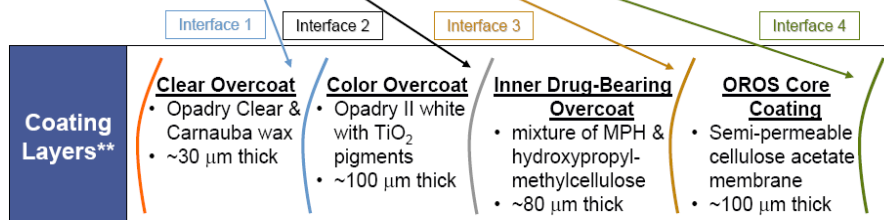
Interface 4 – the interior cellulose acetate coated core of the OROS Tablet



THz Waveform Reflected from Tablet*



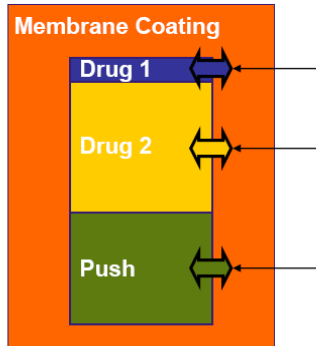
To obtain information about tablet core, focus only on Interface 4 portion of waveform



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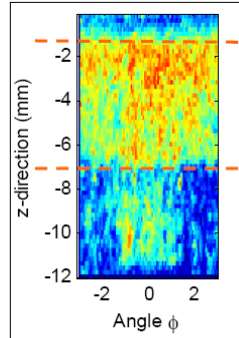


Interface Index Map



Different interfaces between membrane coating, Drug 1, Drug 2 & Push compartments give different interface indices

Interface Index Map



Interfaces clearly visible; effective way to distinguish compartments in tablet core



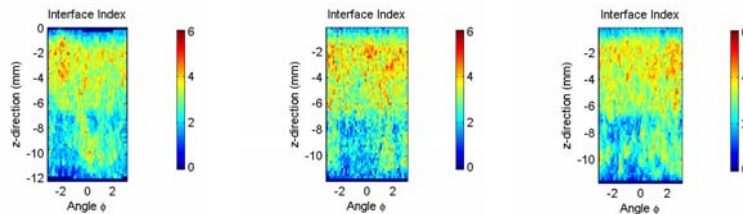
Interface Index 4 – Tablet/Tablet and Lot/Lot Variations Preliminary Survey, 9 Tablets (36 mg)



	Lot 0122224	Lot 0314342	Lot 0400191
Tablet 1			
Tablet 2			
Tablet 3			



Interface Index 4 – NEW DATA Additional TPI scans of Lot 0400191



RESCAN of
Tablet 2

Tablet 4

Tablet 6

TPI scans to map Interface Index 4 for tablets in 7 additional lots were found to be consistent with these results.

(New Slide – not in notes.)

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Preliminary results...



- Terahertz radiation is able to penetrate four layers of coating and image the compartment structure of the tablet core.
- Compartment volumes consistent within and across lots.
- Non-uniformity observed in interface indices
 - Indicative of different interaction between membrane coating and compartments in tablet core?
- Two tablets in one lot (0400191) showed relatively higher interface indices than the others.
 - ~~– Indicative of inconsistency in coating process?~~
 - At this point we can't assess whether this correlates to product quality.

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Summary



The promise of terahertz technology to pharmaceutical PAT...

- Transmission – raw materials screening, polymorph verification, at-line and on-line tablet content (API and excipients).
- TPI – coating thickness, coating quality, coating composition, internal structure.

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Terahertz Research at FDA



Acknowledgments:

- Ajaz Hussain – FDA & Sandoz
- Huiquan Wu, Mansoor Khan, Everett Jefferson(Ret.) - FDA/OPS/DPQR
- Edwin Heilweil – NIST
- Zongming Gao, Terry Moore, Lucinda Buhse, John Kauffman, William Doub – FDA/OPS/DPA
- Don Arnone, Philip Taday, David Newnham, Yaochun Shen, Tomas Lo, Alessia Portieri – TeraView, Ltd.
- Sam Ngai – KLA-Tencor

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Terahertz Research at FDA



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