The relative Strengths and Weaknesses of Spectroscopy across the Spectrum
(Characterisation of Solid Samples)

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QbD/PAT Conference 2013
Heidelberg, Germany
16 October 2013

Outline

1. Introduction and Motivation – The Toolbox
2. Moving across the Spectrum: MHz to EHz – Picking the Right Tool
   - Nuclear Magnetic Resonance (NMR) Spectroscopy
   - Dielectric Spectroscopy
   - Vibrational Spectroscopy: THz
   - Vibrational Spectroscopy: Raman
   - Vibrational Spectroscopy: Near-infrared
3. Summary

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Motivation – Why Spectroscopy?

Current Limitations

- Solid dosage form production: sequence of complex processing steps
- Batch production dominates
- Quality controlled mainly by end product testing
- Very small sample is tested ($< 0.001\,\%$)
- In-process control relatively information poor

Motivation – Why Spectroscopy?

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Spectroscopy

- Information rich spectra
- Data acquisition can be fast (ms) and flexible (fibre coupled optics)
- In-line measurements in real time are possible
- Computational power to process data is available
- Active process control loops can be implemented

Strong potential for synergies – BUT it is important to know: Which technique best, how to get the most out of it?

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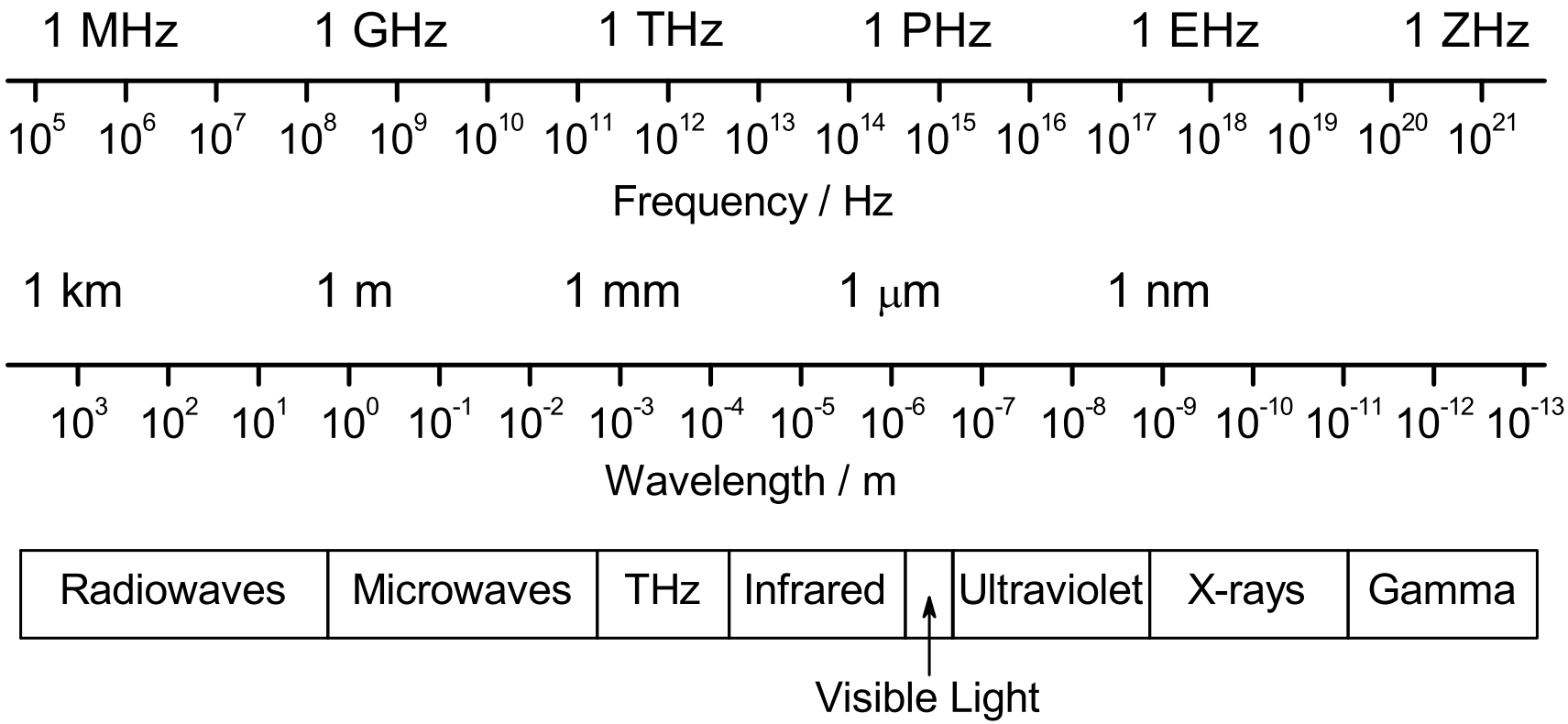
The Electromagnetic Spectrum



Transitions in alignment of nuclear spins

rotational transitions

vibrational transitions

electronic transitions

nuclear processes

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Types of Spectrometers

A range of different technical solutions exist to perform spectroscopy:

Dispersive Spectrometers

- The sample is successively exposed to radiation with a narrow spectral distribution while the spectrum is recorded
- Alternatively the detection is performed using an array detector after dispersion of broadband radiation

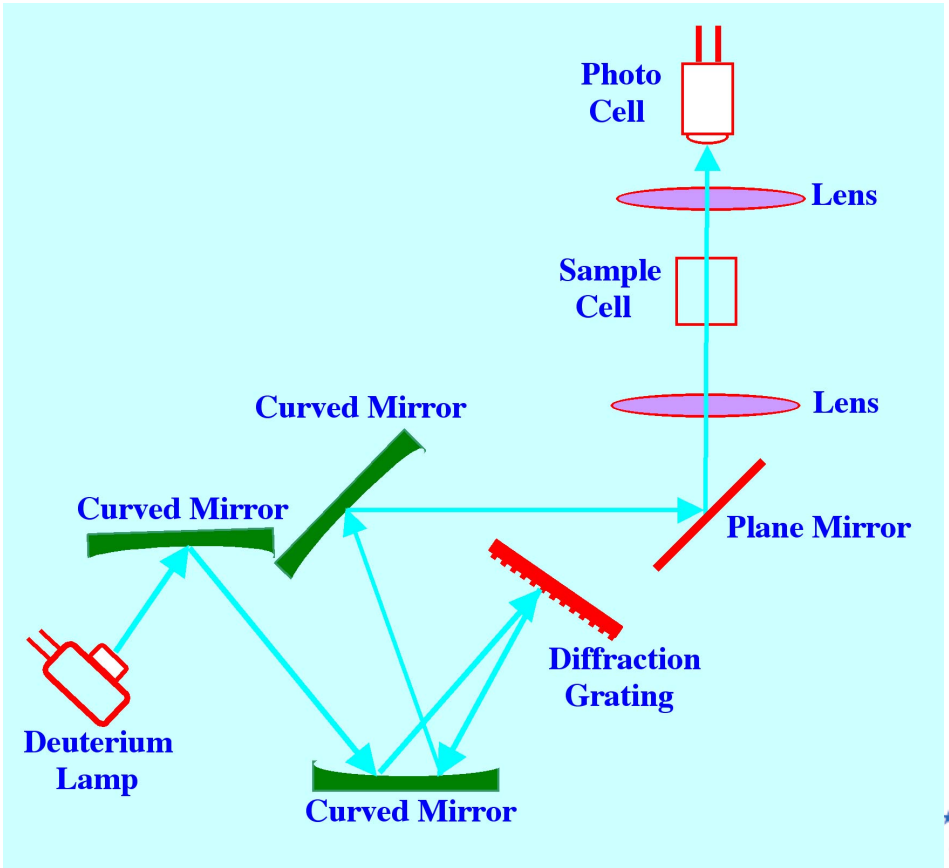

Image source: http://www.analyticalspectroscopy.net

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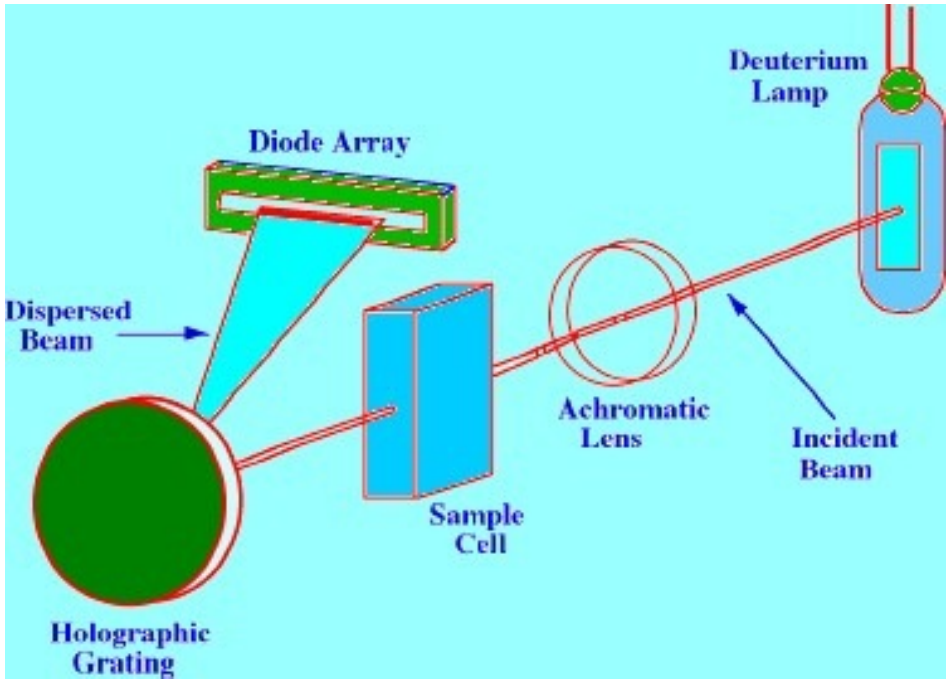


Image source: http://www.analyticalspectroscopy.net

Types of Spectrometers

A range of different technical solutions exist to perform spectroscopy:

Fourier Transform Spectrometer

- Broadband radiation interacts with the sample material
- Typically a Michelson interferometer is used to acquire the interferogram
- Sample spectrum is calculated using a subsequent Fourier transform

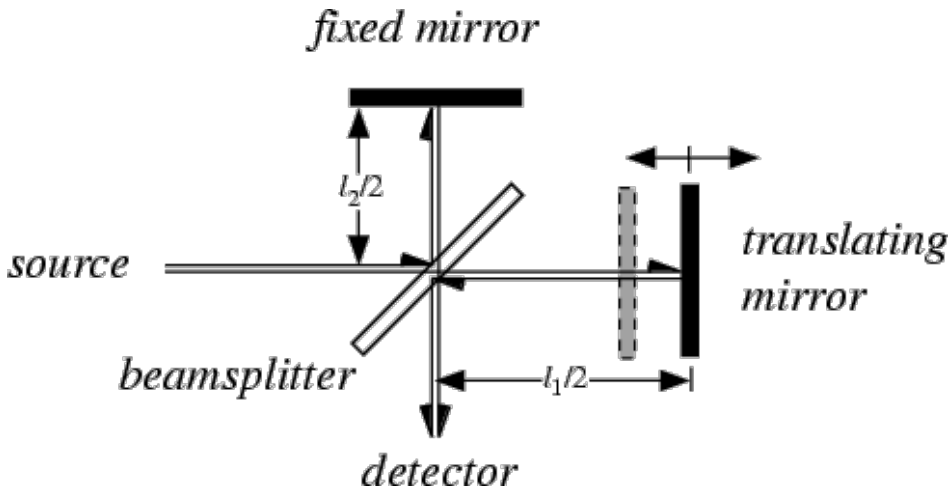


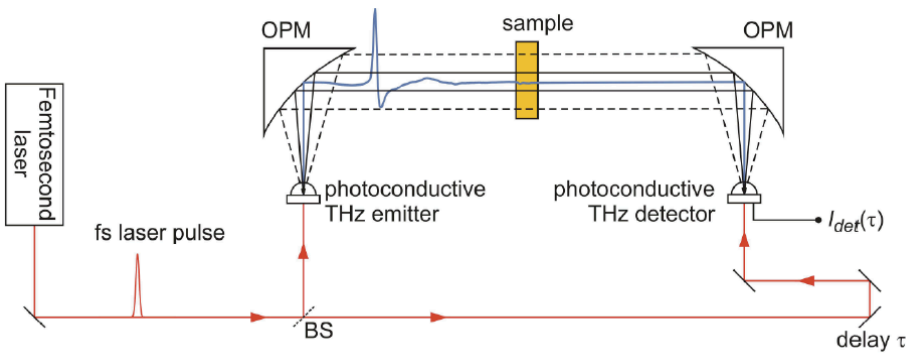
Image source: http://scienceworld.wolfram.com

Types of Spectrometers

A range of different technical solutions exist to perform spectroscopy:

Time-Domain Spectrometer

- Broadband radiation interacts with the sample material
- The time resolved waveform of the electric field is recorded
- Sample spectrum is calculated using a subsequent Fourier transform



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Measurement Flexibility

Image source:
http://www.abb.com

Fibre Coupling

- Fibre optics facilitate in-line measurements
- UV, VIS, NIR and part of IR can be coupled to fibres

Measurement Geometry

Depending on the application and technique measurements can be acquired in transmission, specular or diffuse reflection, attenuated total reflection, scattering, etc.

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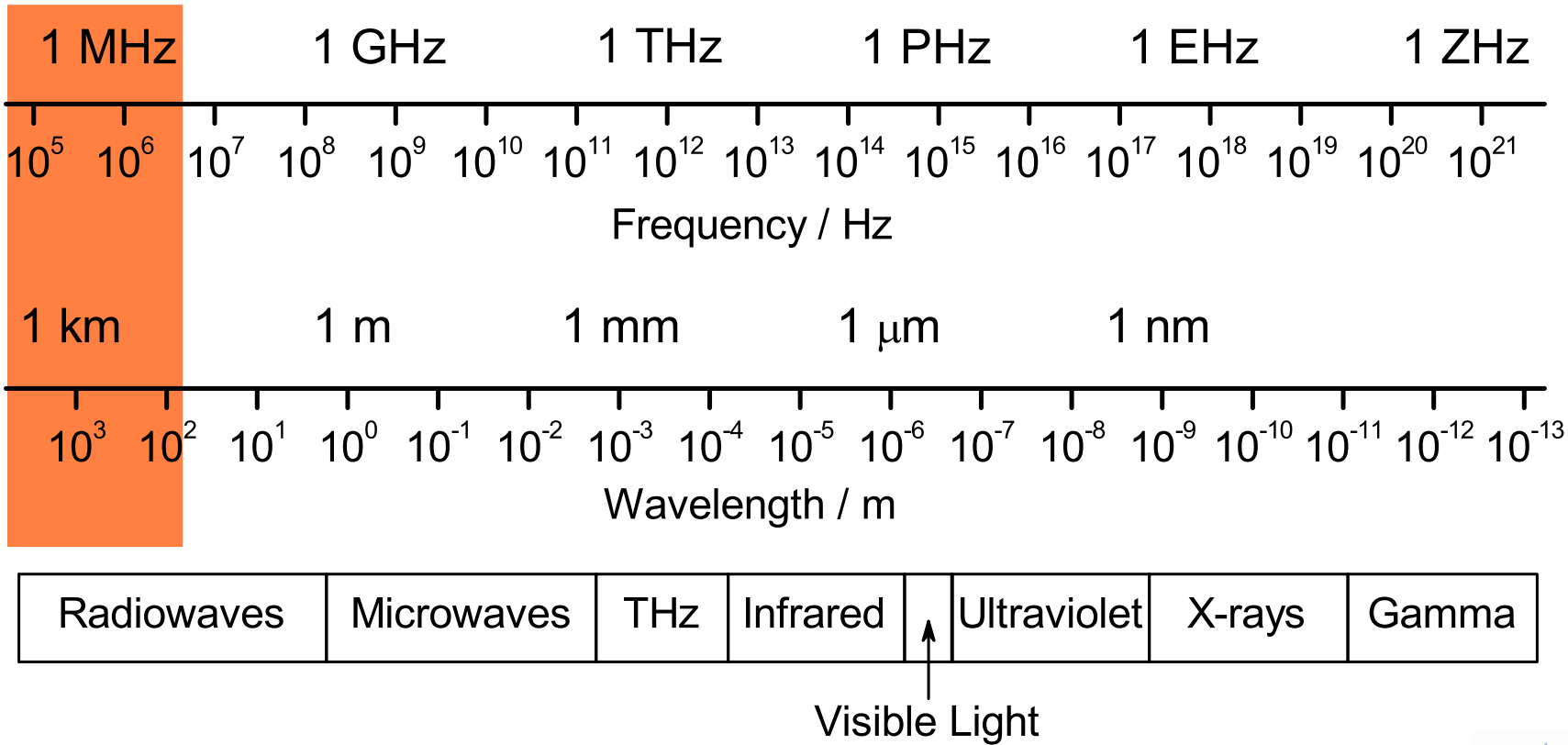
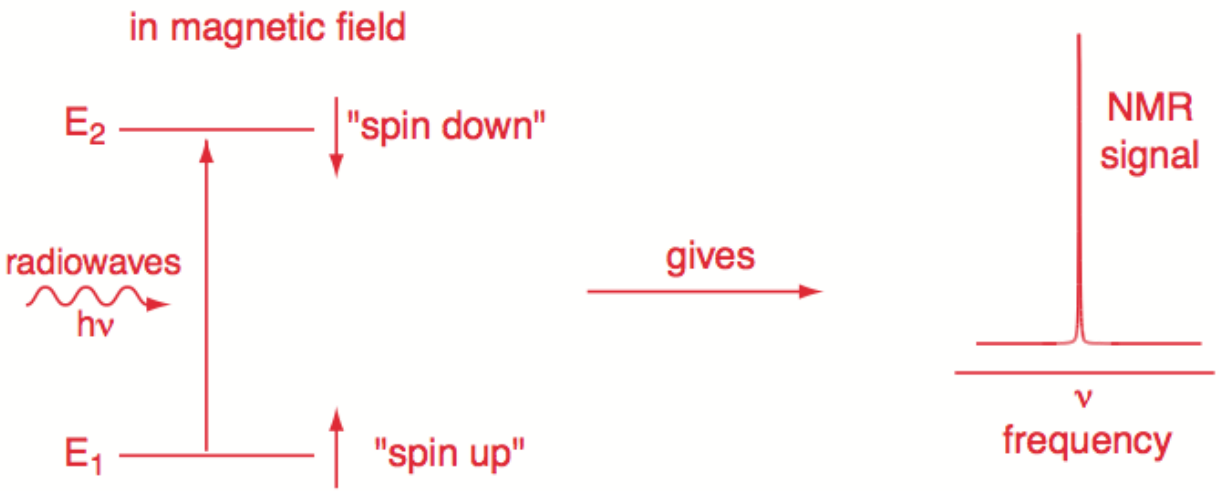
Nuclear Magnetic Resonance (NMR) Spectroscopy



Principles of NMR Spectroscopy

- Certain nuclei (e.g. ^{1}H, ^{13}C, ^{19}F) possess a property called spin and as a result, the nucleus has a very weak magnetic field associated with it
- When placed in a strong magnetic field there is an interaction between this nuclear spin and the applied field which gives rise to a set of nuclear spin energy levels.
- Radiowaves of the appropriate frequency cause transitions between these energy levels and this gives rise to the NMR signal.



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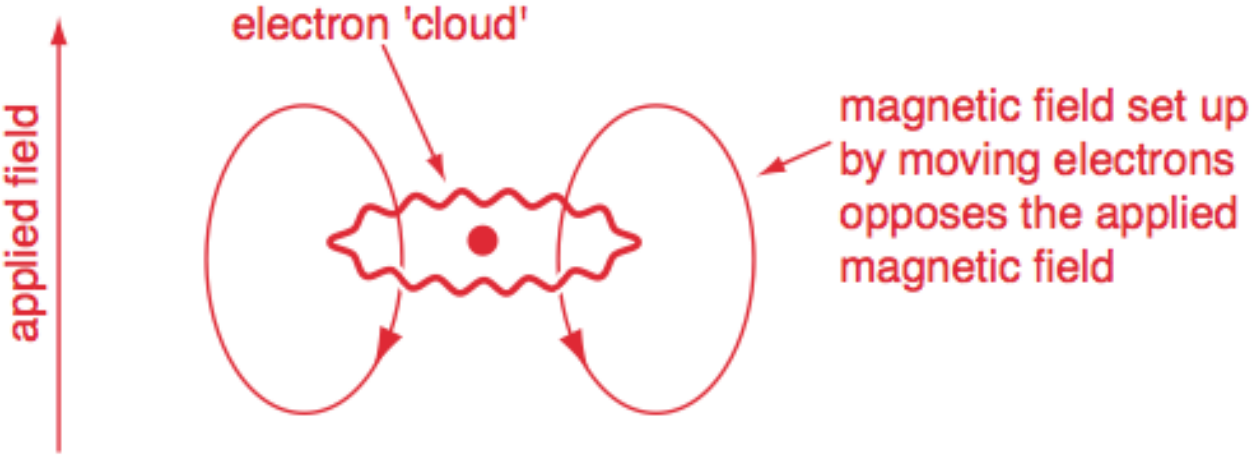
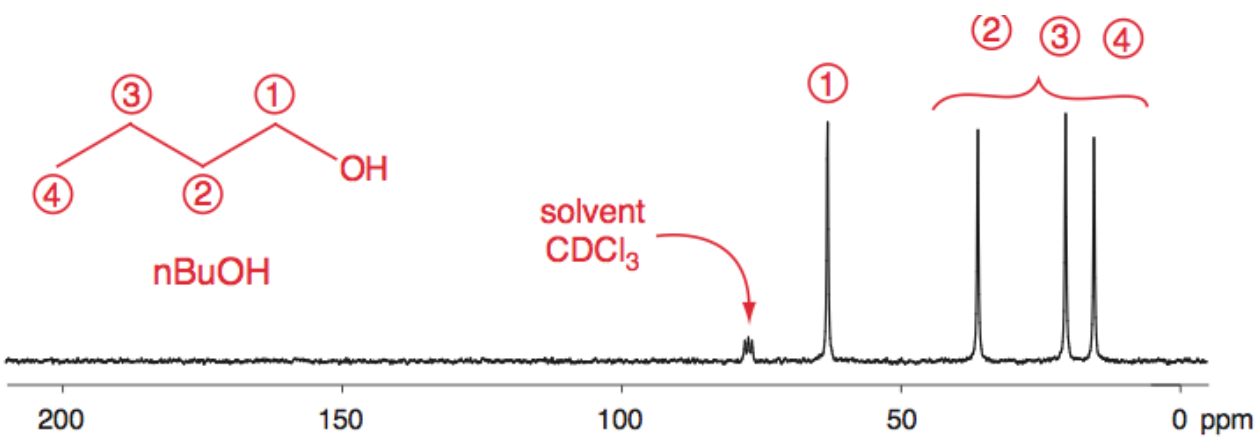
Principles of NMR Spectroscopy

The NMR spectrum is specific to different parts of a molecule due to the local magnetic field experienced by each nucleus which is strongly influenced by electrons moving in its vicinity





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Chemical sensitivity and structural information

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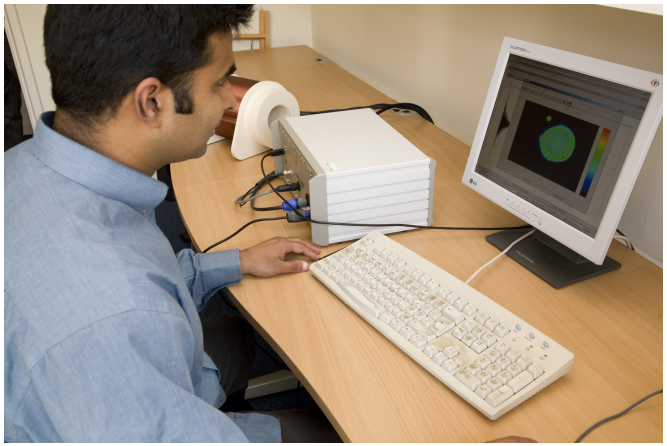
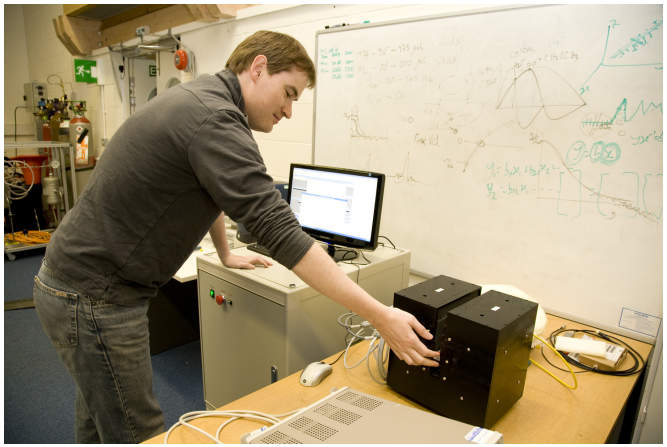
Acquisition time and requirement for local homogenous magnetic field

Low Field NMR



Earth field NMR

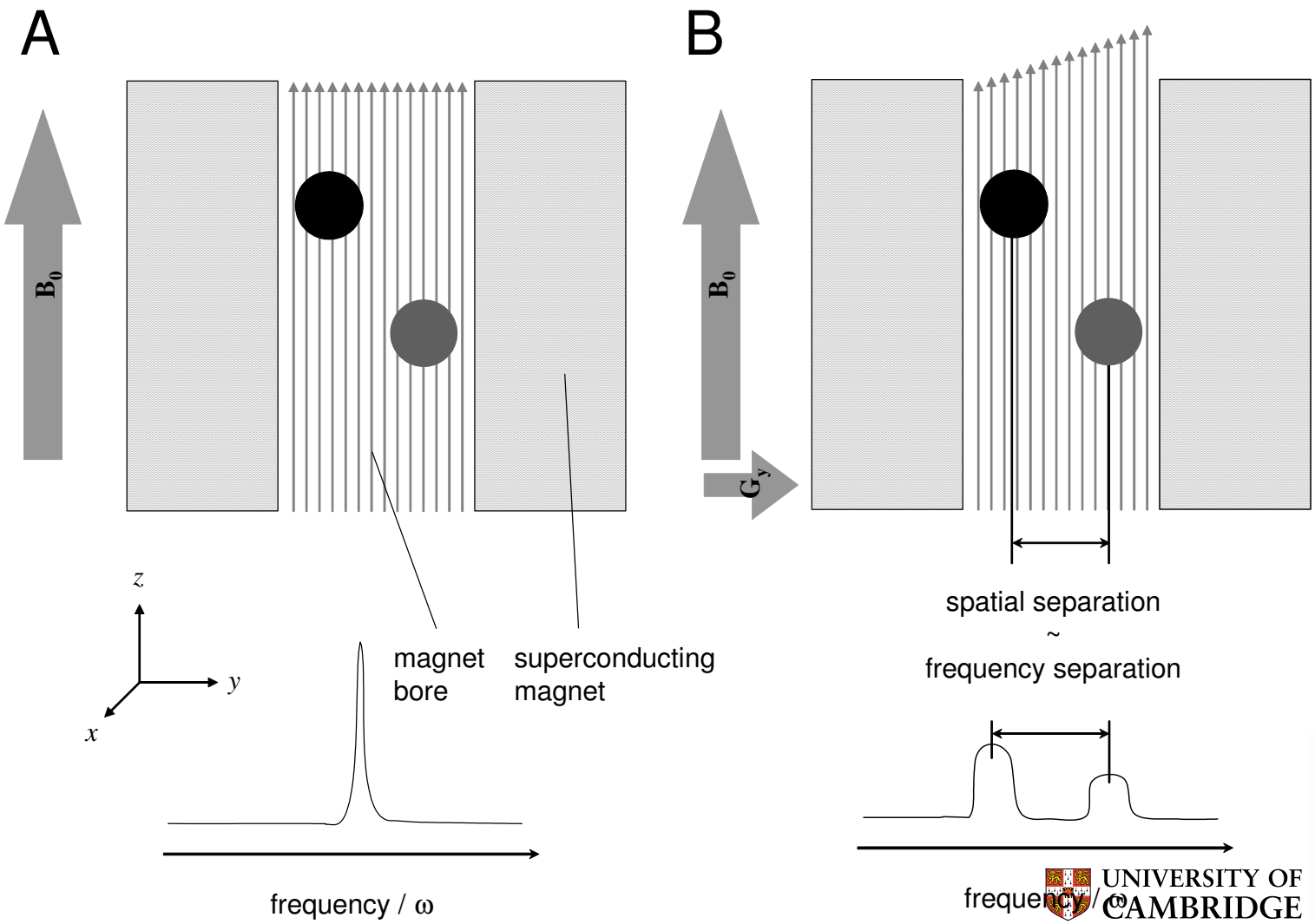


Low field NMR

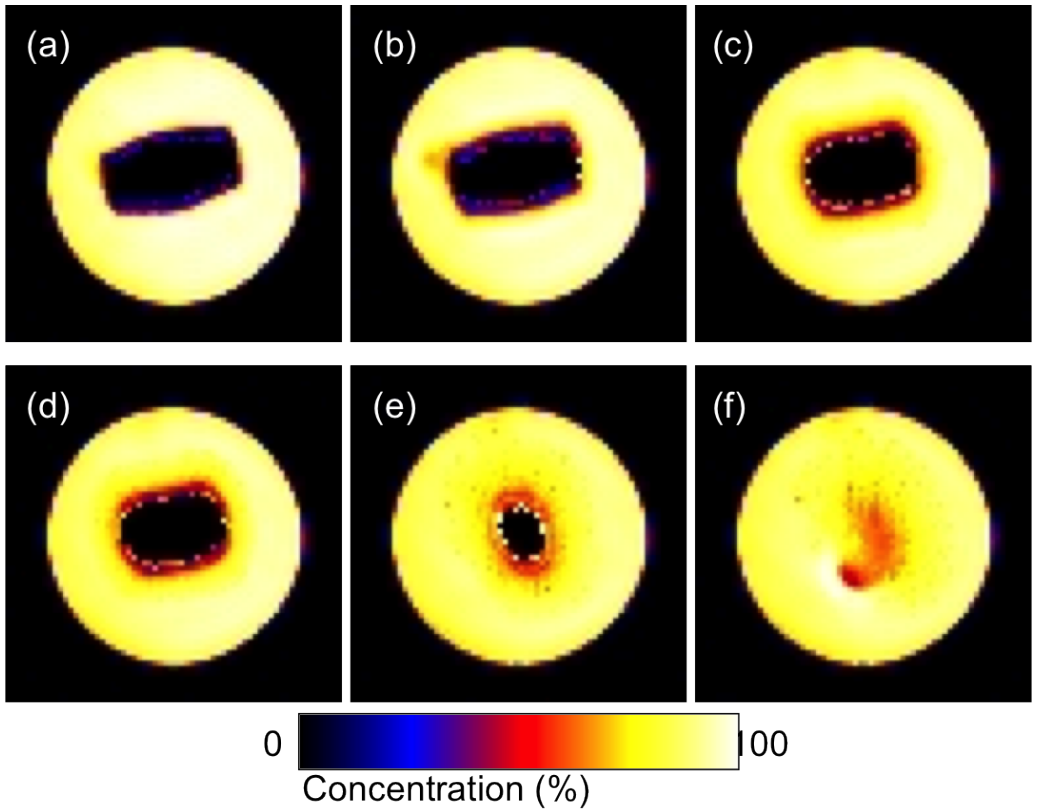
- Low field equipment (< 2 T, no superconducting magnets) readily available
- Not suitable for solid samples, solid state NMR still requires high field instruments
- Potentially very interesting for studying drug release during dissolution from solid dosage forms

H. Metz and K. Mäder, Int. J. Pharm. 364, 170 (2008). M.D. Mantle, Int. J. Pharm. 417, 173 (2011).

Magnetic Resonance Imaging (MRI)



Hydration of HPMC Matrix Tablets



Water concentration maps at different hydration times (hours): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25.

Y.Y. Chen, Hughes, L. P., L.F. Gladden, and M.D. Mantle, J. Pharm Sci. 99, 3462 (2010).

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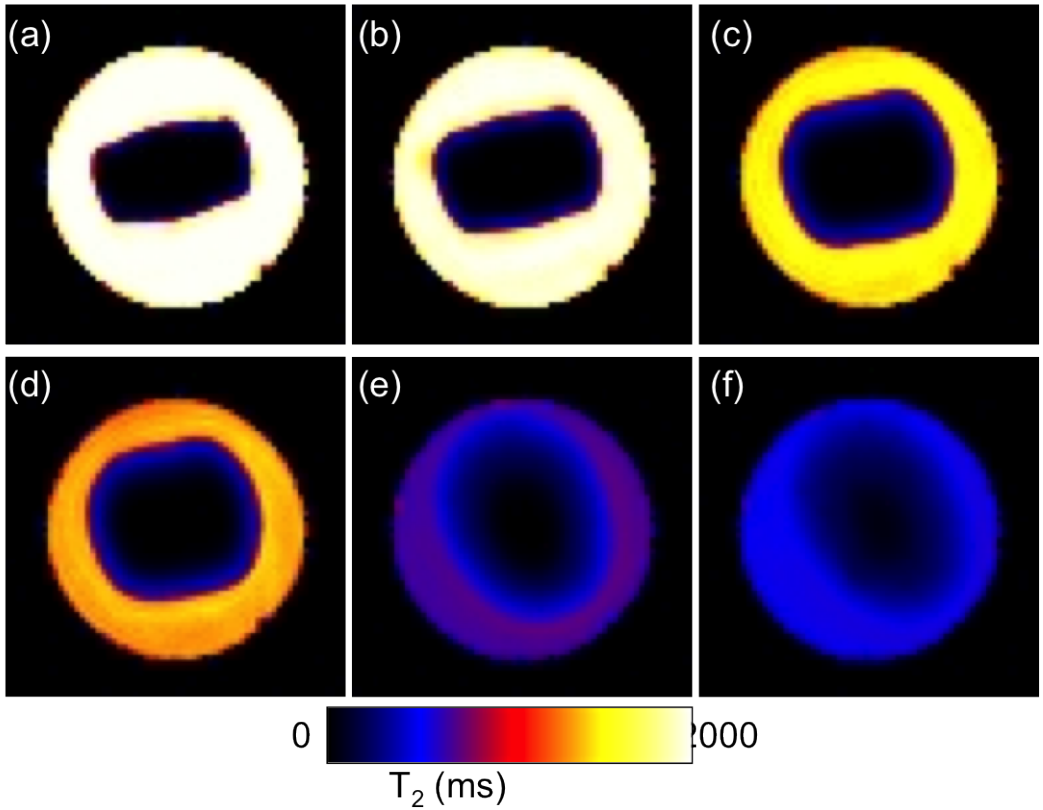

T_2 maps at different hydration times (hours): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25

Y.Y. Chen, Hughes, L. P., L.F. Gladden, and M.D. Mantle, J. Pharm Sci. 99, 3462 (2010).

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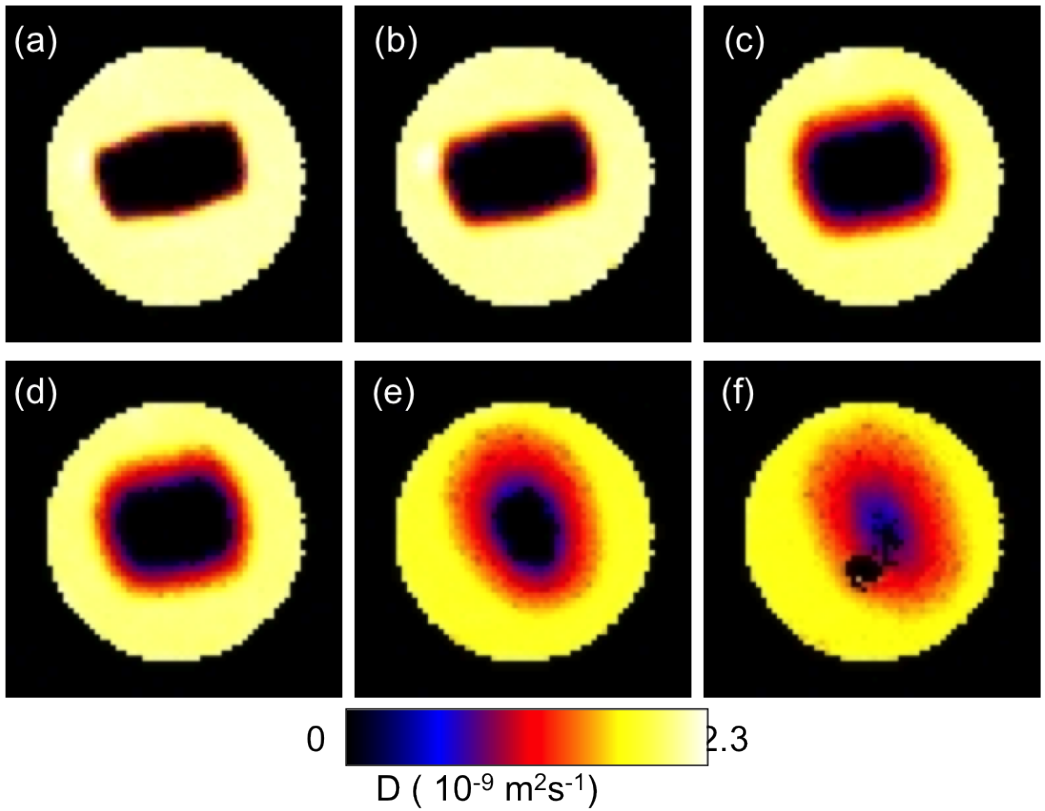
Hydration of HPMC Matrix Tablets



Diffusion coefficient maps at different hydration times (hours): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25.

Y.Y. Chen, Hughes, L. P., L.F. Gladden, and M.D. Mantle, J. Pharm Sci. 99, 3462 (2010).

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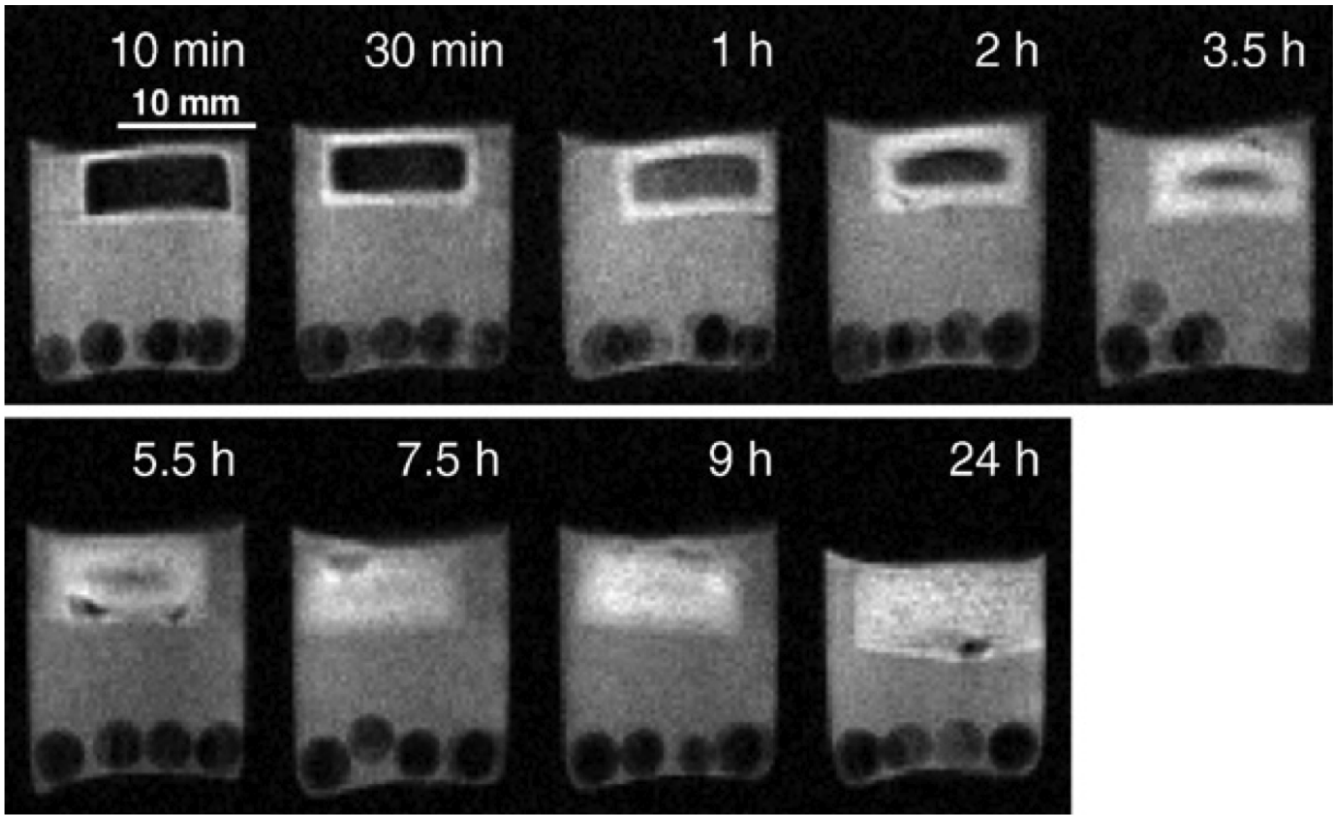
Coated Tablets



Water penetration into matrix tablets with 10% propranolol HCl in 0.1 NHCl as a function of time

S. Strubing, H. Metz, and K. Mader, J. Control. Release 126, 149 (2008).

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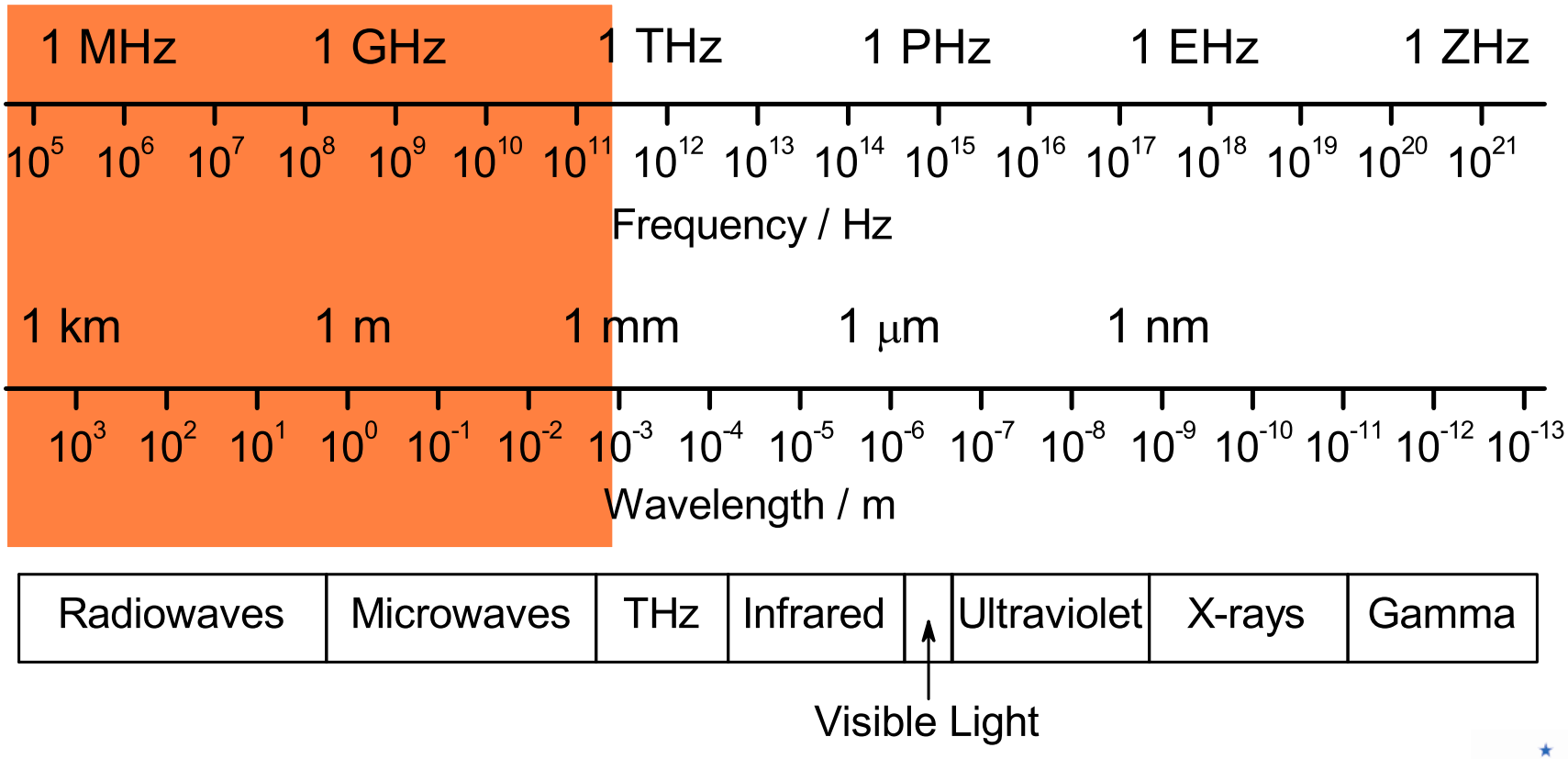
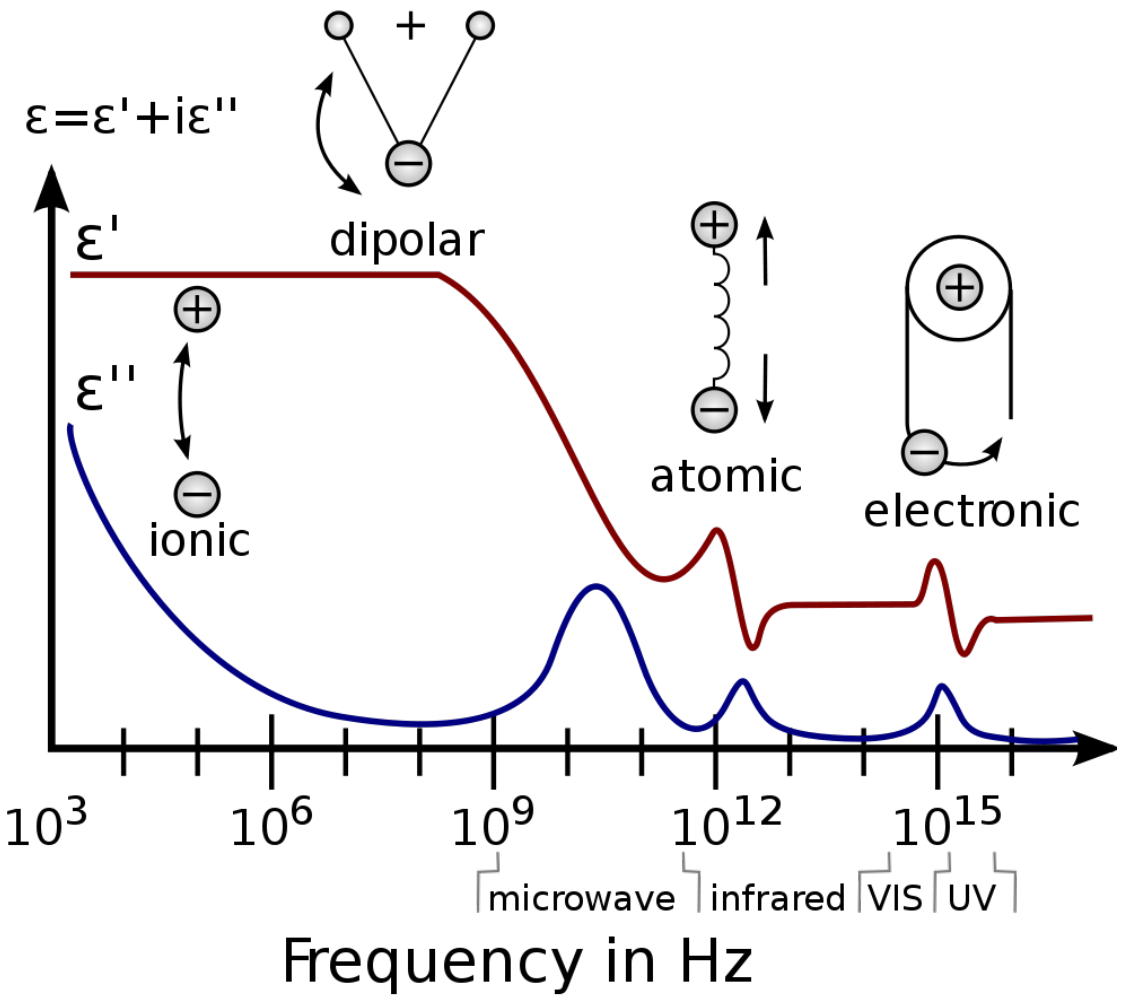
Dielectric Spectroscopy



Dielectric Response



- This technique spans the frequency range over 10^2 to 10^{12} Hz
- Dipoles and charges respond to the excitation by an external electric field and move as a whole during relaxation
- $\hat{\varepsilon} = \varepsilon' + i\varepsilon'' = (n + i\kappa)^2$ where $\alpha = 4\pi\kappa/\lambda_0$

Image source: http://en.wikipedia.org/

Dielectric Relaxation – Molecular Mobility

α-relaxation

- Structural relaxation process
- Relaxation time changes from 10^{-12} to 10^{2} s upon glass transition
- Concept of cooperatively rearranging regions (CRR)

G. Adam and J. H. Gibbs, J. Chem. Phys. 43, 139 (1965).

β-relaxations

- Local motions involving the entire molecule or intra-molecular reorientations
- Much faster than α relaxations
- Commonly observed either as a separate peak or as a high frequency wing of the α-relaxation.

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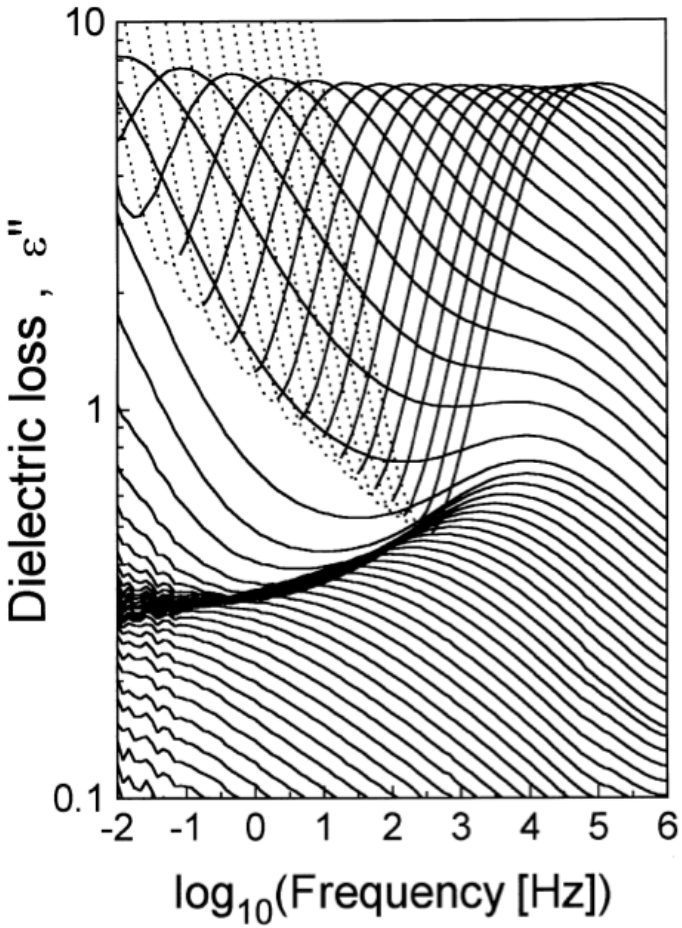
Amorphous Solids – Stability



- α and β relaxation process are separated in frequency (but often overlap)
- Local mobility (β-relaxations), which is significant below the glass transition temperature, could be influencing stability in amorphous solids
- It is possible to directly measure the relaxation times using dielectric spectroscopy

H. Wagner and R. Richert, J. Non-Cryst. Sol. 242, 19 (1998).

S. Bhattacharya and R. Suryanarayanan, J. Pharm Sci. 98, 2935 (2009).

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Dielectric Spectroscopy

Advantages

- Very useful to characterise amorphous materials in particular
- Results give a direct measure of the relative mobility of molecules
- Very good theoretical models exist to interpret the data

Diadvantages

- To cover a wide frequency range multiple measurements need to be combined
- Temperature dependent measurements are difficult to achieve over a wide range (below T_g)
- Sample handling

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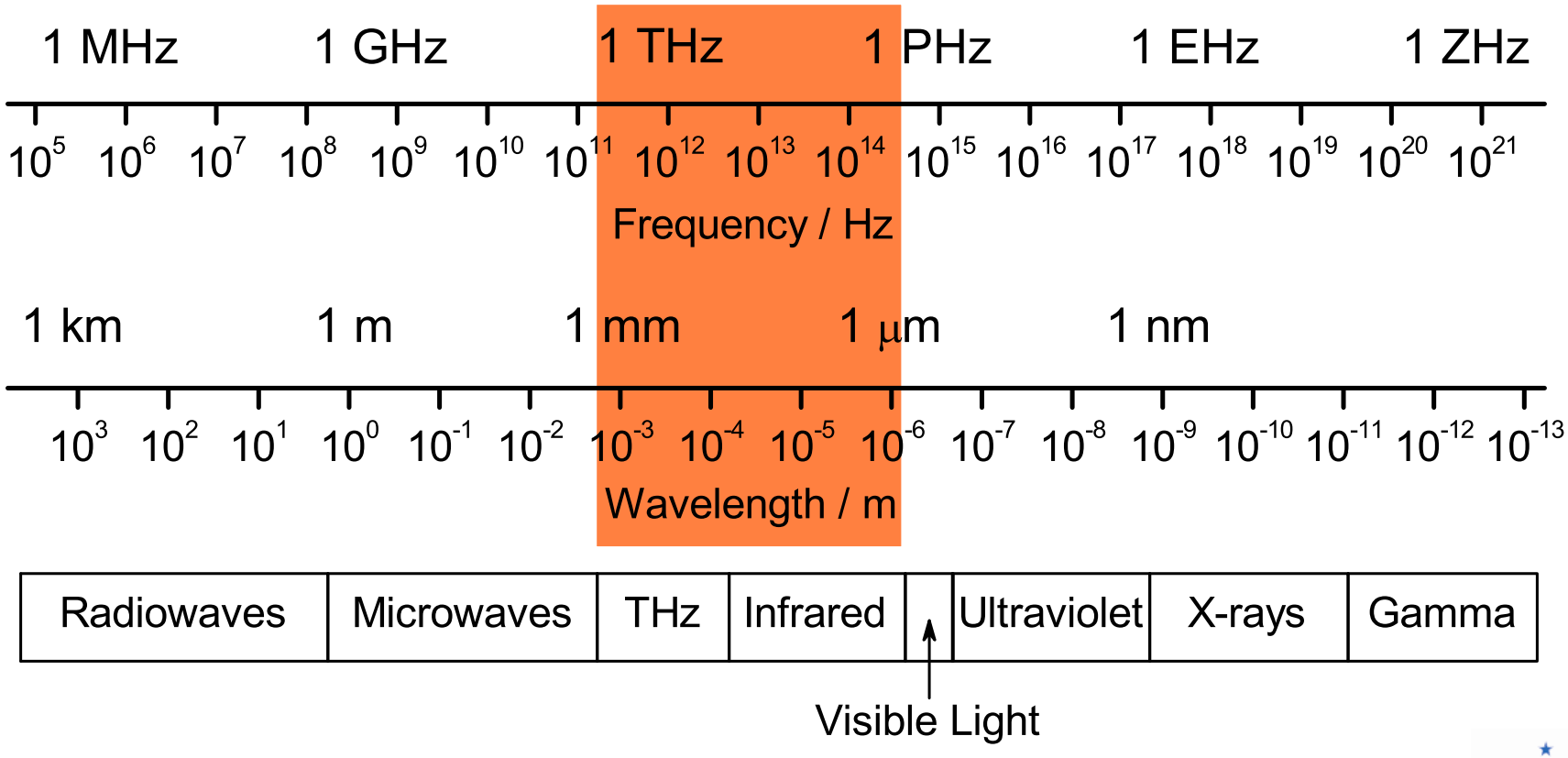
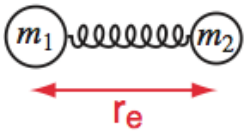
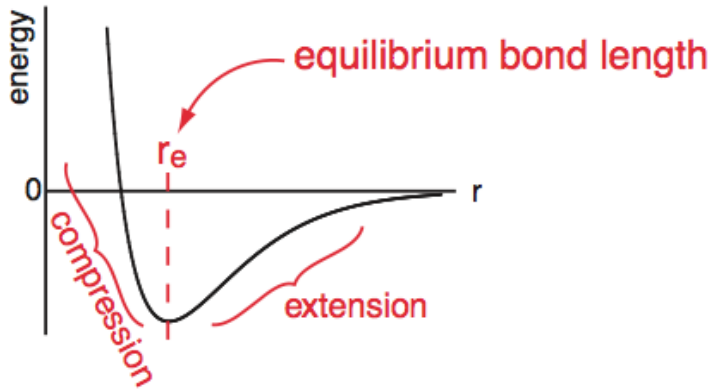
Vibrational Spectroscopy (THz, Raman, IR, NIR)



Vibrational Spectroscopy

Transitions between different vibrational energy levels in molecules. Whereas NMR gives us information about the different environments of nuclei in a sample, vibrational spectroscopy gives us information about the types of bonds present.





The frequency of the oscillations depends on two things, how heavy the weight is and how stiff the spring is: the fastest oscillations occur with a stiff spring and a light mass. The relationship between these parameters is given by Hooke's law:

$$\nu \propto \sqrt{k/m}$$

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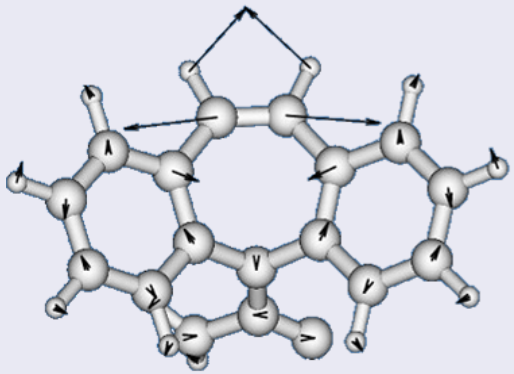
Terahertz Spectroscopy

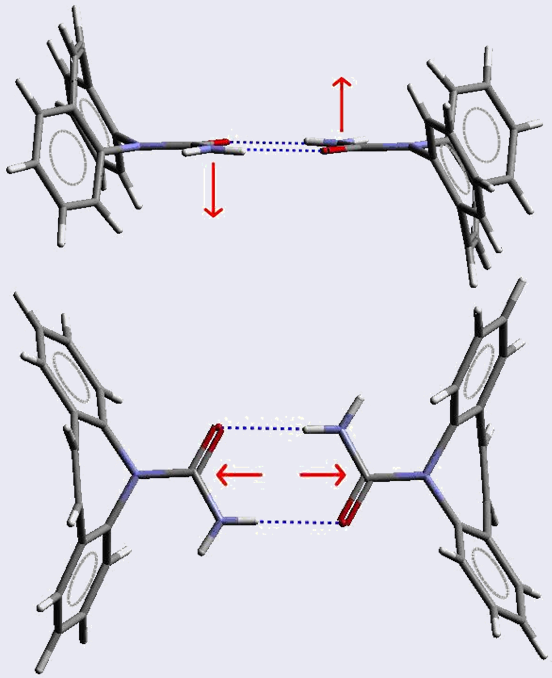
Mid-infrared



Intramolecular Modes

Information about the structure of a single molecule, identification of molecules

Terahertz



Intermolecular Modes

Information about the structure and dynamics of molecular interaction

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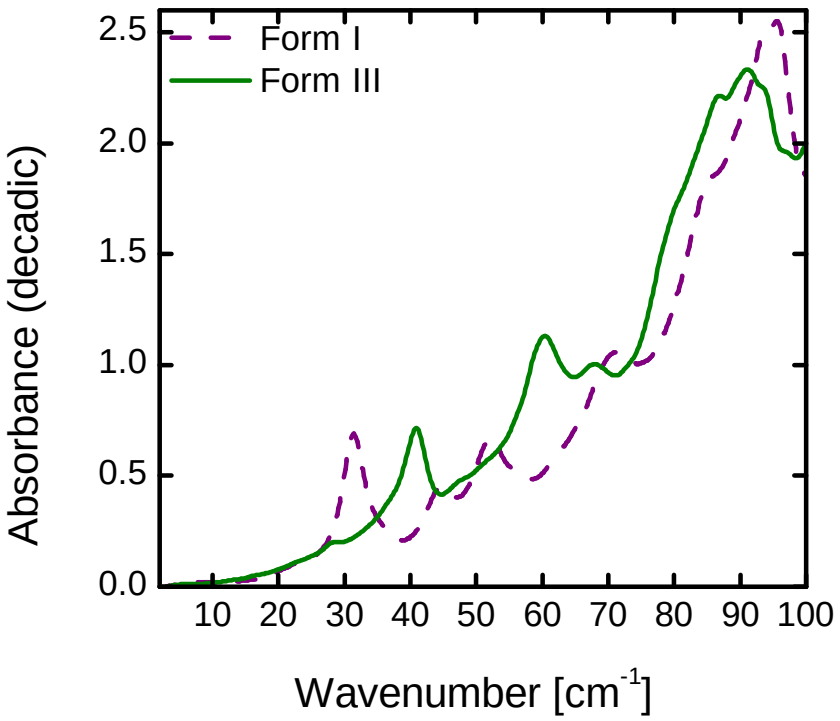
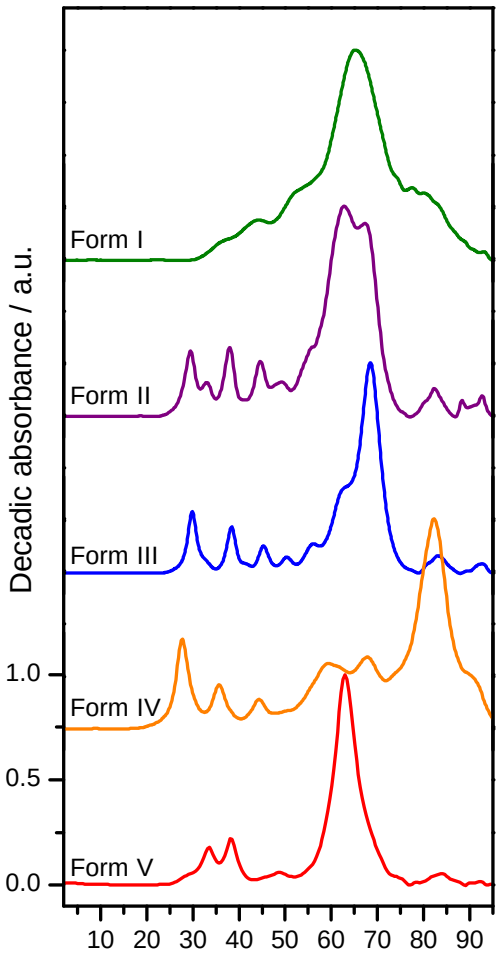
Polymorphism



Carbamazepine

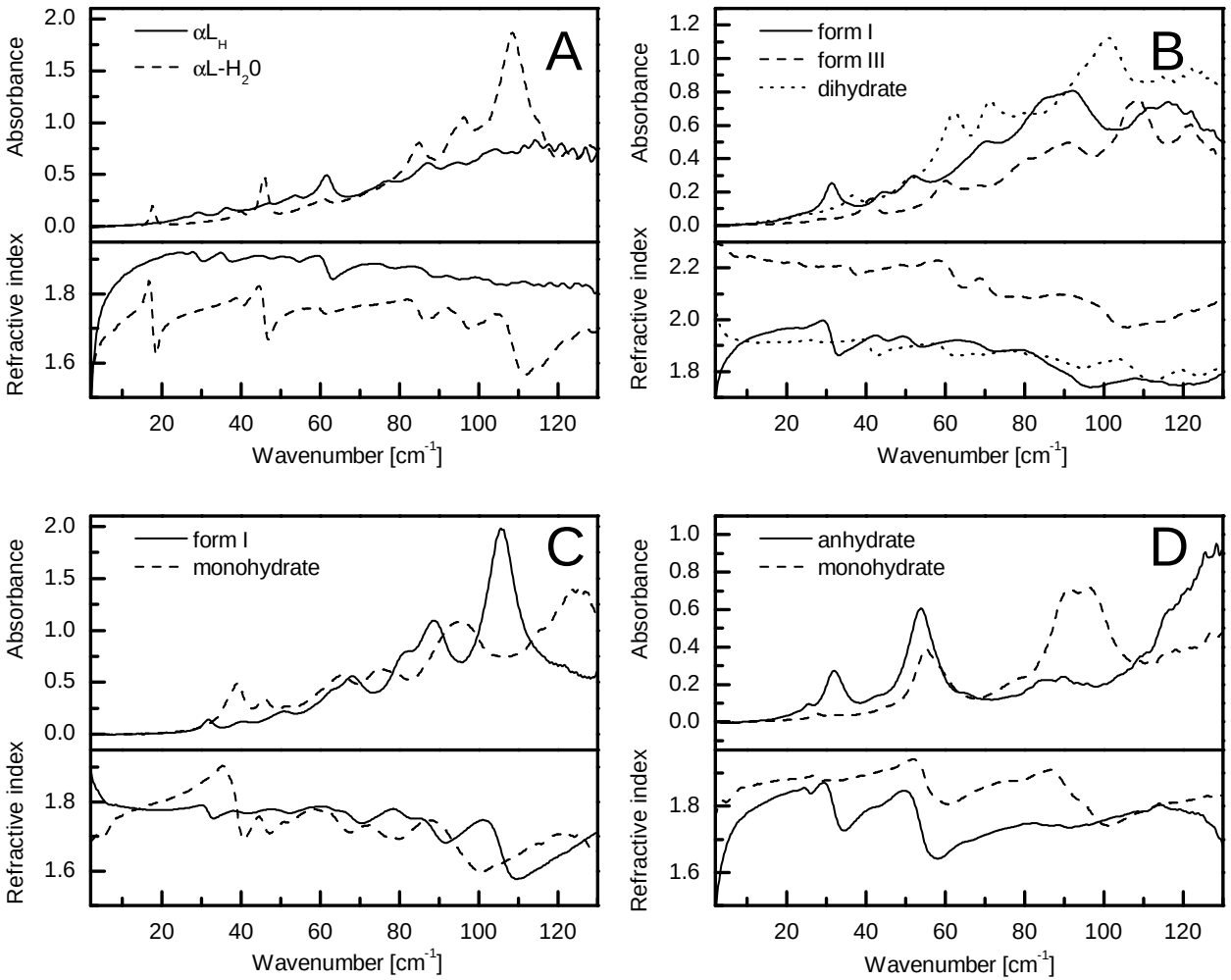


Sulfathizole

C. J. Strachan *et al.*, Chem. Phys. Lett. 390, 20 (2004).

L. A. Zeitler *et al.*, J. Pharm. Sci. 95, 2486 (2006).

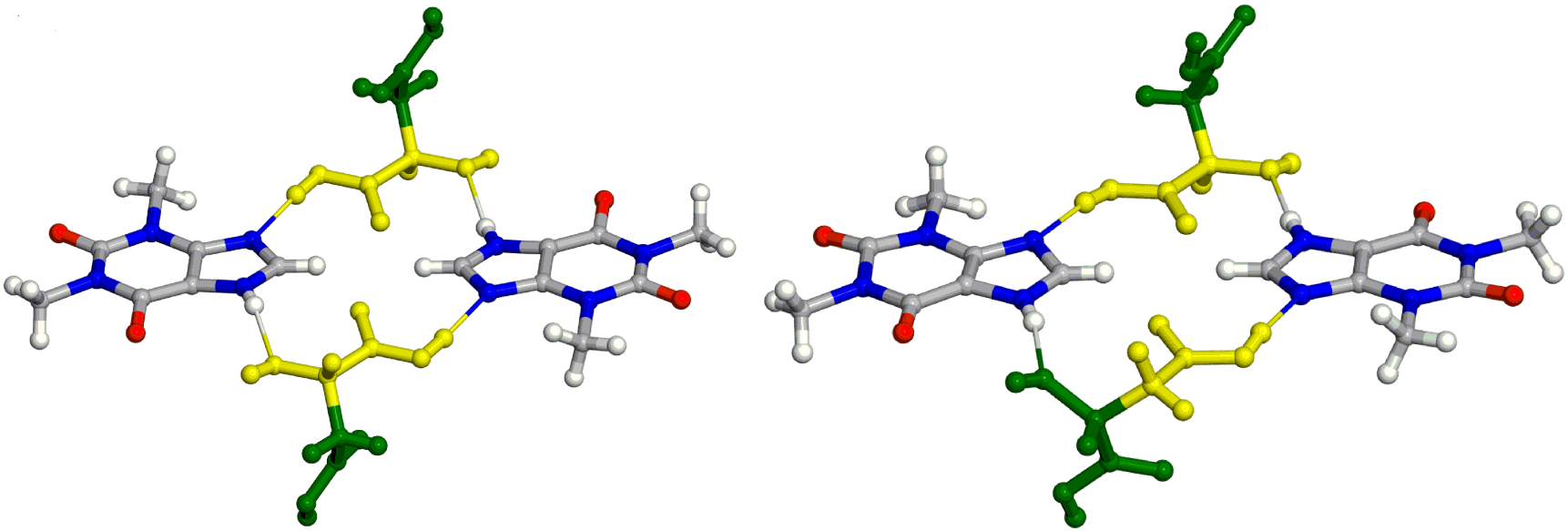
Hydrates



A) Lactose, B) carbamazepine, C) piroxicam and D) theophylline

J. A. Zeitler *et al.*, Int. J. Pharm. 334, 78 (2007).

Structural Sensitivity – Isostructural Cocrystals



Crystal structure of the isostructural cocrystals of (theophylline)·(DL-malic acid) and (theophylline)·(L-malic acid).

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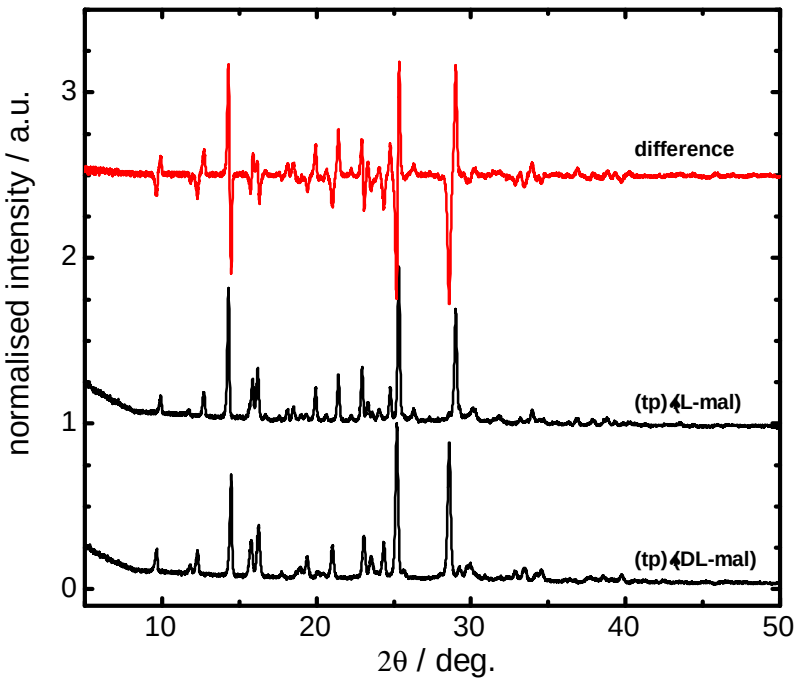
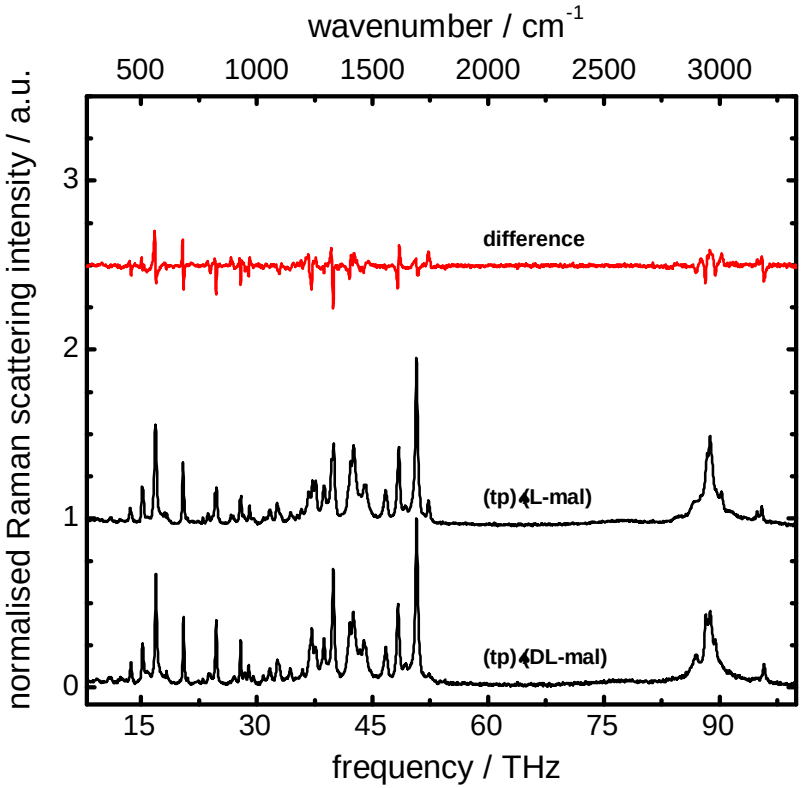
E.P.J. Parrott *et al.*, Crystal Growth & Design, 9, 1452 (2009).

Structural Sensitivity – Isostructural Cocrystals

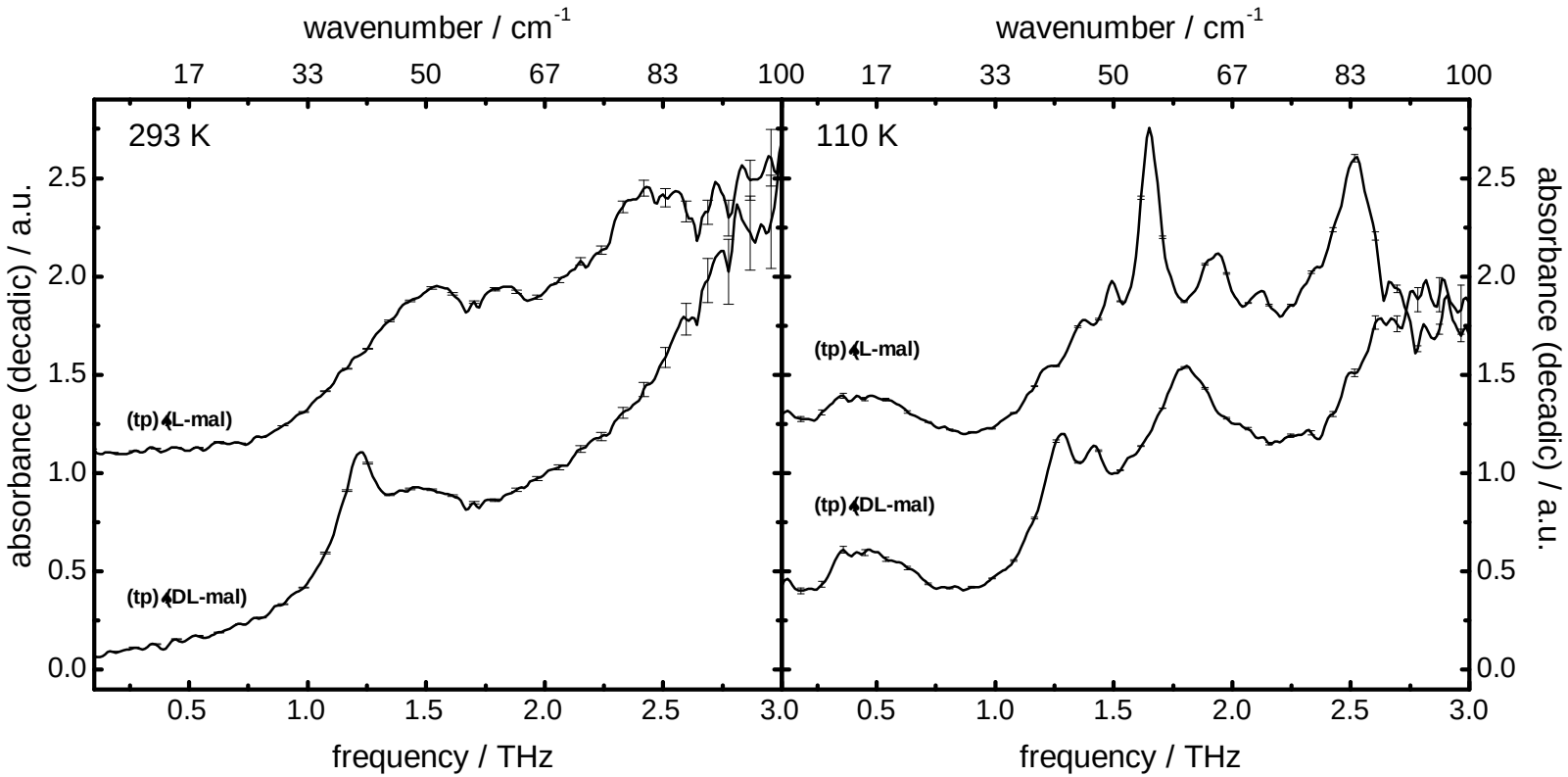




X-Ray powder diffractograms (left) and Raman spectra (right) of the isostructural cocrystals

E.P.J. Parrott *et al.*, Crystal Growth & Design, 9, 1452 (2009).

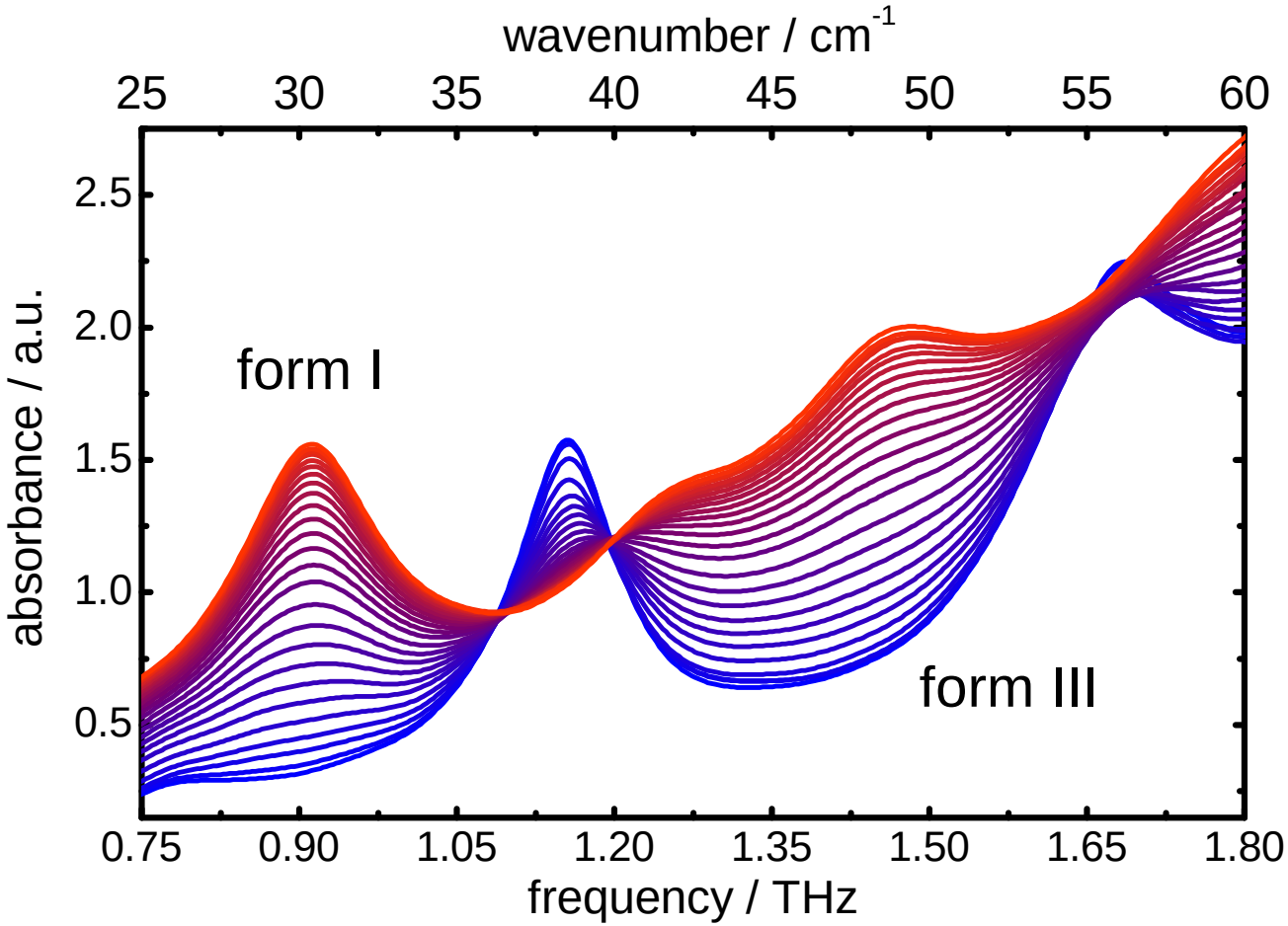
Structural Sensitivity – Isostructural Cocrystals



Terahertz spectra at room temperature (left) and at 110 K (right) – using terahertz spectroscopy the two cocrystals can be readily distinguished

E.P.J. Parrott *et al.*, Crystal Growth & Design, 9, 1452 (2009).

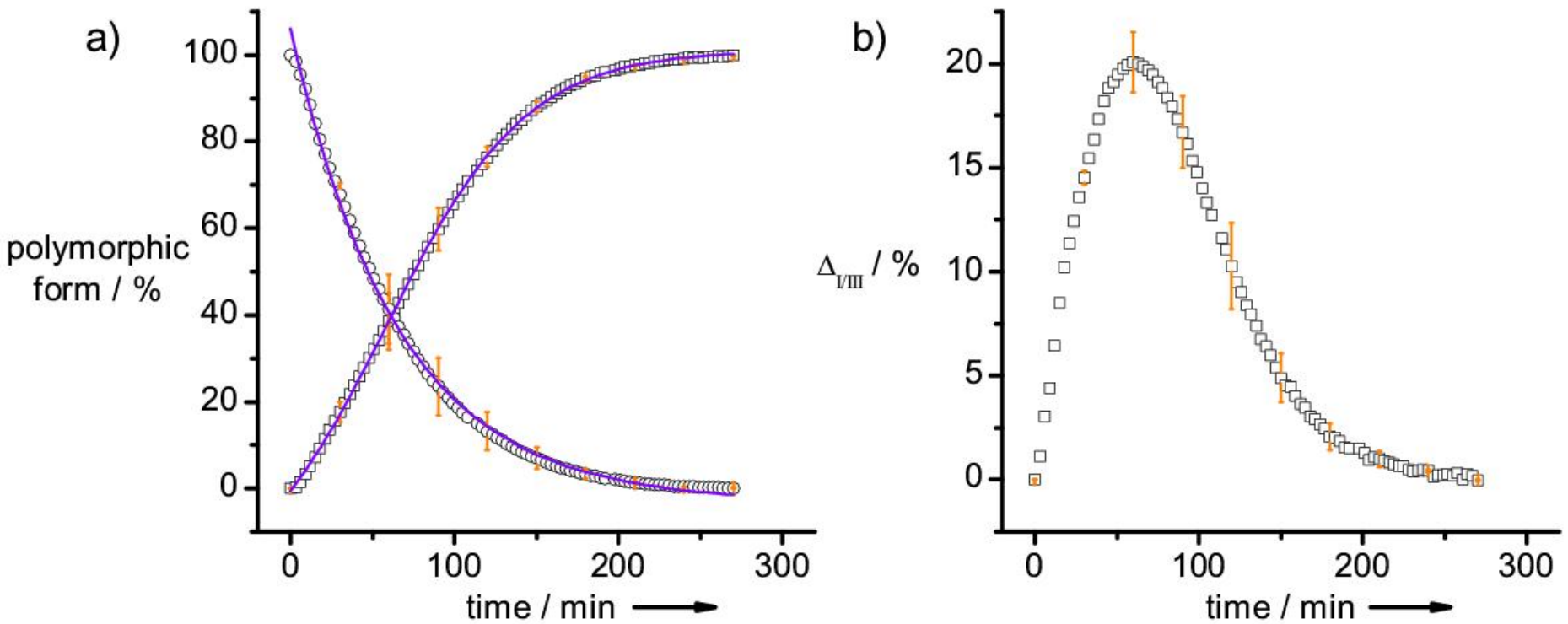
Phase Transitions – *in situ* Spectroscopy



Conversion of carbamazepine form III to I at 433 K

J.A. Zeitler et al., Thermochim. Acta 436, 71 (2005).

Phase Transitions – Kinetics



Kinetics of the solid state transition. Mechanism occurs as solid-gas-solid transition. This is in agreement with optical microscopy data and DSC measurements but ↯ previously reported mechanism by Raman and XRPD!

J.A. Zeitler et al., ChemPhysChem 8, 1924 (2007).

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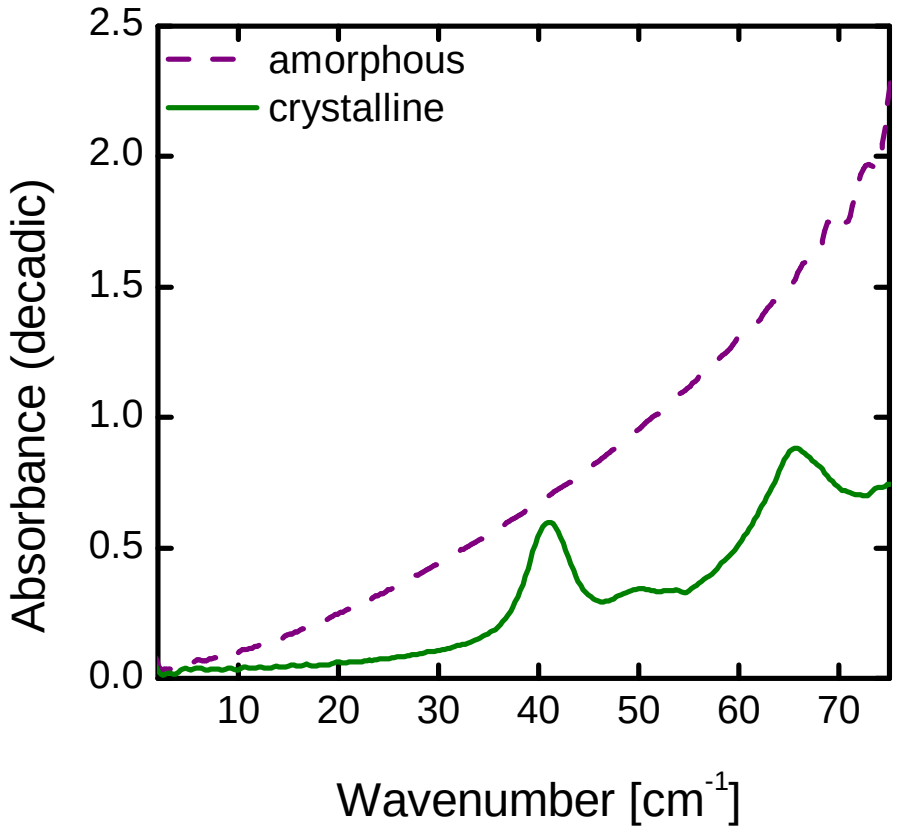
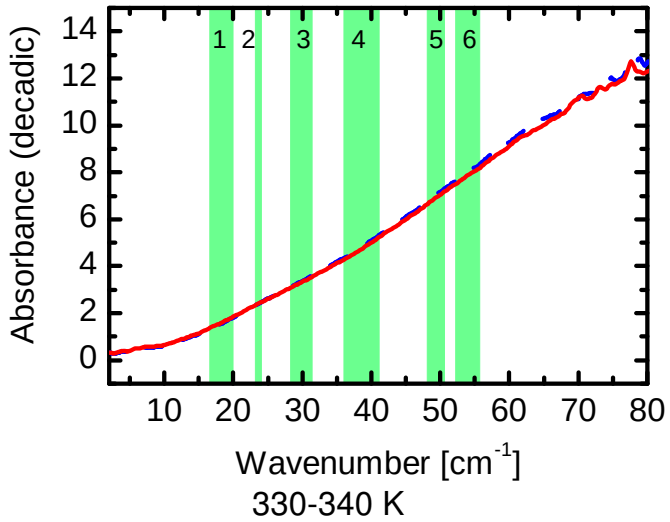
THz Spectra of Amorphous Materials



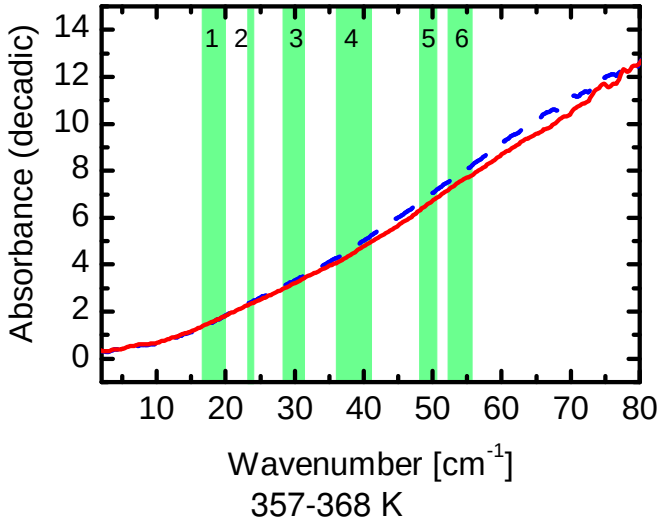
Crystalline vs. amorphous indomethacine.

C.J. Strachan *et al.*, Chem. Phys. Lett. 390, 20 (2004).

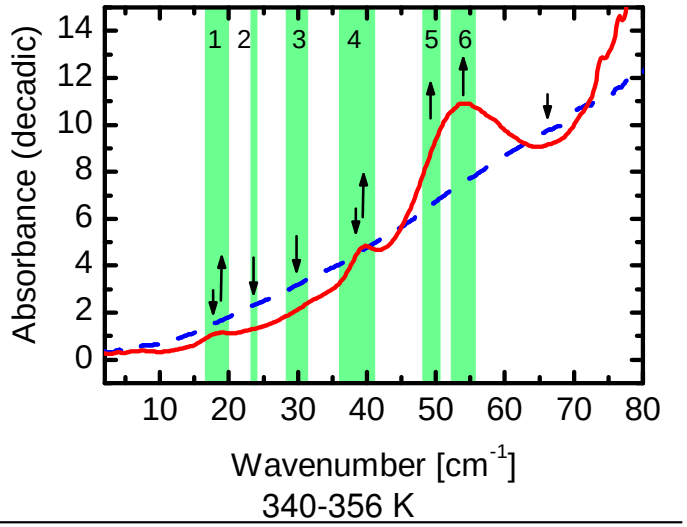
Relaxation and Crystallisation of Amorphous Materials



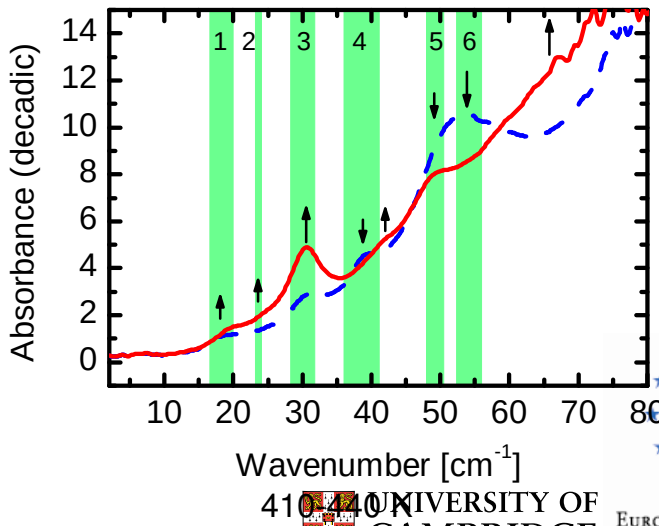
330-340 K



357-368 K



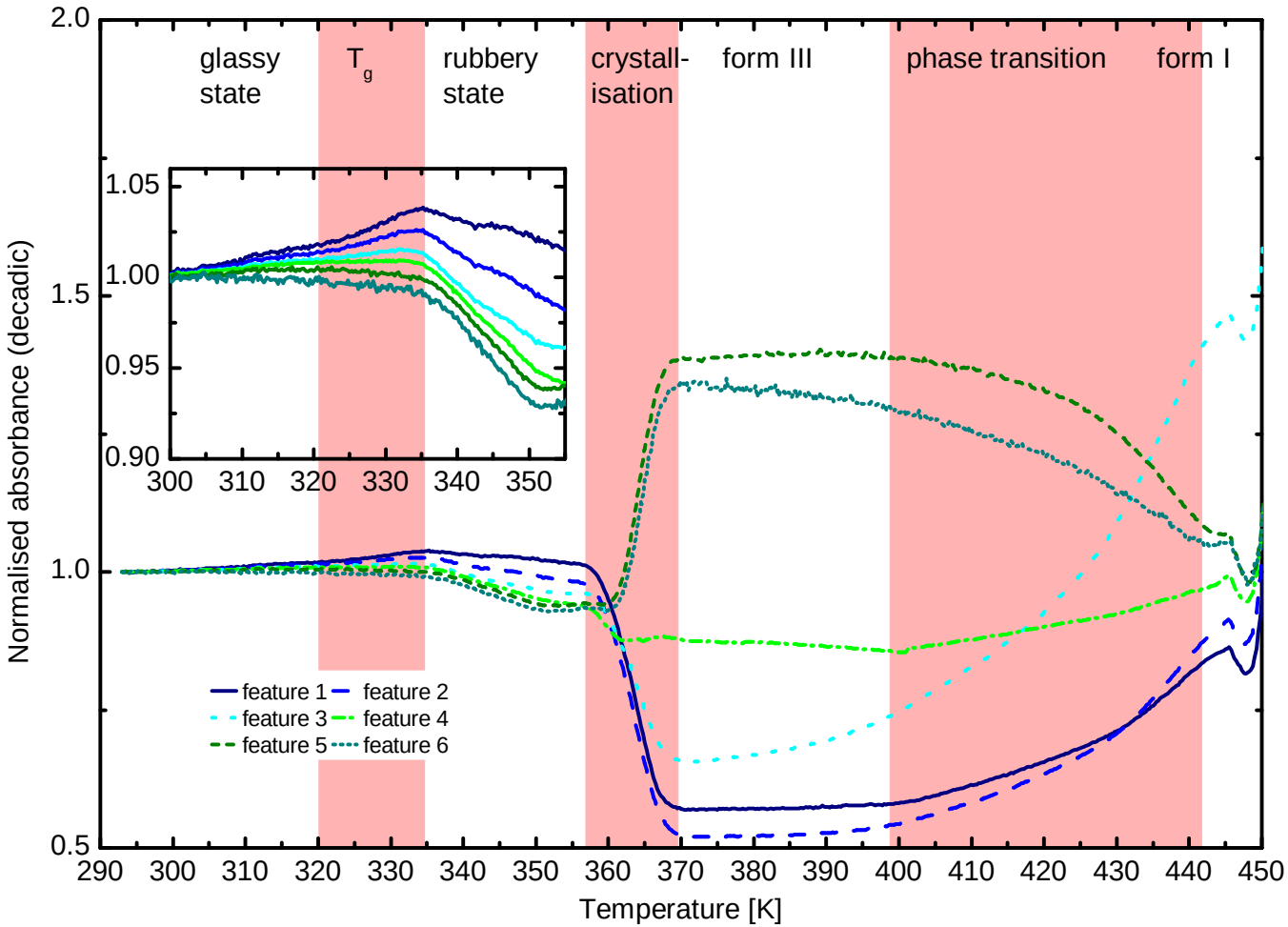
340-356 K



410-440 K

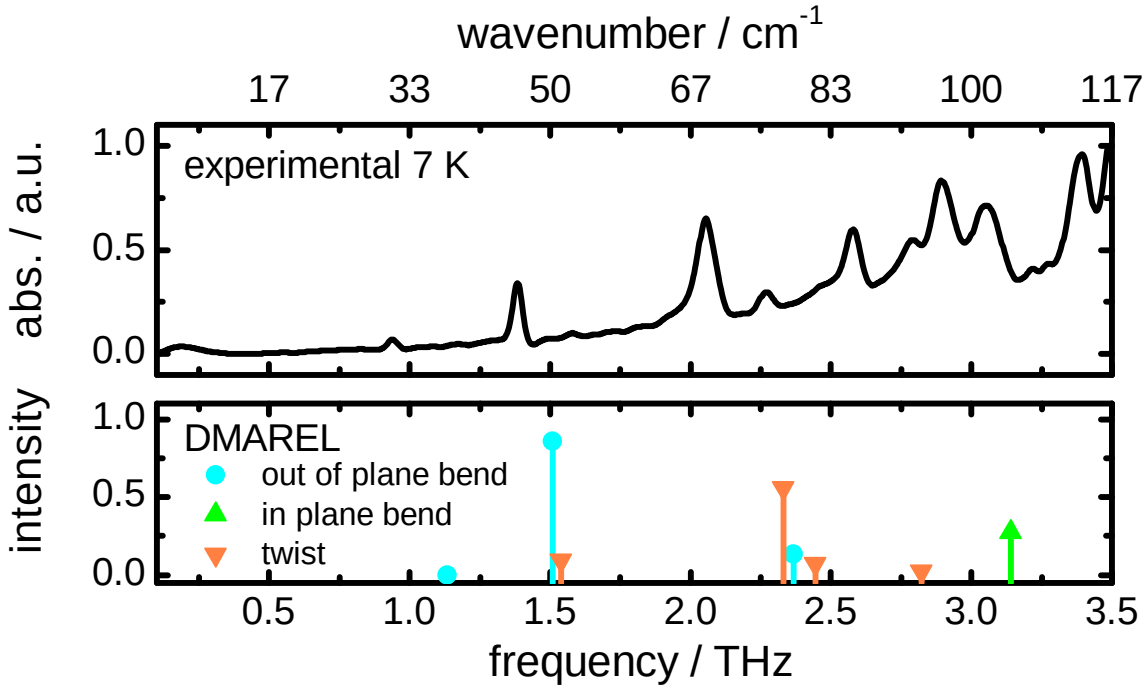
J.A. Zeitler et al., J. Pharm. Sci. 96, 2703 (2007).

Change in Absorbance



J.A. Zeitler et al., J. Pharm. Sci. 96, 2703 (2007).

Carbamazepine Polymorphs



Initial Success

Polymorphism of carbamazepine – vibrational modes in periodic crystalline structures as predicted by rigid molecule atom-atom potential calculations (DMAREL)

G.M. Day et al., J. Phys. Chem. B 111, 447-456 (2006).

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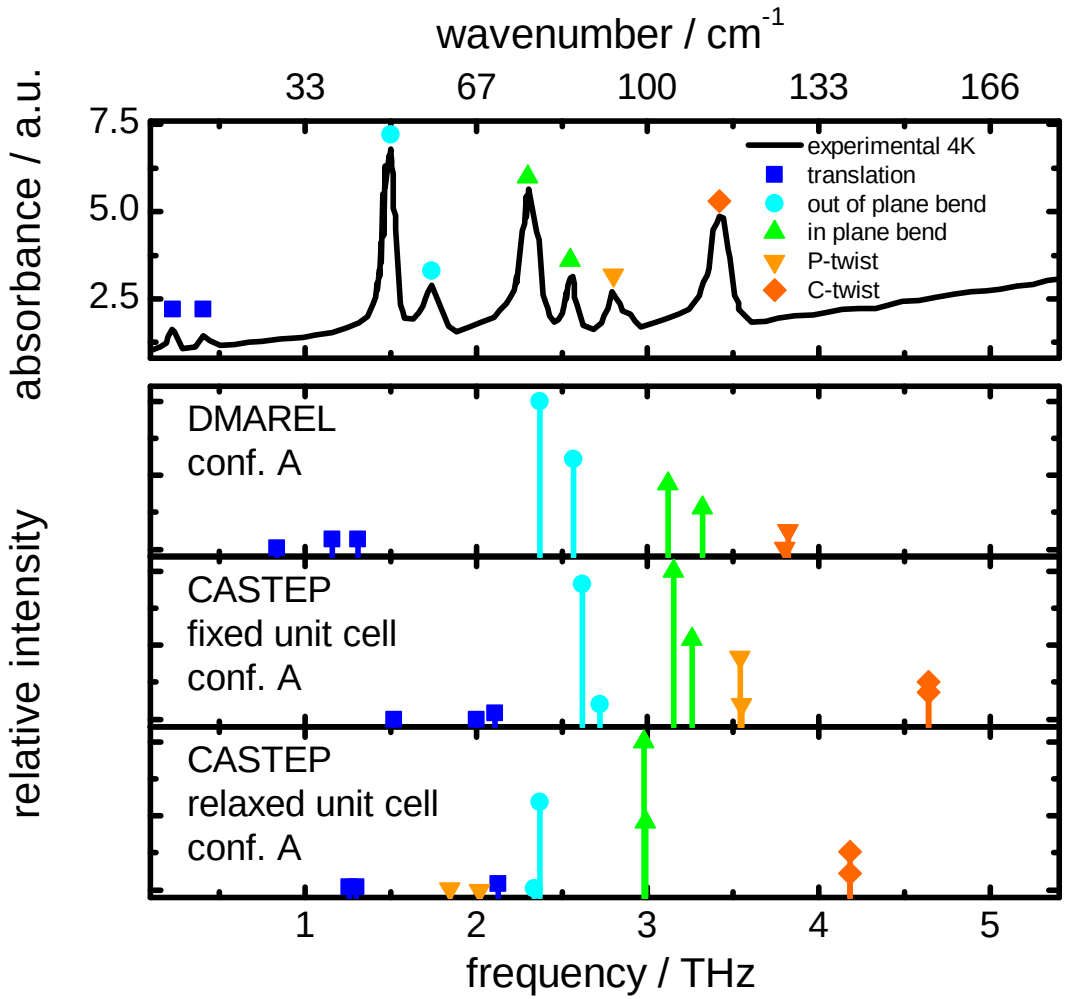
Terahertz Band Assignments



Results of the calculations for benzoic acid using DMAREL and periodic density functional theory (CASTEP)

R. Li et al., Phys. Chem. Chem. Phys., 12, 5329-5340 (2010).

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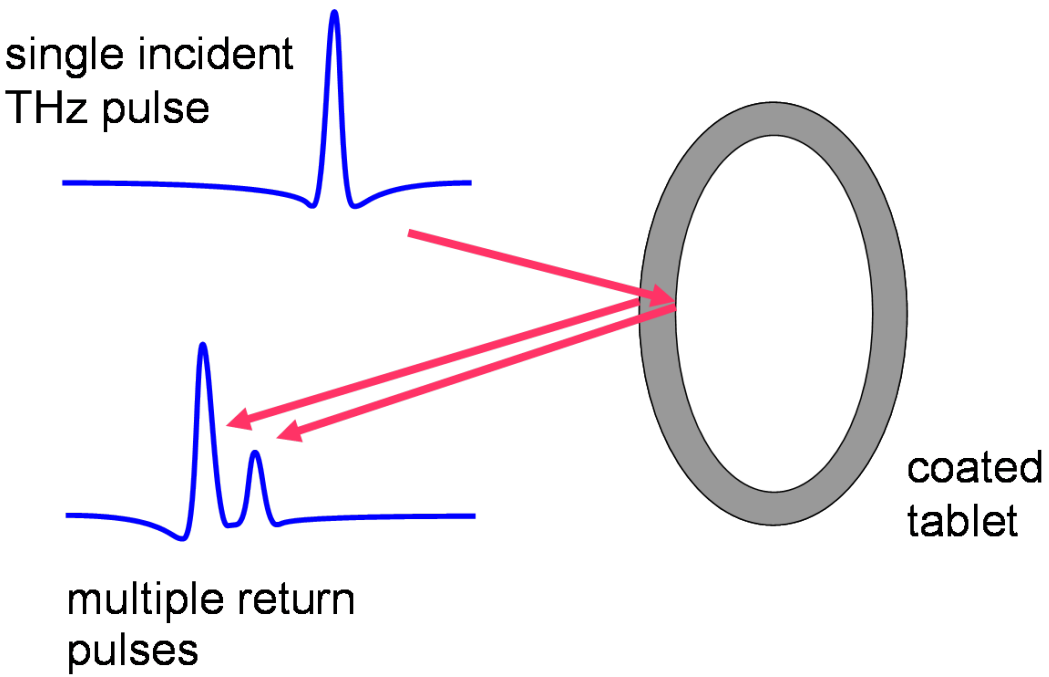
Terahertz Imaging



Imaging Principle

- Similar concept to radar or ultrasound measurements
- Unique penetration properties and short pulse duration ($< 10^{-12}$s)
- Spectral information can be recovered at depth
- Contrast due to change in refractive index

Reflection Coefficients = Contrast

$$r_{01} = \frac{n_1 - n_0}{n_0 + n_1}$$

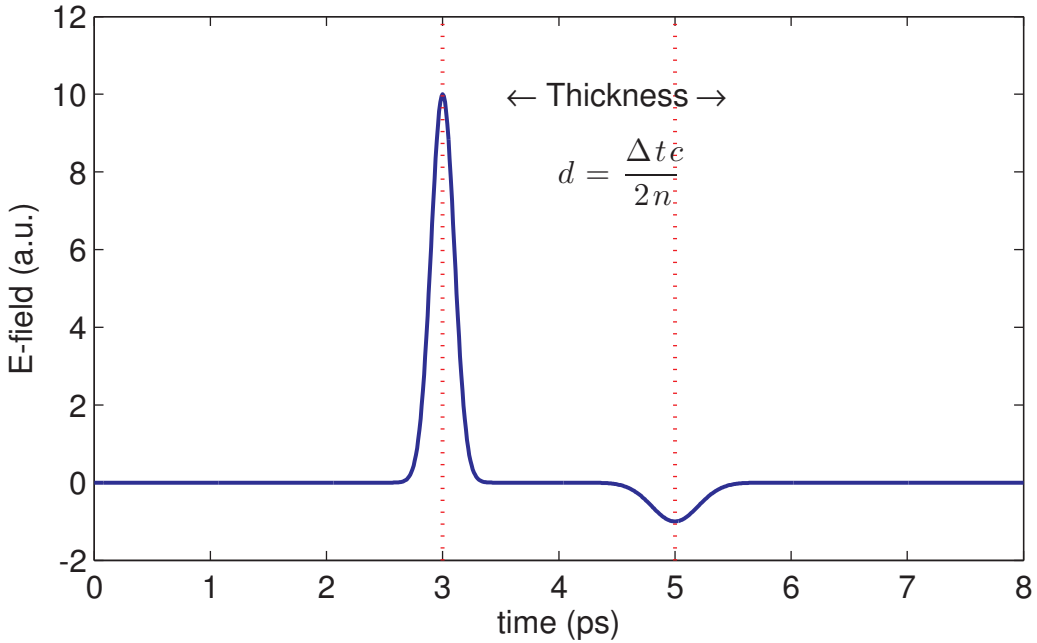
n_0, n_1 refractive indices in propagation direct.

Coating Thickness

$$d_{\mathrm{TPI}} = \frac{\Delta t c}{2n}$$

Δt time-of-flight, c speed of light

Terahertz Imaging



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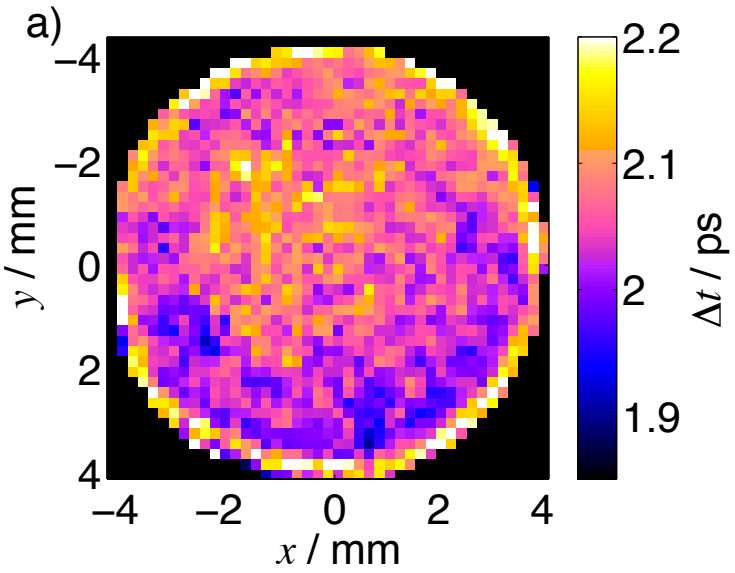
Coating Thickness Map



- Time-of-flight map representing precise variations in thickness

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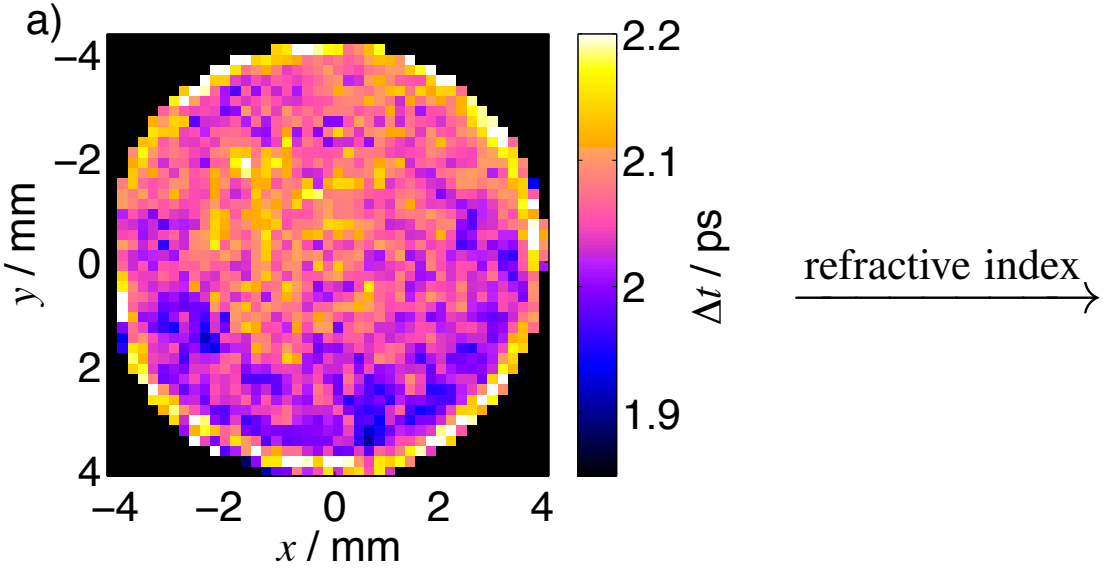
Coating Thickness Map



- Time-of-flight map representing precise variations in thickness
- The absolute thickness of the coating layer is calculated by specifying the refractive index n of the polymer

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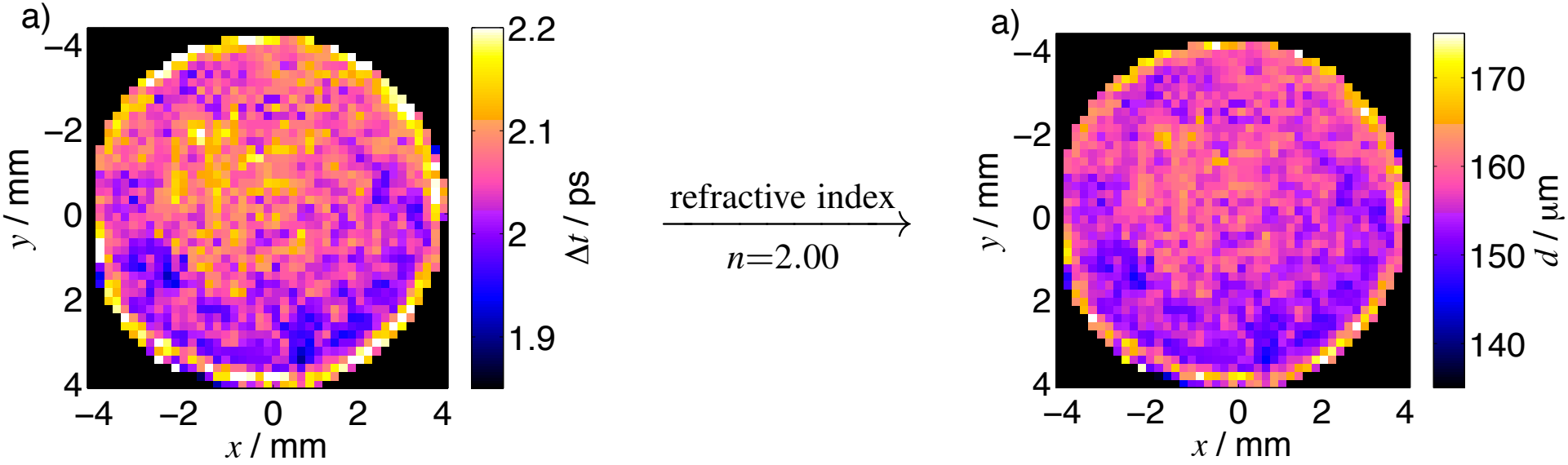
Coating Thickness Map



- Time-of-flight map representing precise variations in thickness
- The absolute thickness of the coating layer is calculated by specifying the refractive index n of the polymer
- In order to obtain accurate thickness information n must be known

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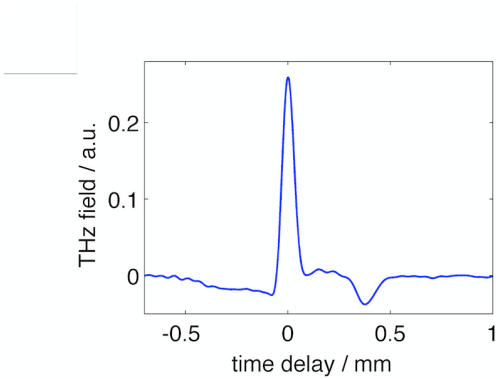
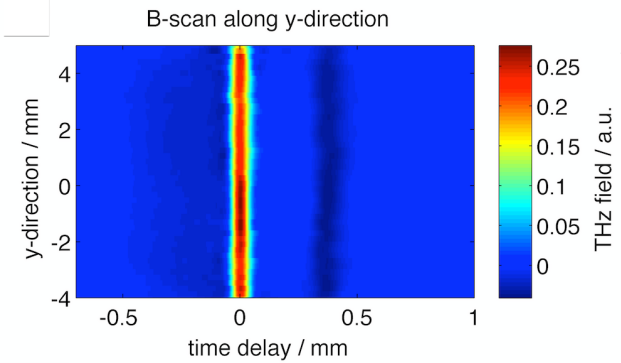
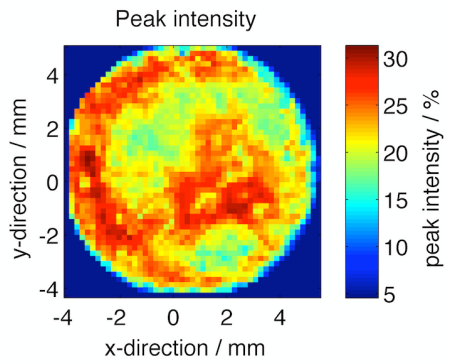
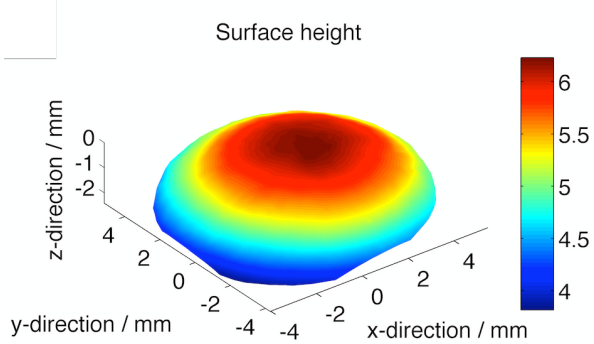
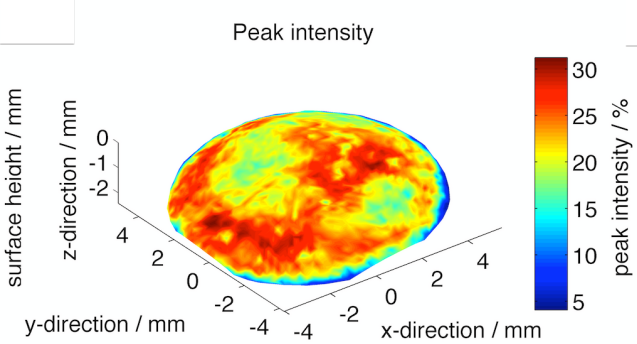
3D Tomography

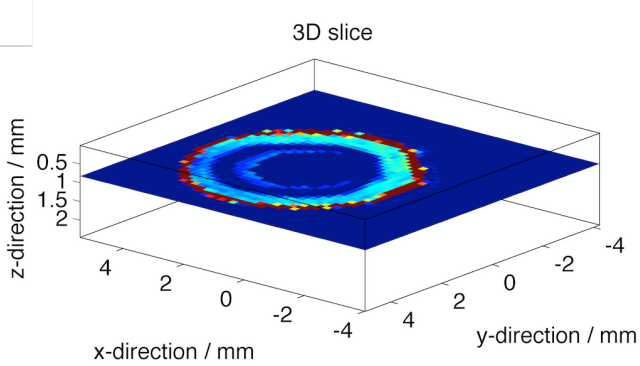




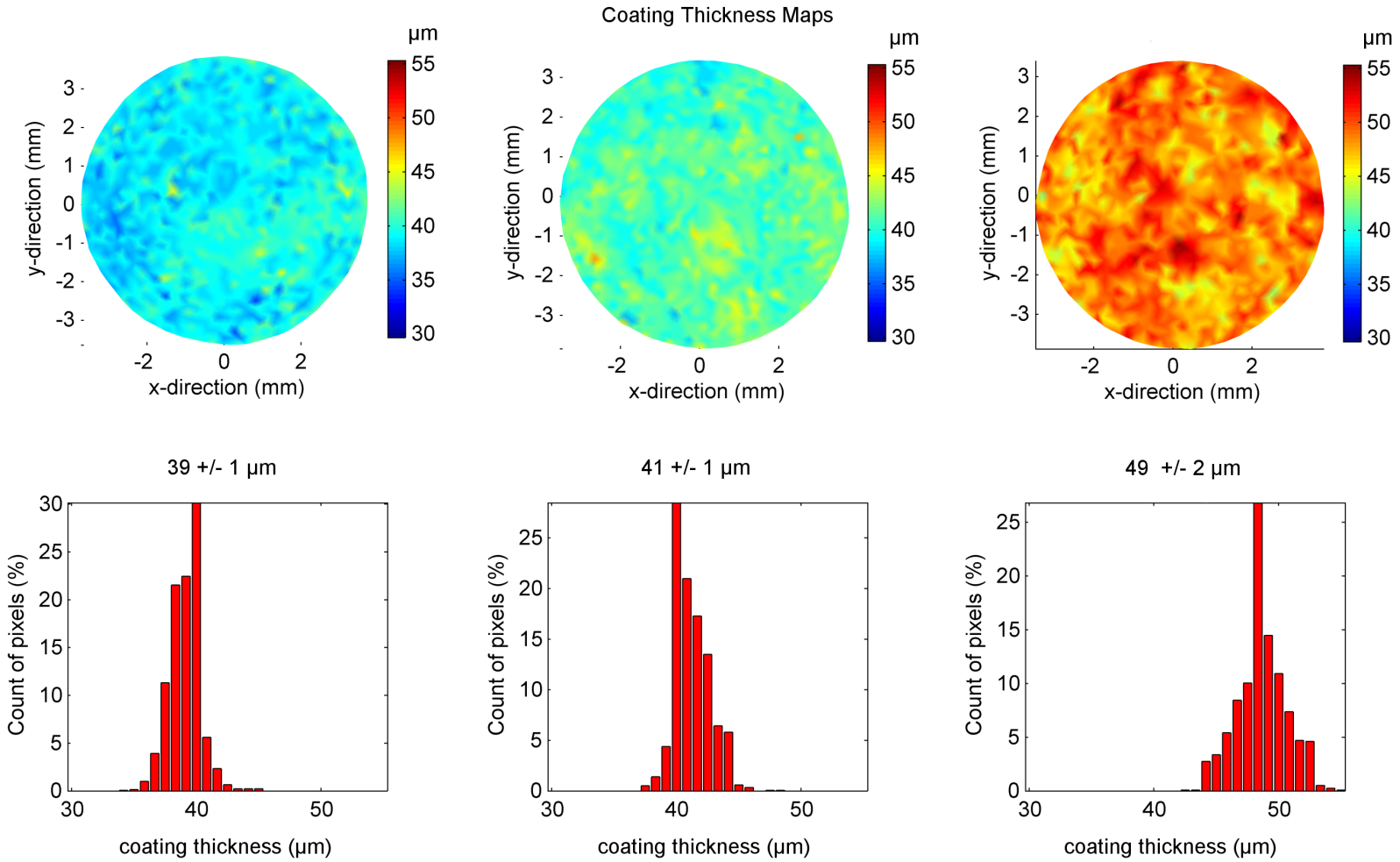








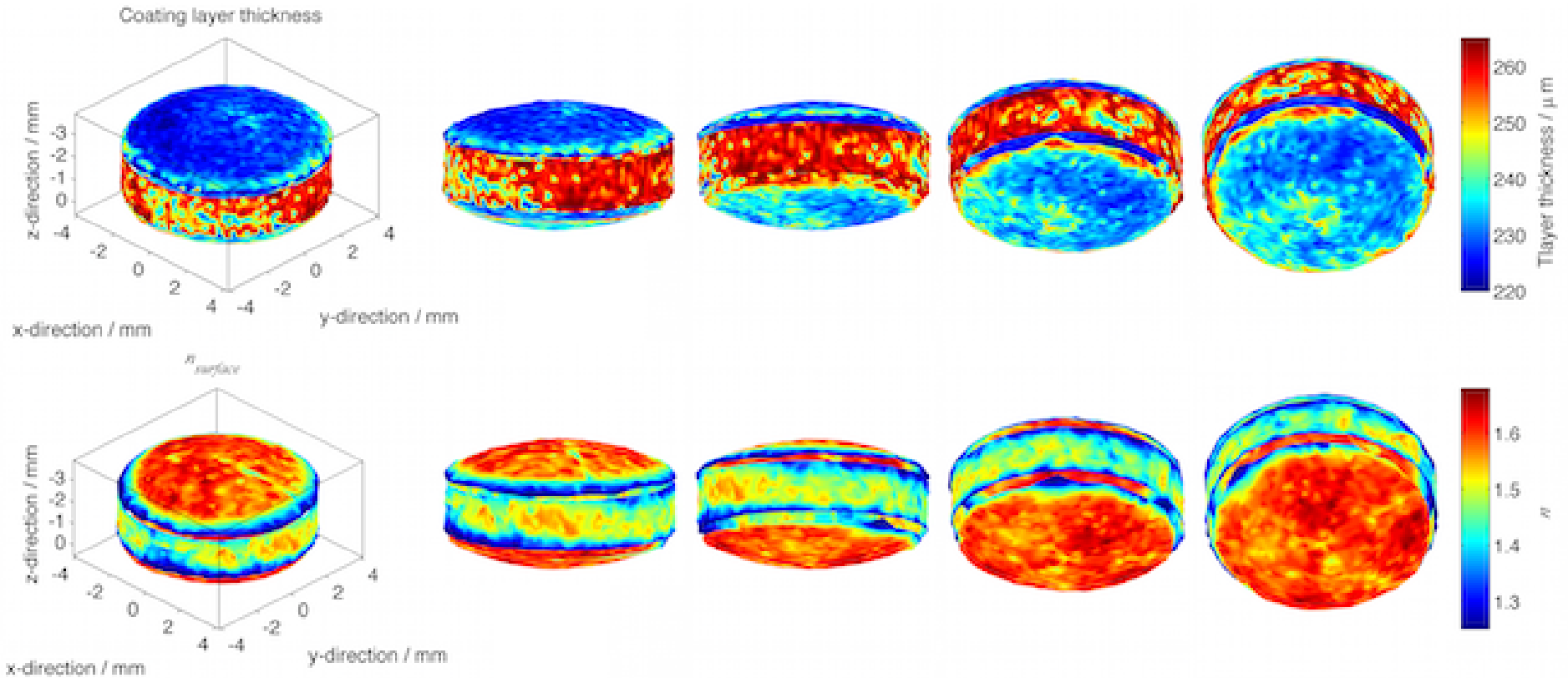
Coating Inhomogeneity – Tablet to Tablet Variation



Good homogeneity on each tablet but large variation within the batch

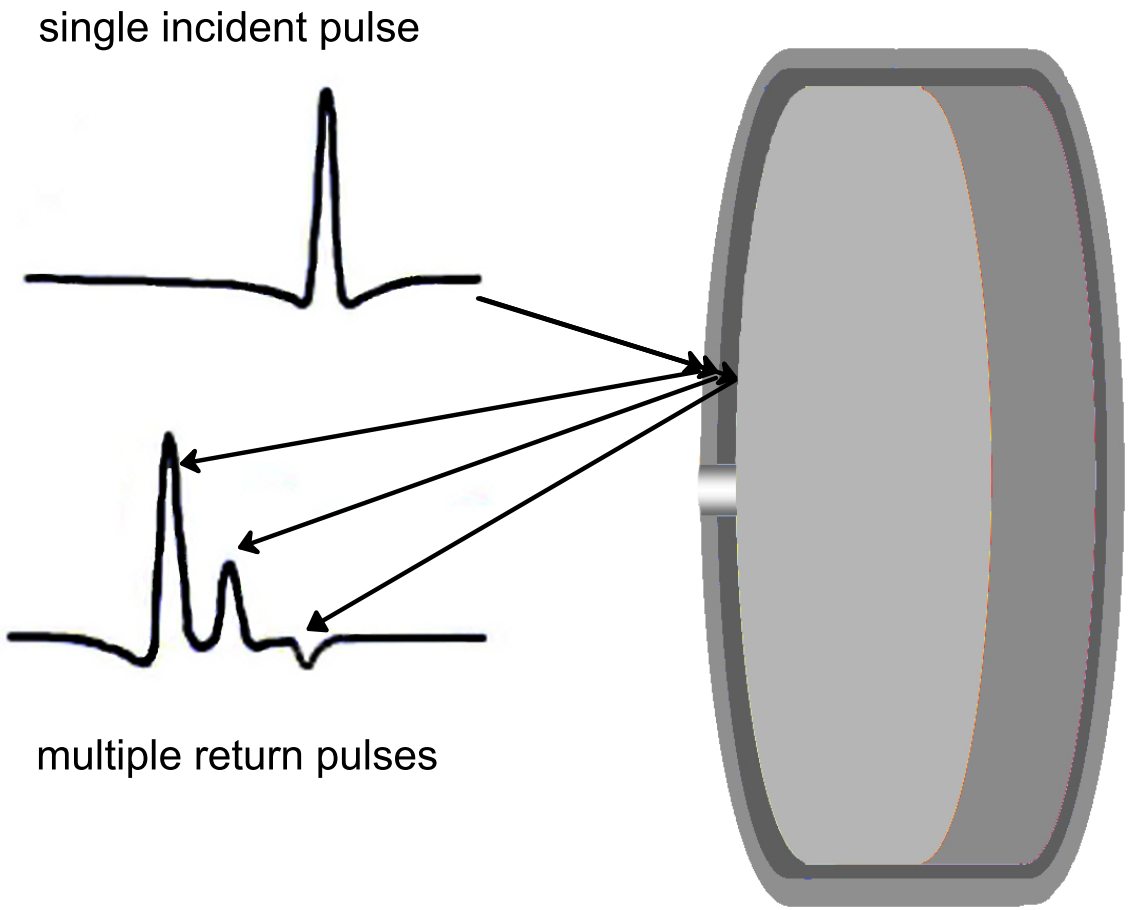
J.A. Zeitler *et al.*, J. Pharm. Sci. 96, 330 (2007).

Intratablet Variation



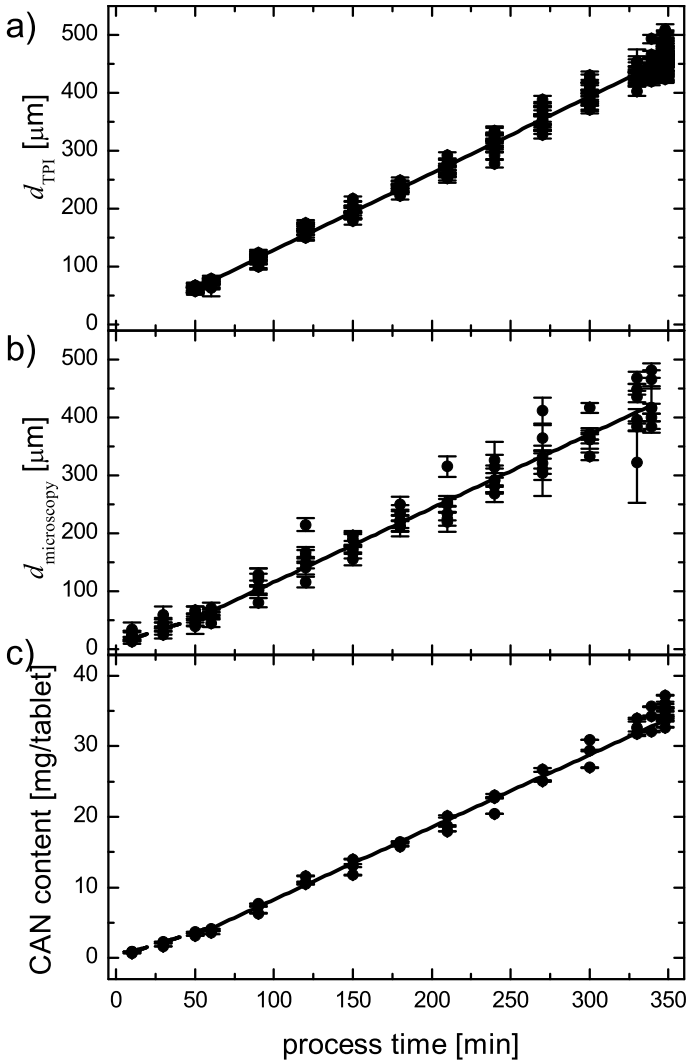
Much thinner coating is observed around the central band and inhomogeneities in coating thickness on one of the surfaces (coating thickness in μm, x, y and z dimensions in mm).

Content Uniformity in Active Coating



Active coating on top of a push-pull osmotic systems, comprising a two-layer tablet core

Active Coating – Content Uniformity



- TPI was superior to optical microscopy regarding the determination of coating thickness, as artefacts due to sample preparation could be avoided.
- TPI is a potential PAT tool for content measurements during coating and endpoint determination
- The TPI layer thickness measurement is directly based on the physical properties of the sample microstructure rather than relying on any chemical information from the coating layer.

D. Brock et al., Int. J. Pharm., vol. 439, pp. 289?295, 2012.

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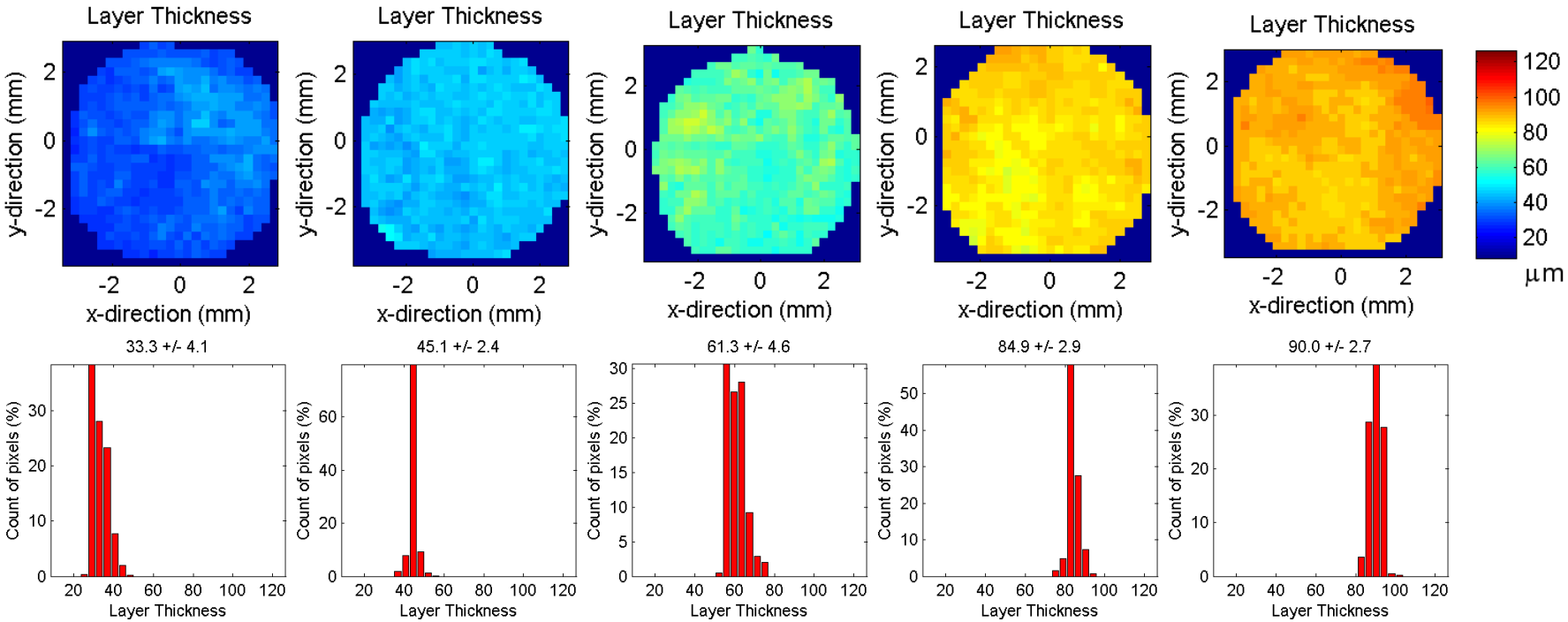
Coating Uniformity During Film Coating Process



TPI maps of the thickness distribution over the surface of typical tablets with process time. From left to right: 1, 2, 3, 4 and 5 hours

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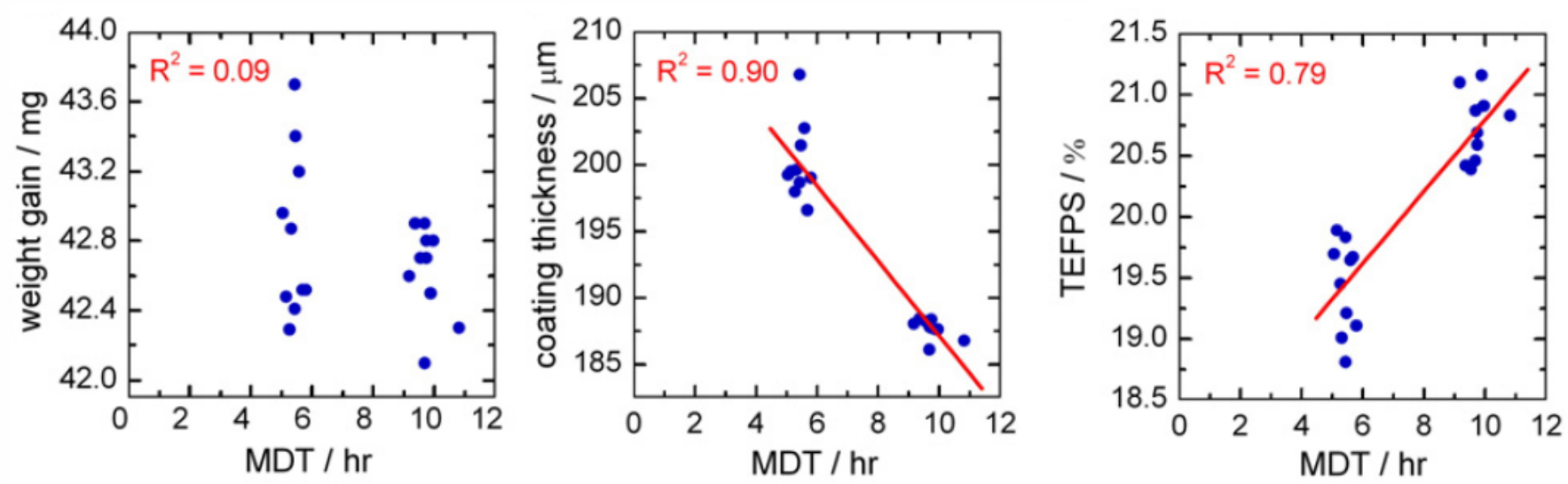
Sustained Release Coatings – Scale-Up



- Scale-up of a film coating process results in batches with significantly different mean dissolution times (MDT)
- Both batches exhibit identical weight gain, but it is possible to correlate the terahertz parameters to the MDT
- Tablets with thicker but less dense coating release faster than the tablets with the thin but dense coatings

Ho *et al.*, J. Contr. Rel. 127, 79-87 (2008).

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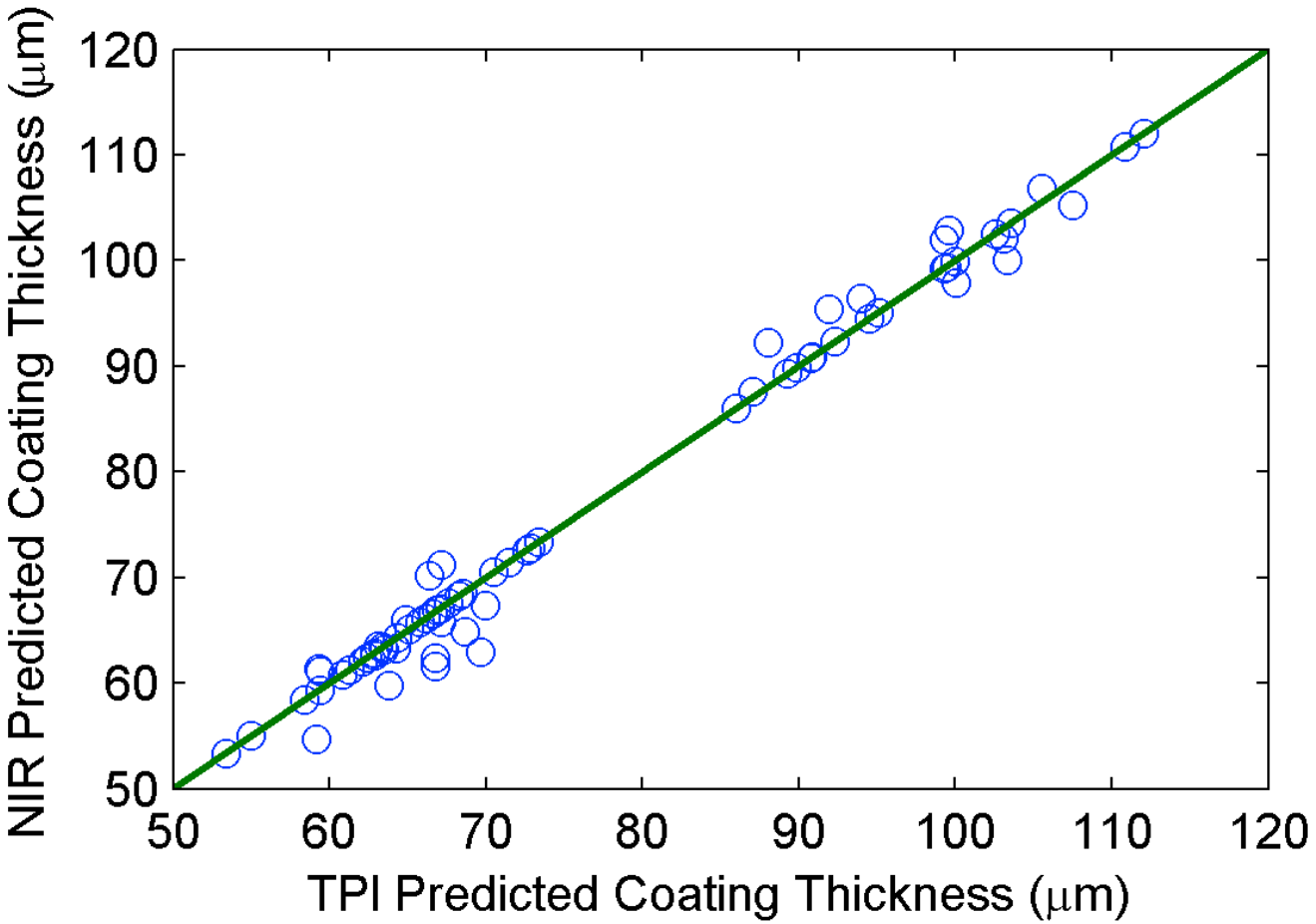
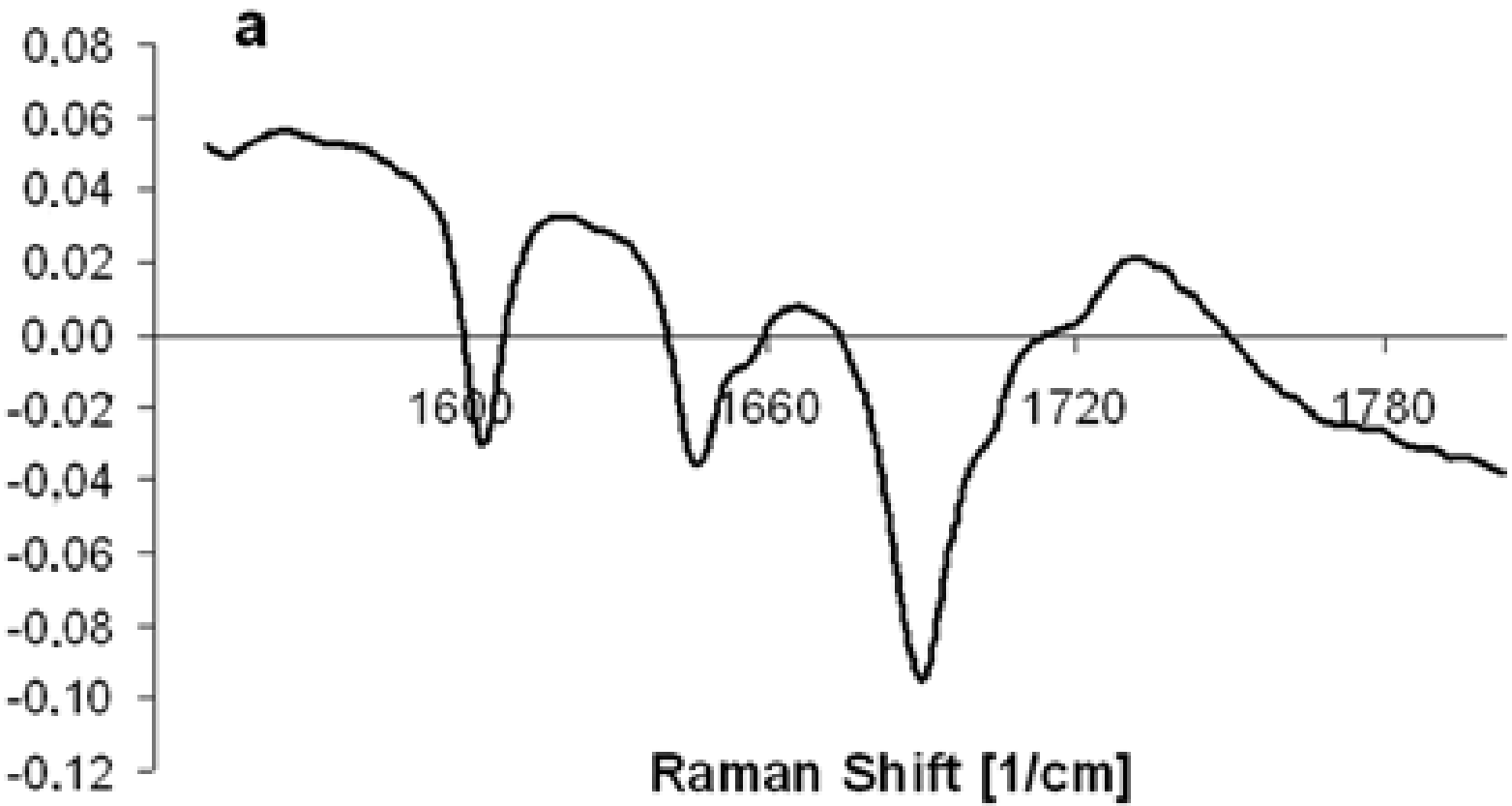
Providing Non-Destructive Reference Data



TPI can be used to accurately measure the coating thicknes on tablets over a range of thicknesses to build an NIR calibration dataset for quantitative multivariate analysis

S. Zhong *et al.* IEEE Proceedings of the IRMMW-THz (2009).

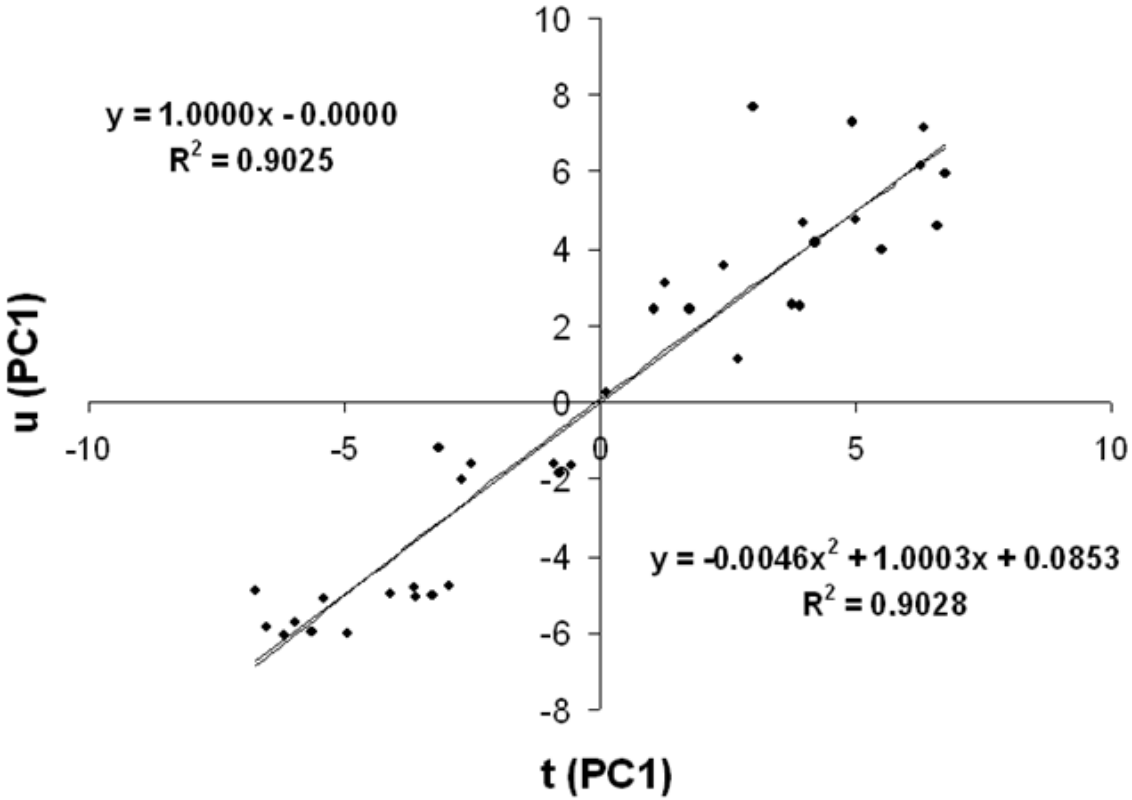
Calibration of Raman Sensors



Loading plot of Raman PLS model

J. Müller et al., Eur. J. Pharm. Biopharm. (2012).

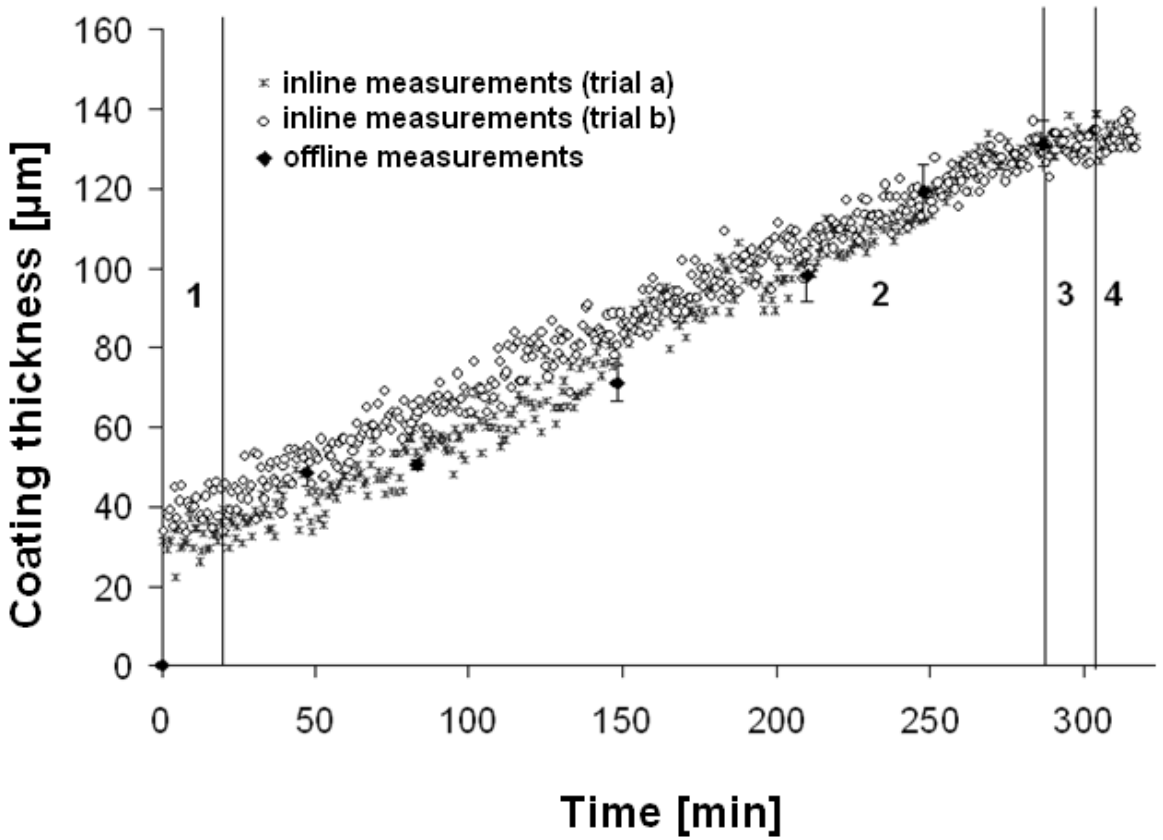
Calibration of Raman Sensors



Score plot of the first principal component

J. Müller et al., Eur. J. Pharm. Biopharm. (2012).

Calibration of Raman Sensors

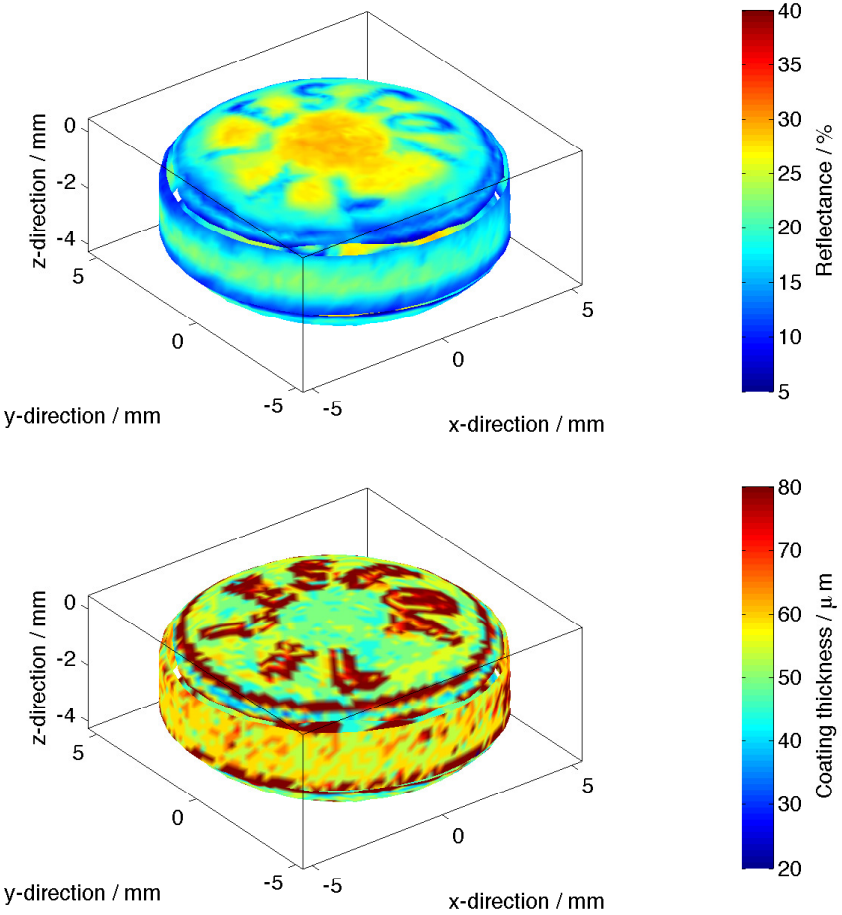


Predicted coating thickness (μm) for trials A and B from in-line data (n = 10; mean $\pm$ CI 95%); process steps: 1, warm up; 2, coating; 3, drying; and 4, cooling

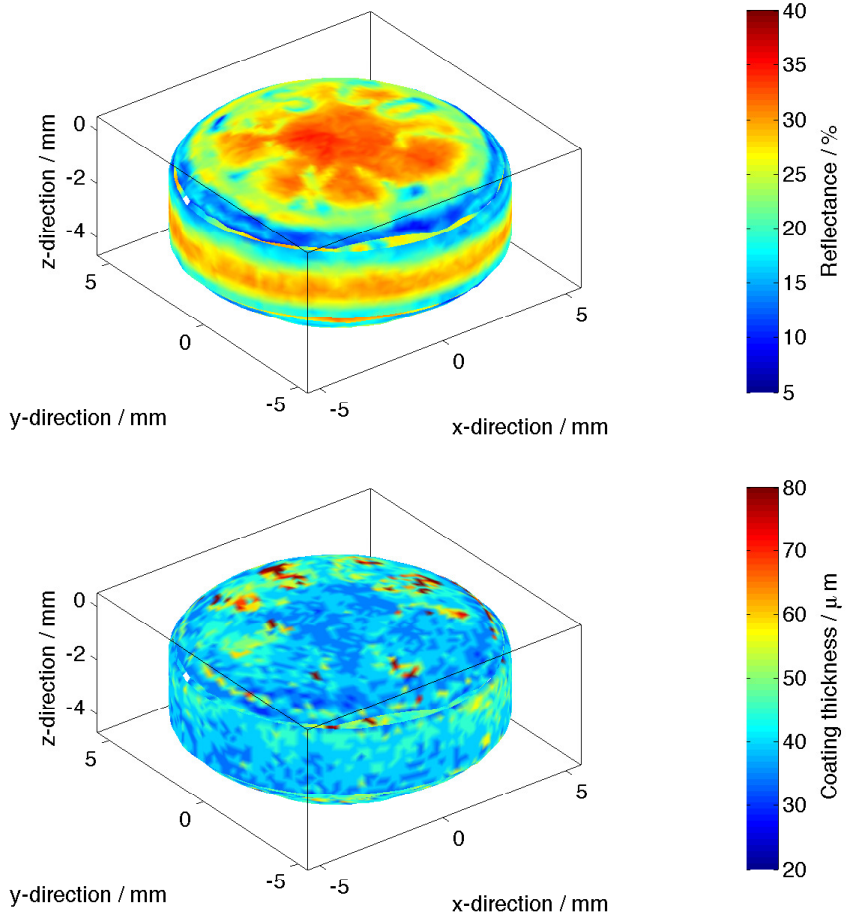
J. Müller et al., Eur. J. Pharm. Biopharm. (2012).

Stress Testing

unstressed



stressed



Q. Zhang et al., Pharmaceutics, in press (2013).

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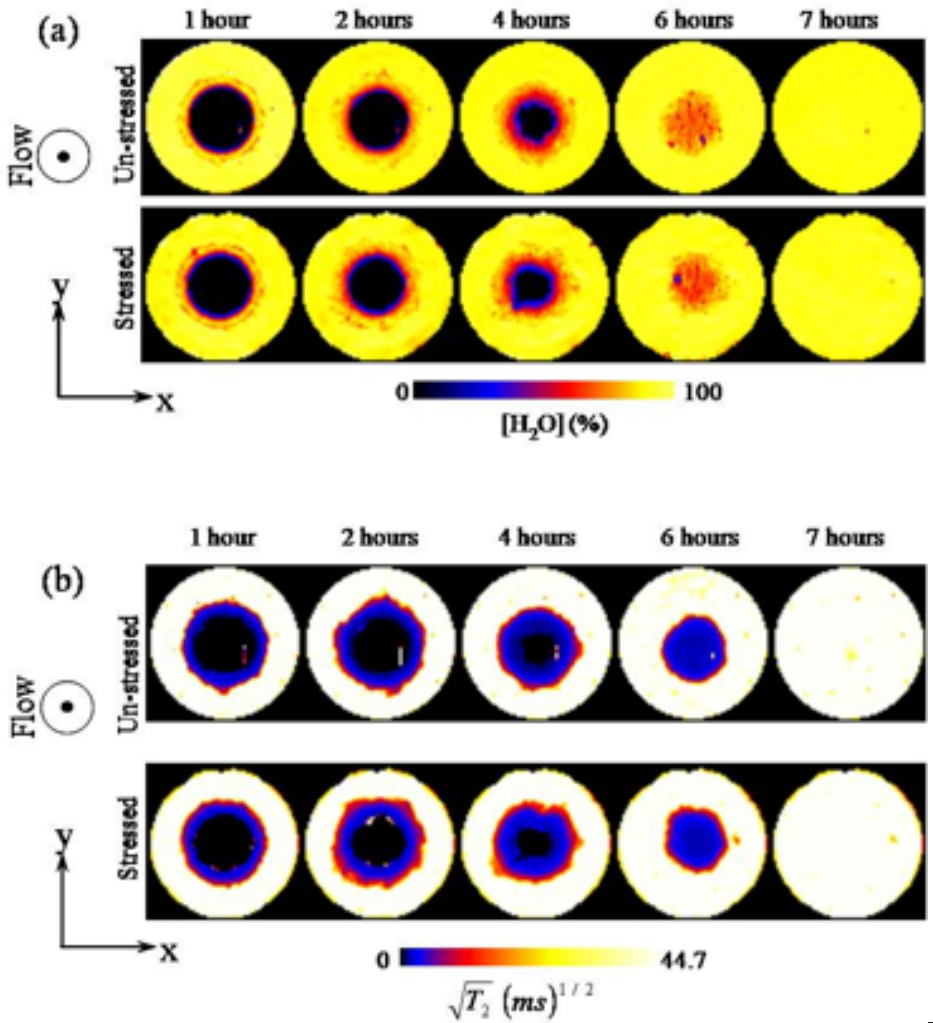
MRI of Dissolution Test



Q. Zhang et al., Pharmaceutics, in press (2013).

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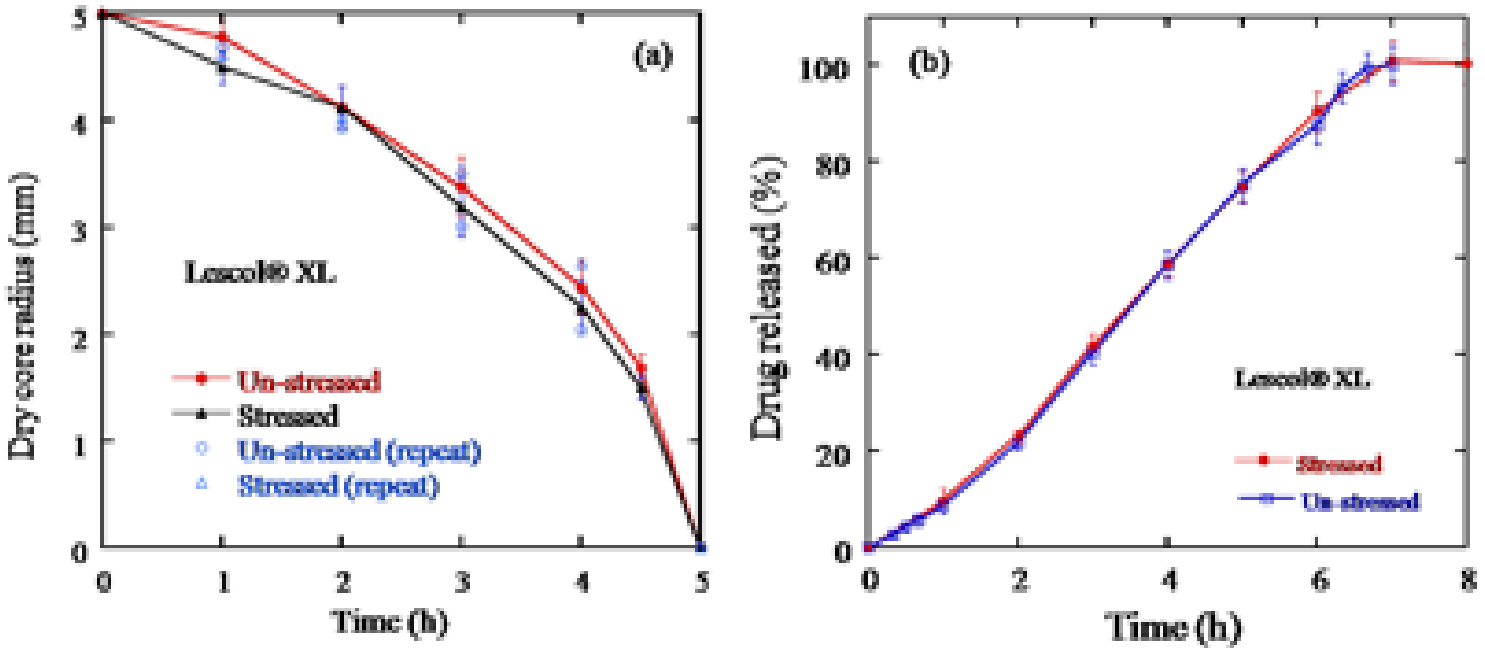
Drug Release



Q. Zhang et al., Pharmaceutics, in press (2013).

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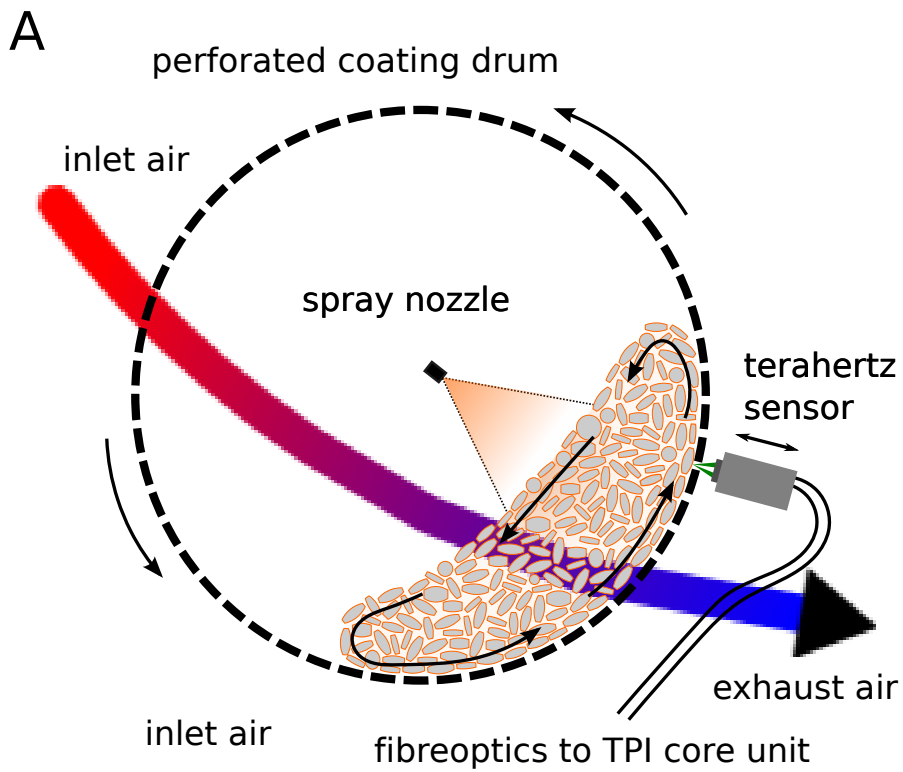
In-Line Terahertz Sensor



Terahertz sensor mounted directly in pilot scale film coater

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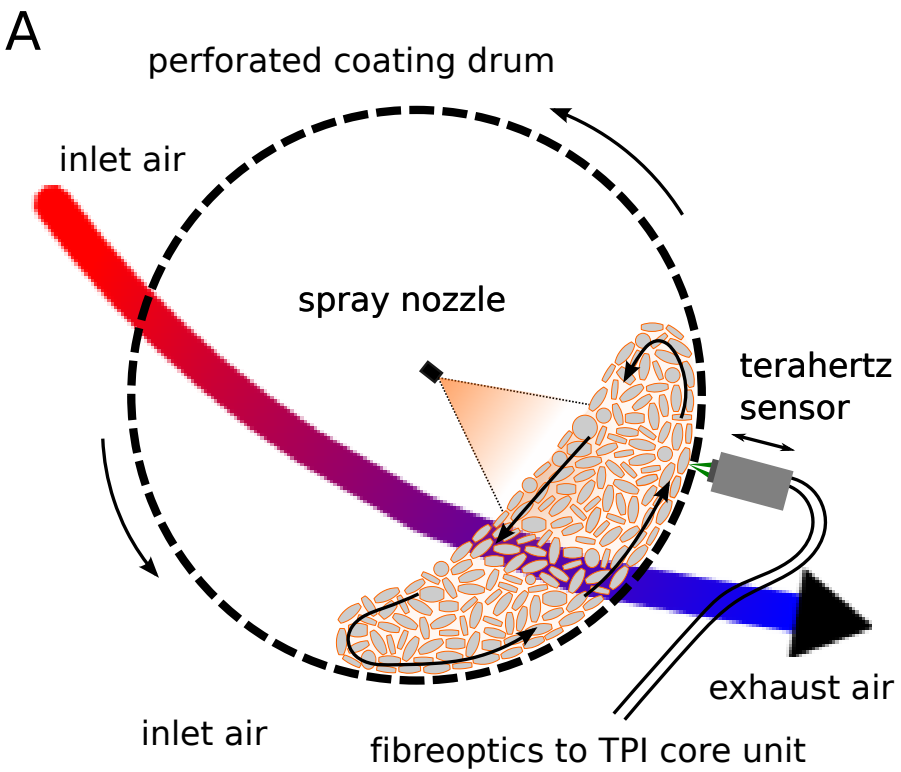
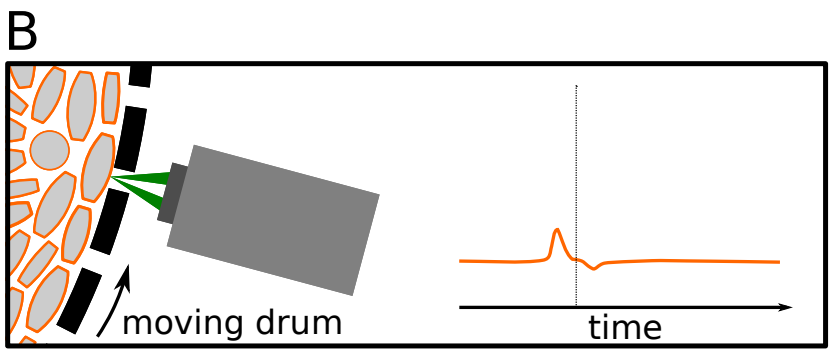
In-Line Terahertz Sensor





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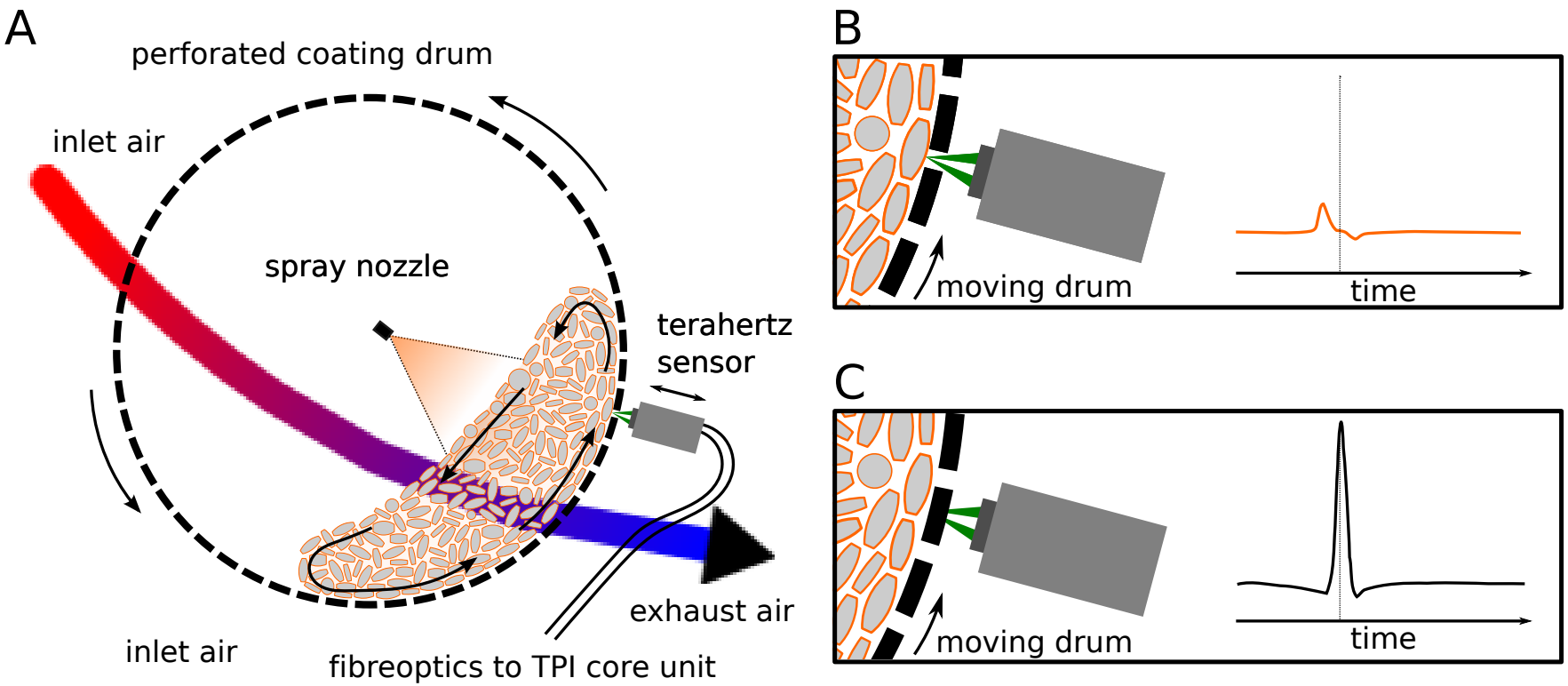
In-Line Terahertz Sensor



Terahertz sensor mounted directly in pilot scale film coater

Real-Time Sensors for Process Control

Terahertz sensor mounted directly in pilot scale film coater

R.K. May et al., J. Pharm Sci. 100, 1535 (2011).

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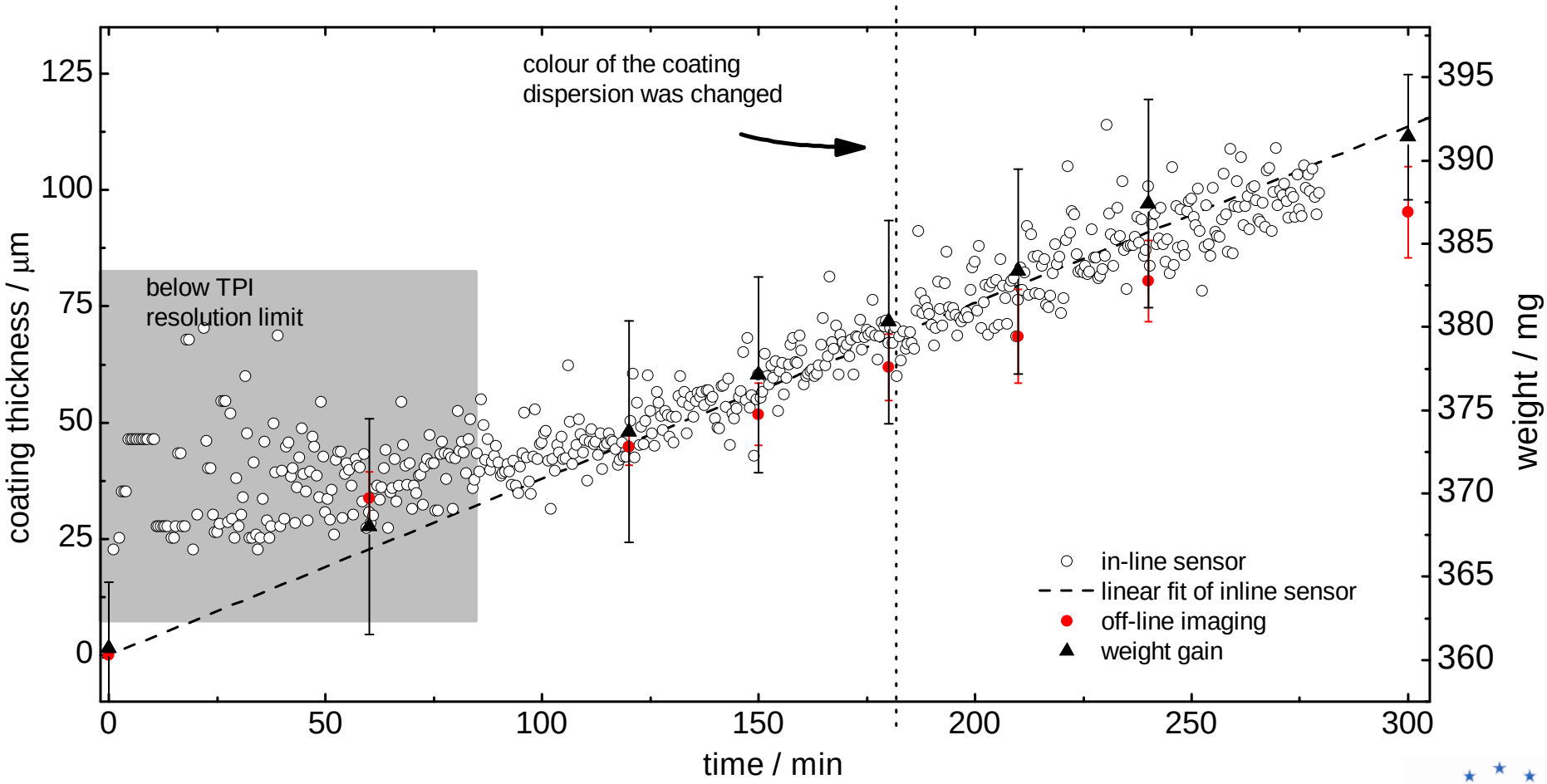
Real-Time Sensors for Process Control

Terahertz sensor mounted directly in pilot scale film coater

R.K. May et al., J. Pharm Sci. 100, 1535 (2011).

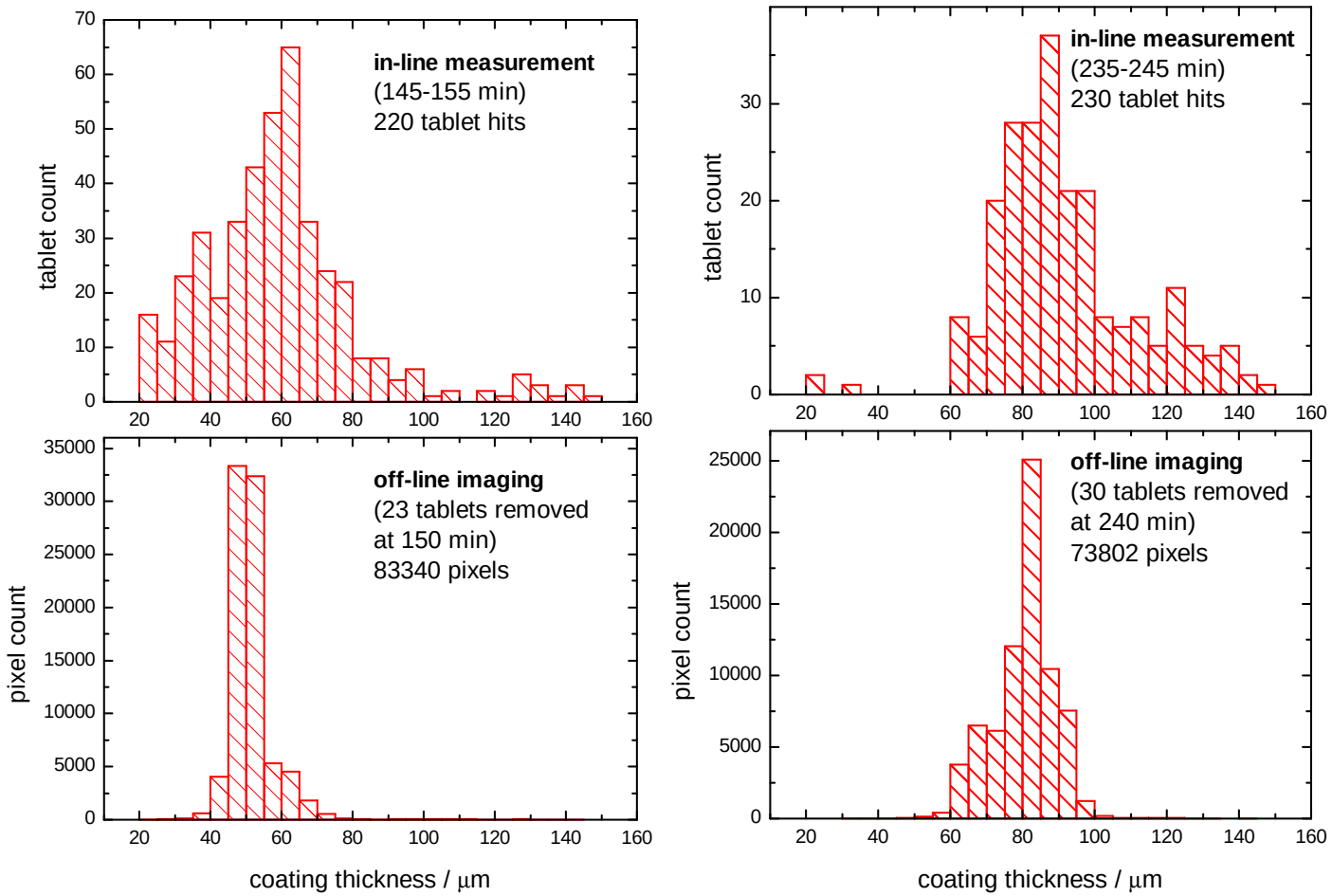
Coating Thickness Measurements



Coating thickness measured by the in-line process sensor during process time. For clarity the datapoints of the in-line measurements represent the average over 30 second measurement time

R.K. May et al., J. Pharm Sci. 100, 1535 (2011).

Coating Thickness Measurements



Coating thickness distribution between 145-155 min and 235-245 min process time measured using the in-line terahertz sensor and the corresponding off-line imaging analysis by TPI

R.K. May et al., J. Pharm Sci. 100, 1535 (2011).

Terahertz Spectroscopy

Advantages

- Unique sensitivity to intermolecular interactions in solids
- Fingerprint spectrum for each crystalline solid state form
- Interesting information form amorphous materials
- Very fast technique
- High penetrative power
- Interesting imaging applications

Diadvantages

- Spectral assignment still very difficult
- Relatively less mature technology
- Limited spectral range
- Samples need to be pressed into pellets (though ATR possible)

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Outline

1. Introduction and Motivation – The Toolbox
2. Moving across the Spectrum: MHz to EHz – Picking the Right Tool
   - Nuclear Magnetic Resonance (NMR) Spectroscopy
   - Dielectric Spectroscopy
   - Vibrational Spectroscopy: THz
   - Vibrational Spectroscopy: Raman
   - Vibrational Spectroscopy: Near-infrared
3. Summary

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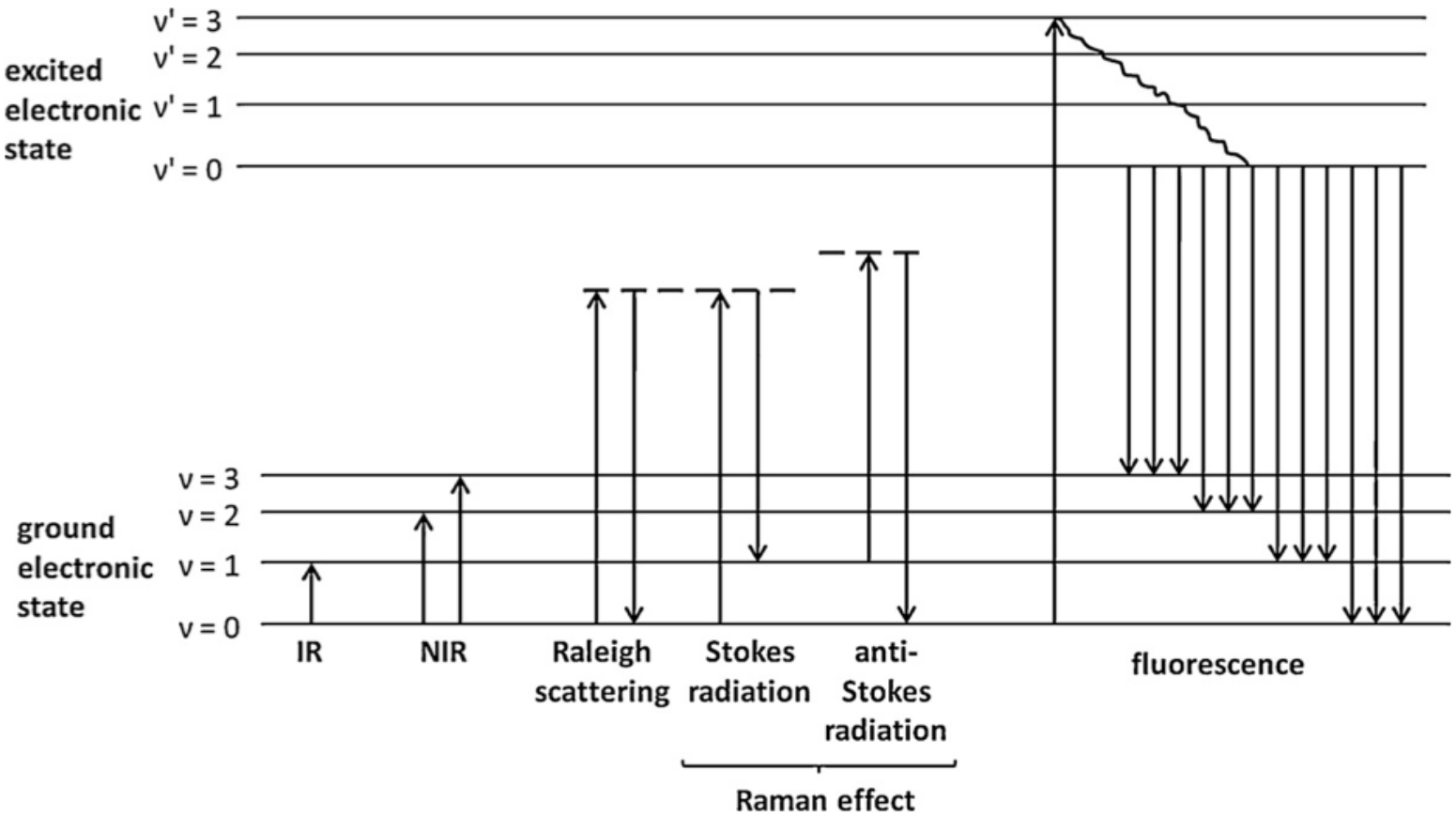
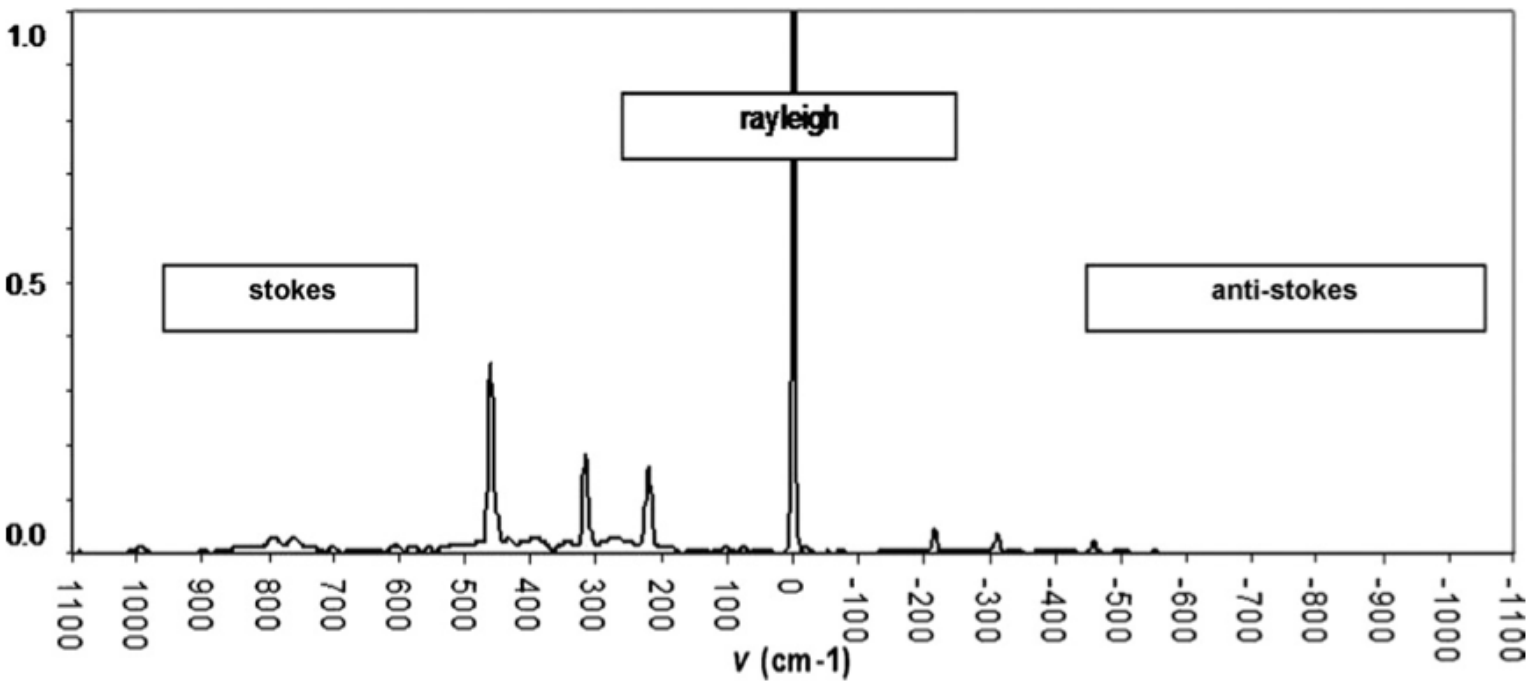
Raman Spectroscopy



T. de Beer et al., Int. J. Pharm. 417, 32 (2011).

Raman Spectroscopy



T. de Beer et al., Int. J. Pharm. 417, 32 (2011).

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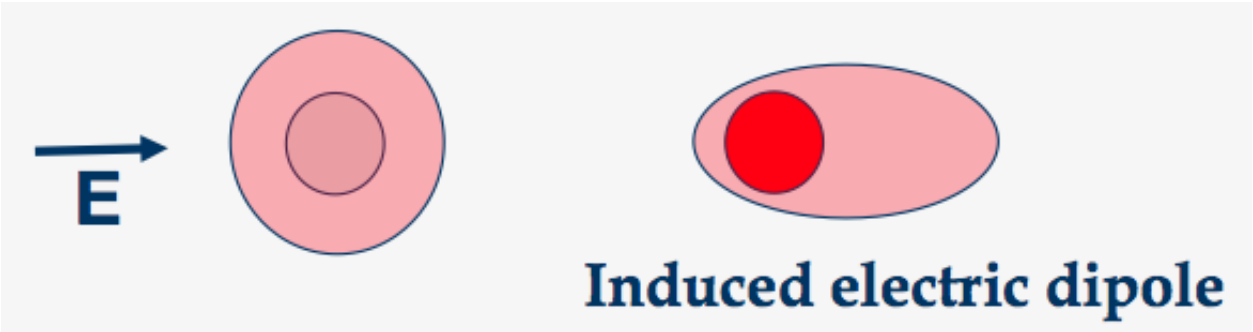
Raman Spectroscopy

- Raman spectroscopy probes the polarisability of a bond, the ease with which the electron density around individual atoms can be displaced by an external electric field
- The polarisability is a function of bond length
- Using recent technology in notch filters to better separate the Rayleigh scattering near the excitation line it is possible to perform Raman spectroscopy down to < 1 Thz $(33\,\mathrm{cm}^{-1})$



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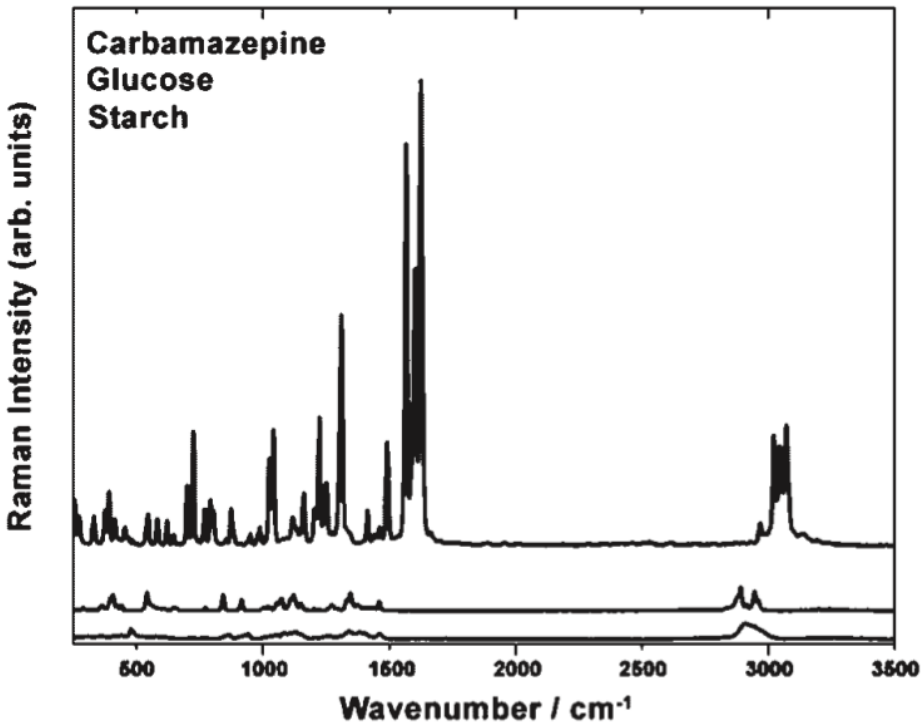
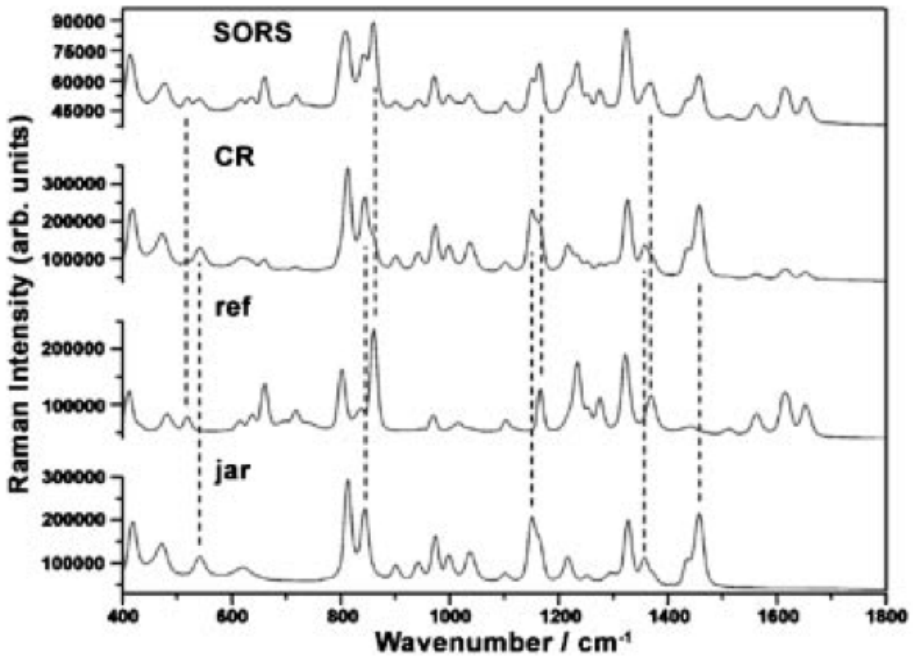
Raman Spectroscopy – Band Intensity

- The intensity of a Raman band is associated with the change in polarisability of the molecule.
- Active pharmaceutical ingredients (APIs) typically contain aromatic conjugated systems which show strong Raman transitions.
- In contrast, excipients such as starch are weaker Raman scatterers due to a lack of π-bonding



C. McGoverin, T. Rades, and K. Gordon, J. Pharm Sci. 97, 4598 (2008).

Raman Spectroscopy



Using Raman spectroscopy it is possible to measure through containers (here paracetamol tablets)

C. McGoverin, T. Rades, and K. Gordon, J. Pharm Sci. 97, 4598 (2008).

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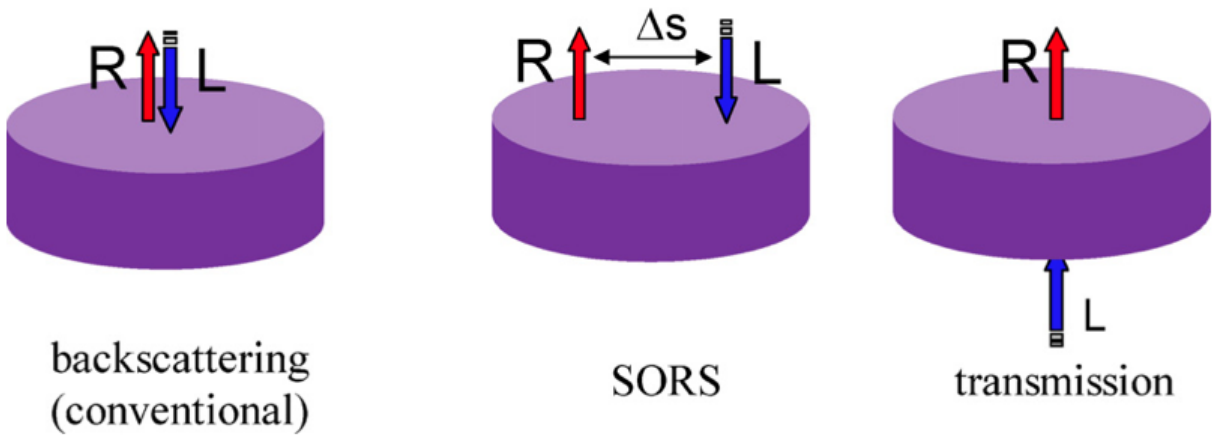
Transmission Raman

- Raman spectroscopy typically suffers from a small sampling volume
- Using transmission or spatially offset (SORS) techniques this can be overcome



K. Buckley and P. Matousek, J. Pharm. Biomed. Anal. 55, 645 (2011).

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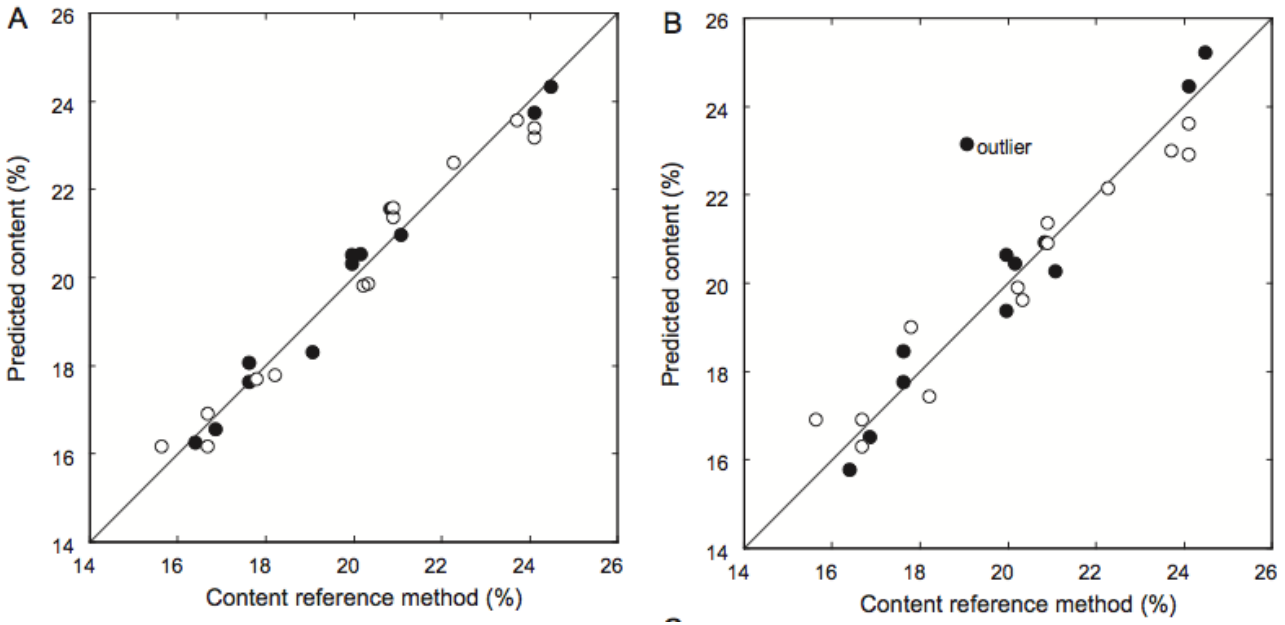
Transmission Raman



Propranolol contents measured from whole tablets in transmission (left) and traditional backscatter (right)

K. Buckley and P. Matousek, J. Pharm. Biomed. Anal. 55, 645 (2011).

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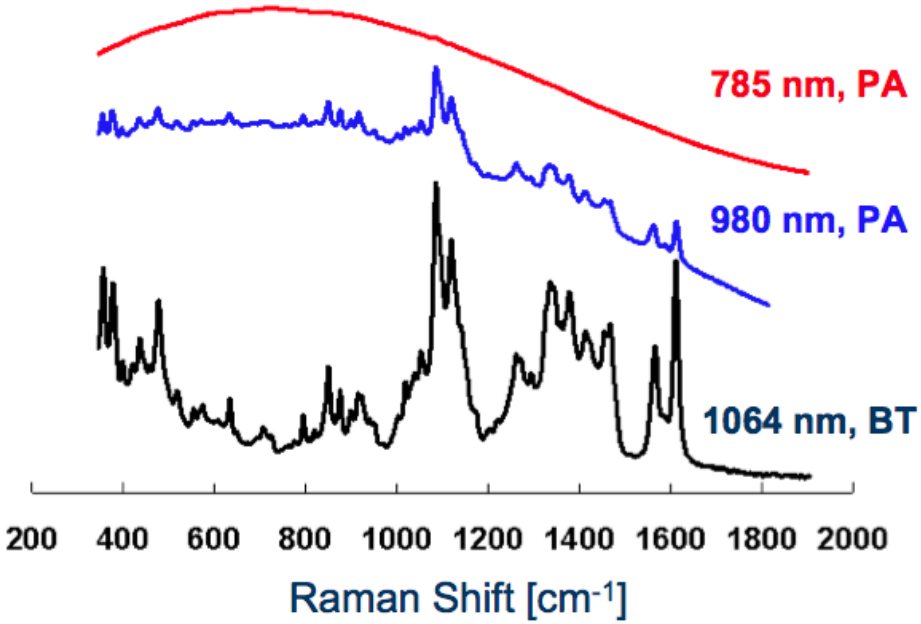
Fluorescence



Effect of laser excitation wavelength on the fluorescence in the Raman signal

S. Romero-Torres et al., American Pharmaceutical Review, 2009

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Raman Spectroscopy

Advantages

- Works well for symmetric molecules that do not show up in IR (no dipole)
- Relatively good sensitivity for crystal structure
- Little sample preparation required
- Can be coupled to fibre optics
- Spectral modes can be assigned, chemometrics not always required

Diadvantages

- Fluorescence
- High laser power can heat the sample locally
- Little sensitivity to water
- Raman scattering is a weak effect; rel. long measurement time

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Outline

1. Introduction and Motivation – The Toolbox
2. Moving across the Spectrum: MHz to EHz – Picking the Right Tool
   - Nuclear Magnetic Resonance (NMR) Spectroscopy
   - Dielectric Spectroscopy
   - Vibrational Spectroscopy: THz
   - Vibrational Spectroscopy: Raman
   - Vibrational Spectroscopy: Near-infrared
3. Summary

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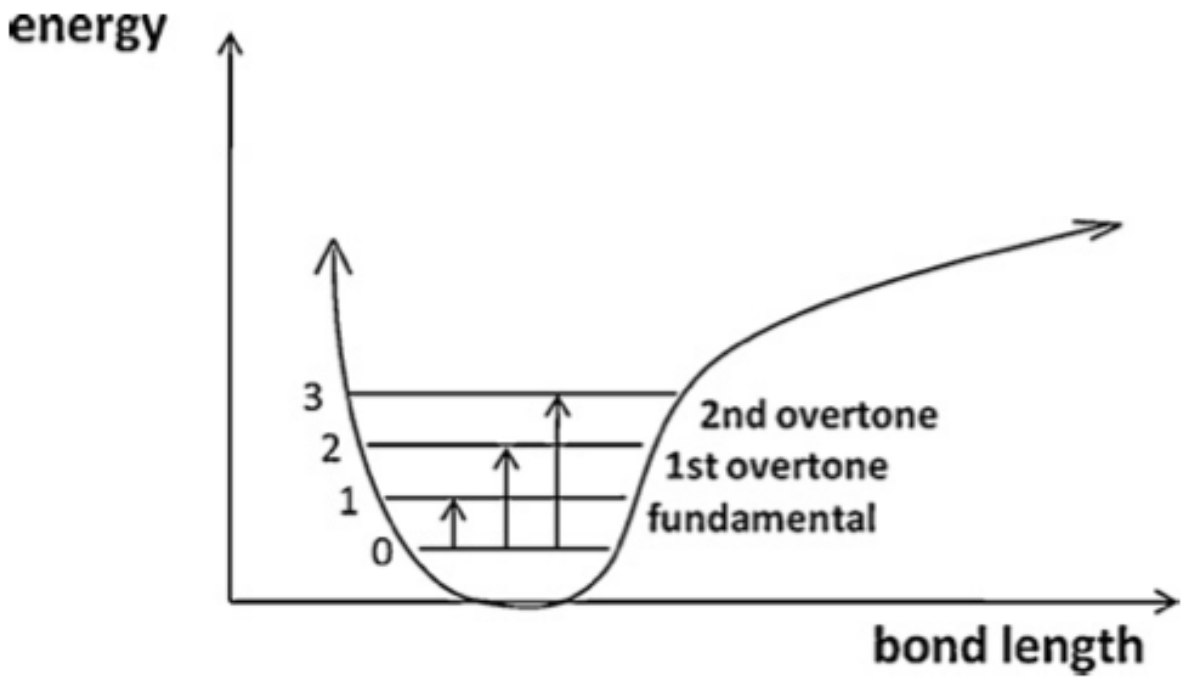
Near-infrared Spectroscopy



T. de Beer et al., Int. J. Pharm. 417, 32 (2011).

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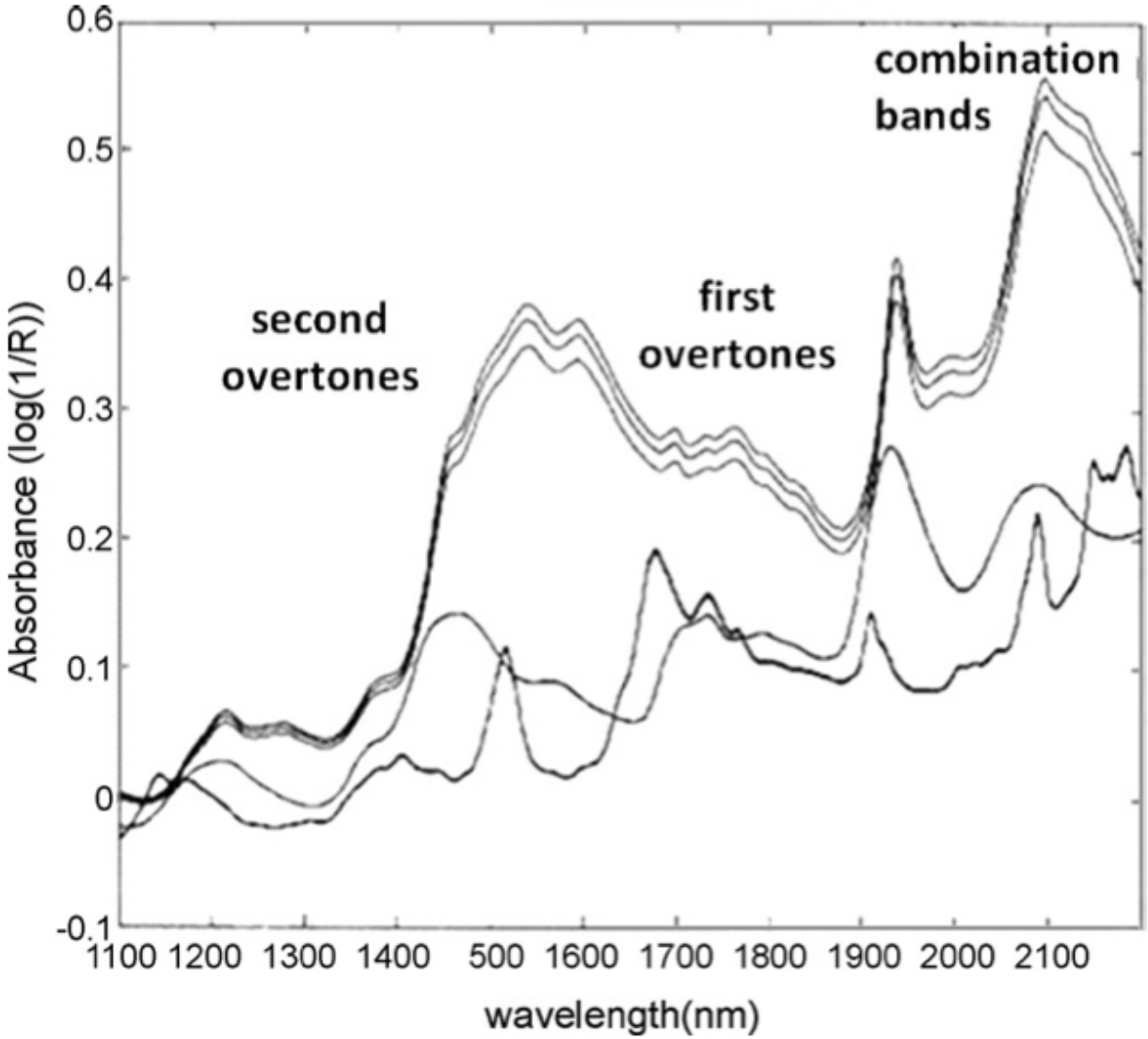
Near-infrared Spectroscopy



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Near-infrared Spectroscopy

- Probes overtones and combination bands
- Comparatively weak signal due to relatively low population of these energy levels
- Can be used in transmission or reflection
- Imaging is fast (array detectors)
- Very established for PAT applications
- Strong absorption of water, used to monitor drying processes

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A. Burggraeve et al., Eur. J. Pharm. Biopharm. (2012).

J. Luypaert, D. L. Massart, and Y. van der Heyden, Talanta 72, 865 (2007).

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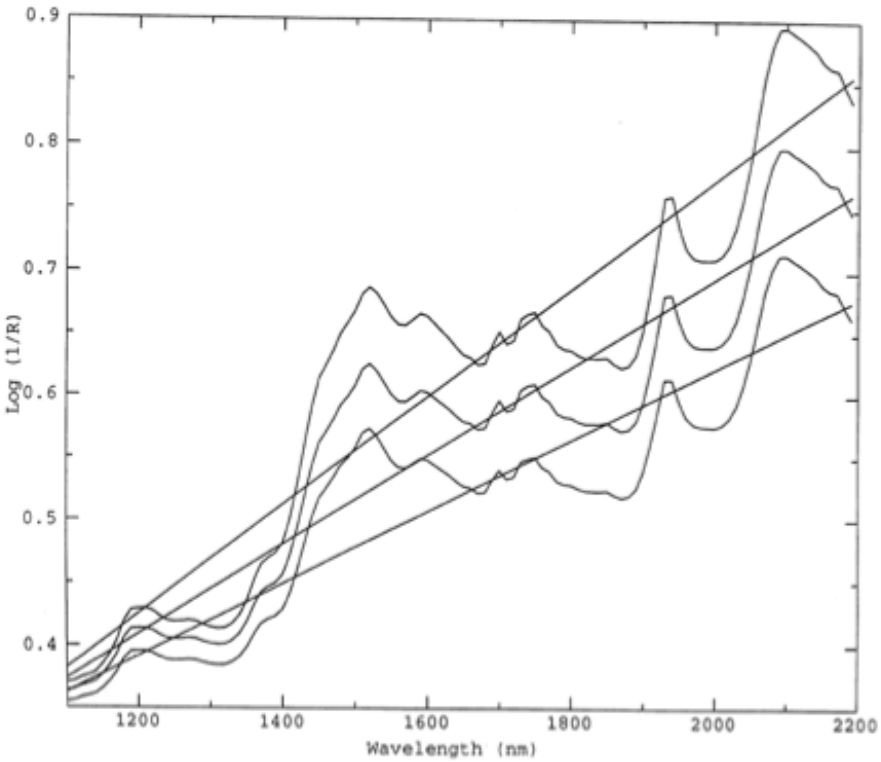
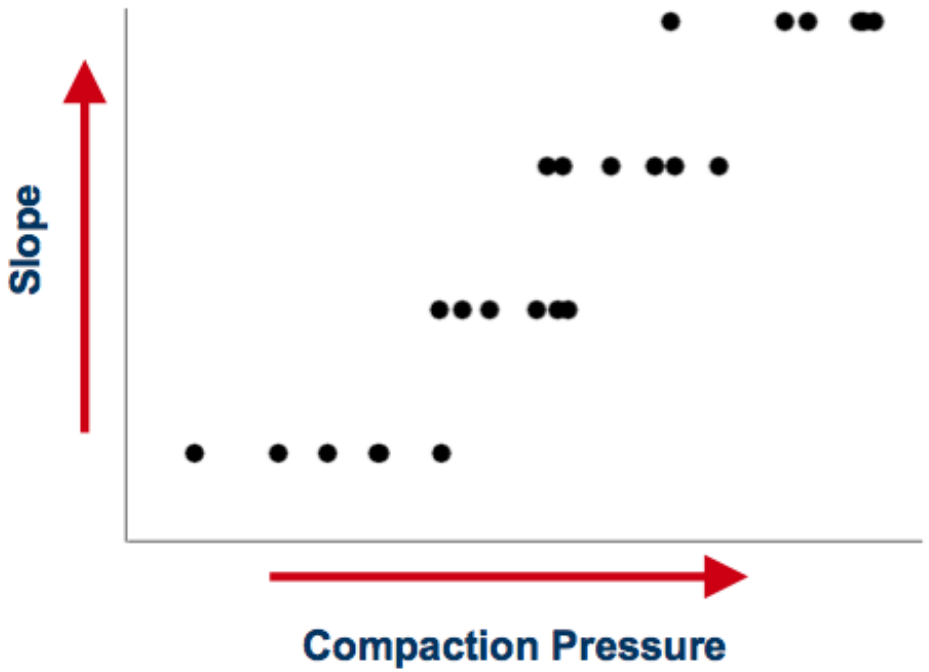
Tablet Hardness





J. D. Kirsch and J. K. Drennen, Chem. Phys. Lett. 19, 351 (1999).

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Tablet Hardness

- NIR methods effectively measure the change in reflectivity (how "glossy" the surface is)
- This shifts the NIR baseline due to the change in scattering response (scattering in the NIR corresponds to changes in length scale of $\approx 1\ \mu$m)
- Typically a chemometric model is used to quantify this change
- This is a surface property only and not necessarily representative of the bulk mechanical property ("hardness")
- Care needs to be taken when particle size distributions change in the formulation or excipients are switched to a different supplier
- Alternative techniques: ultrasound, terahertz pulsed imaging

R.K. May et al., J. Pharm Sci. 102, 2179 (2013).

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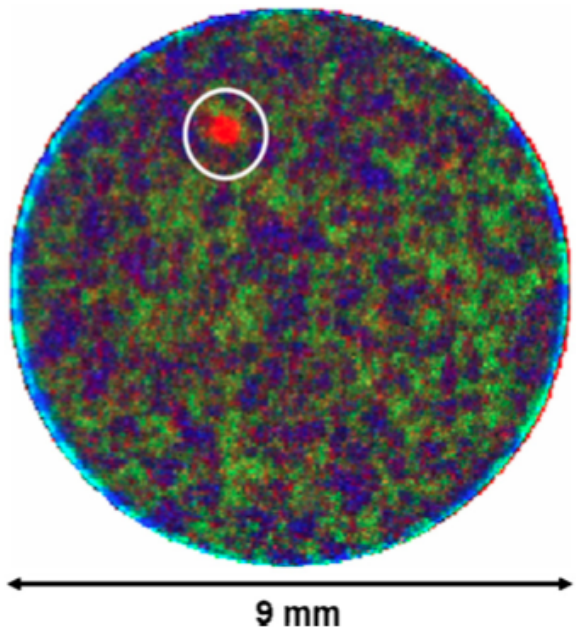
Near-infrared Imaging



Tablet containing 3% API scanned by an NIR imaging system. Red depicts API, green cellulose, and blue lactose.

C. Gendrin, Y. Roggo, and C. Collet, J. Pharm. Biomed. Anal. 48, 533 (2008).

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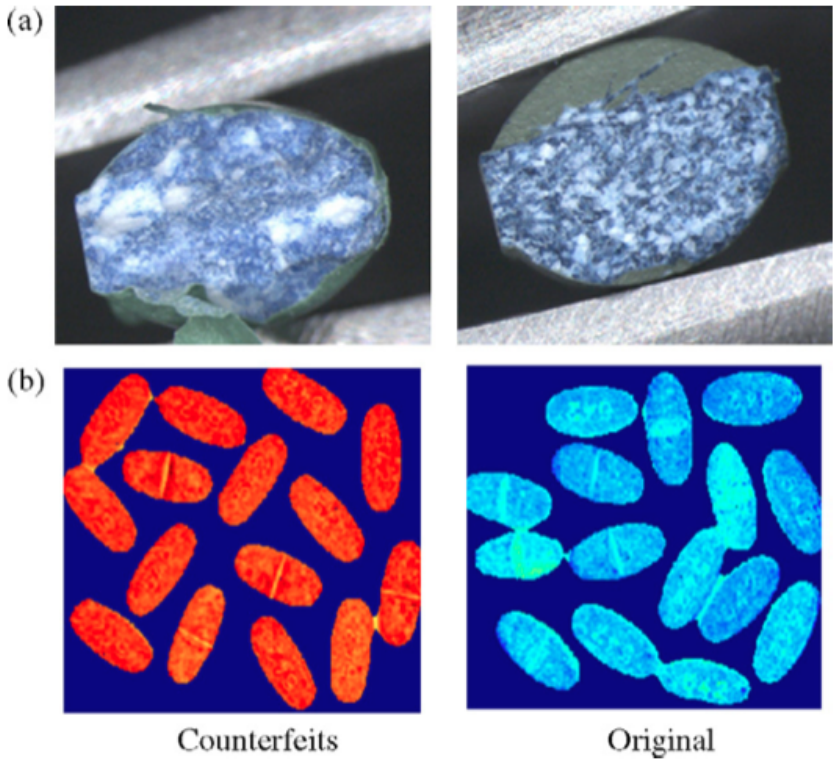
Near-infrared Imaging



Photograph and NIR Score images for the second principal component. PCA reveals clearly different composition between the two types of tablets.

C. Gendrin, Y. Roggo, and C. Collet, J. Pharm. Biomed. Anal. 48, 533 (2008).

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Near-infrared Spectroscopy

Advantages

- Fast spectroscopic imaging possible
- Very good for content uniformity measurements
- Well established technology, robust and relaible

Diadvantages

- Typically requires chemometric models that need to be calibrated and maintained
- Array imaging is fast but leads to diffuse reflection artefacts
- Destructive imaging technique when the internal structure of the dosage form is imaged

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Summary

- Different spectroscopic techniques yield very different information and by selecting a useful combination of techniques it is possible to understand the microstructure within the sample
- The physical structure of the dosage form itself is of significant importance and not all techniques are equally capable of measuring non-destructively
- Measurement techniques vary greatly in spatial and time resolution – trade-off between these properties needs to be taken into account
- For process understanding you need fast measurements

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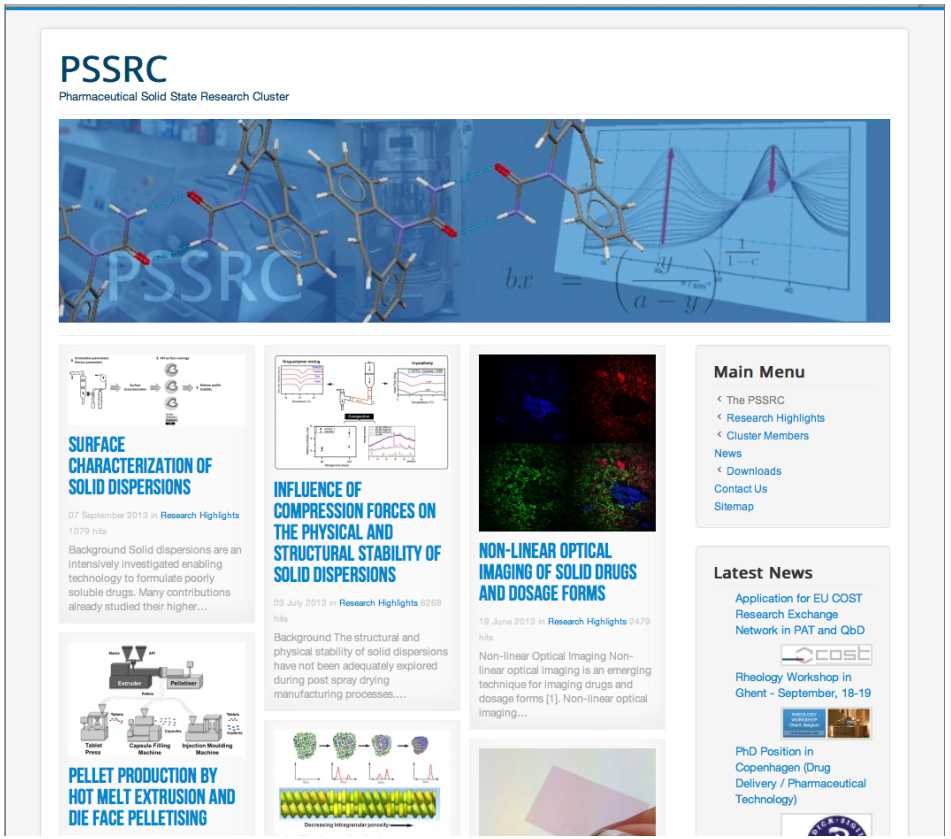
Further Information

- J. A. Zeitler and L. F. Gladden, Eur. J. Pharm. Biopharm. 71, 2 (2009).
- Y. Perrie and T. Rades, Int. J. Pharm. 417, 1 (2011).

For further information and updates on solid state research in the pharmaceutical sciences please visit `www.pssrc.org`, follow us on Twitter `@PSSRCNews` or connect with us on LinkedIn!



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References I

- Gerold Adam and Julian H Gibbs, On the temperature dependence of cooperative relaxation properties in glass-forming liquids, *The Journal of Chemical Physics*, 43:139, 1965.
- Sisir Bhattacharya and Raj Suryanarayanan, Local Mobility in Amorphous Pharmaceuticals-Characterization and Implications on Stability, *Journal of Pharmaceutical Sciences*, 98(9):2935–2953, January 2009. doi:10.1002/jps.21728.
- D. Brock, J Axel Zeitler, A. Funke, K. Knop, and P Kleinebudde, A comparison of quality control methods for active coating processes, *International Journal of Pharmaceutics*, 439:289–295, 2012. doi:10.1016/j.ijpharm.2012.09.021.
- Kevin Buckley and Pavel Matousek, Recent advances in the application of transmission Raman spectroscopy to pharmaceutical analysis, *Journal of Pharmaceutical and Biomedical Analysis*, 55(4):645–652, June 2011. doi:10.1016/j.jpba.2010.10.029.
- Anneleen Burggraeve, Tinne Monteyne, Chris Vervaet, Jean-Paul Remon, and Thomas De Beer, Process analytical tools for monitoring, understanding and control of pharmaceutical fluidized bed granulation: a review, *European Journal of Pharmaceutics and Biopharmaceutics*, 2012. doi:10.1016/j.ejpb.2012.09.008.
- G M Day, J Axel Zeitler, W Jones, Thomas Rades, and Philip F Taday, Understanding the influence of polymorphism on phonon spectra: lattice dynamics calculations and terahertz spectroscopy of carbamazepine., *The Journal of Physical Chemistry B*, 110(1):447–456, January 2006. doi:10.1021/jp055439y.
- T de Beer, A Burggraeve, M Fonteyne, L Saerens, J P Remon, and C Vervaet, Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes, *International Journal of Pharmaceutics*, 417(1-2):32–47, September 2011. doi:10.1016/j.ijpharm.2010.12.012.

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References II

- C Gendrin, Y Roggo, and C Collet, Pharmaceutical applications of vibrational chemical imaging and chemometrics: A review, *Journal of Pharmaceutical and Biomedical Analysis*, 48(3):533–553, November 2008. doi:10.1016/j.jpba.2008.08.014.
- Louise Ho, Ronny Mueller, Keith C. Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F Taday, and J Axel Zeitler, Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance, *Journal of Controlled Release*, 127(1):79–87, 2008. doi:10.1016/j.jconrel.2008.01.002.
- John D Kirsch and James K Drennen, Nondestructive tablet hardness testing by near-infrared spectroscopy: a new and robust spectral best-fit algorithm, *J. Pharm. Biomed. Anal.*, 19(3-4):351–362, March 1999. doi:10.1016/S0731-7085(98)00132-0.
- Ruoyu Li, J Axel Zeitler, Daniele Tomerini, Edward P.J. Parrott, Lynn F. Gladden, and Graeme Day, A study into the effect of subtle structural details and disorder on the terahertz spectrum of crystalline benzoic acid, *Physical Chemistry Chemical Physics*, 12(20):5329–5340, 2010. doi:10.1039/b926536h.
- J Luypaert, D L Massart, and Y vander Heyden, Near-infrared spectroscopy applications in pharmaceutical analysis, *Talanta*, 72(3):865–883, May 2007. doi:10.1016/j.talanta.2006.12.023.
- M. D. Mantle, Quantitative magnetic resonance micro-imaging methods for pharmaceutical research, *International Journal of Pharmaceutics*, 417(1-2):173–195, September 2011. doi:10.1016/j.ijpharm.2010.11.035.
- Michael D Mantle, NMR and MRI studies of drug delivery systems, *Current opinion in colloid & interface science*, 18(3): 214–227, June 2013. doi:10.1016/j.cocis.2013.03.006.

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References III

- Robert K. May, Michael J. Evans, Shuncong Zhong, Ian Warr, Lynn F. Gladden, Yaochun Shen, and J Axel Zeitler, Terahertz In-Line Sensor for Direct Coating Thickness Measurement of Individual Tablets During Film Coating in Real-Time, *Journal of Pharmaceutical Sciences*, 100(4):1535–1544, 2011.
doi:10.1002/jps.22359.
- Robert K. May, Ke Su, Lianghao Han, Shuncong Zhong, James A Elliott, Lynn F. Gladden, Mike Evans, Yaochun Shen, and J Axel Zeitler, Hardness and density distributions of pharmaceutical tablets measured by terahertz pulsed imaging, *Journal of Pharmaceutical Sciences*, 102:2179–2186, April 2013.
doi:10.1002/jps.23560.
- C McGoverin, Thomas Rades, and K Gordon, Recent Pharmaceutical Applications of Raman and Terahertz Spectroscopies, *Journal of Pharmaceutical Sciences*, 97(11):4598–4621, November 2008.
doi:10.1002/jps.21340.
- J Müller, D. Brock, K. Knop, and J Axel Zeitler, Prediction of dissolution time and coating thickness of sustained release formulations using Raman spectroscopy and terahertz pulsed imaging, *European Journal of . . .*, 2012.
doi:10.1016/j.ejpb.2011.12.003.
- Edward P.J. Parrott, J Axel Zeitler, T Friscic, M Pepper, W Jones, G Day, and Lynn F. Gladden, Testing the Sensitivity of Terahertz Spectroscopy to Changes in Molecular and Supramolecular Structure: A Study of Structurally Similar Cocrystals, *Crystal Growth & Design*, 9(3):1452–1460, 2009.
doi:10.1021/cg8008893.
- S P Simonaho, T A Takala, M Kuosmanen, and J Ketolainen, Ultrasound transmission measurements for tensile strength evaluation of tablets, *International Journal of Pharmaceutics*, 409(1):104–110, 2011.
doi:10.1016/j.ijpharm.2011.02.033.
- Clare J Strachan, Thomas Rades, D Newnham, K Gordon, M Pepper, and Philip F Taday, Using terahertz pulsed spectroscopy to study crystallinity of pharmaceutical materials, *Chemical Physics Letters*, 390(1-3):20–24, May 2004.
doi:10.1016/j.cplett.2004.03.117.

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References IV

- Hermann Wagner and Ranko Richert, Spatial uniformity of the β-relaxation in D-sorbitol, *Journal of Non-Crystalline Solids*, 242(1):19–24, 1998.
- J Axel Zeitler, David A Newnham, Philip F Taday, Clare J Strachan, Michael Pepper, Keith C. Gordon, and Thomas Rades, Temperature dependent terahertz pulsed spectroscopy of carbamazepine, *Thermochimica Acta*, 436(1-2):71–77, October 2005.
doi:10.1016/j.tca.2005.07.006.
- J Axel Zeitler, D Newnham, Philip F Taday, T Threlfall, R Lancaster, R Berg, Clare J Strachan, M Pepper, K Gordon, and Thomas Rades, Characterization of temperature-induced phase transitions in five polymorphic forms of sulfathiazole by terahertz pulsed spectroscopy and differential scanning calorimetry, *Journal of Pharmaceutical Sciences*, 95(11):2486–2498, November 2006.
doi:10.1002/Jps.20719.
- J Axel Zeitler, K Kogermann, J Rantanen, Thomas Rades, Philip F Taday, M Pepper, J Aaltonen, and Clare J Strachan, Drug hydrate systems and dehydration processes studied by terahertz pulsed spectroscopy, *International Journal of Pharmaceutics*, 334(1-2):78–84, 2007a.
doi:10.1016/j.ijpharm.2006.10.027.
- J Axel Zeitler, Yaochun Shen, Colin Baker, Philip F Taday, Michael Pepper, and Thomas Rades, Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging, *Journal of Pharmaceutical Sciences*, 96(2):330–340, 2007b.
doi:10.1002/jps.20789.
- J Axel Zeitler, Philip F Taday, K C Gordon, M Pepper, and Thomas Rades, Solid-State Transition Mechanism in Carbamazepine Polymorphs by Time-Resolved Terahertz Spectroscopy, *ChemPhysChem*, 8(13):1924–1927, 2007c.
doi:10.1002/cphc.200700261.
- J Axel Zeitler, Philip F Taday, M Pepper, and Thomas Rades, Relaxation and crystallization of amorphous carbamazepine studied by terahertz pulsed spectroscopy, *Journal of Pharmaceutical Sciences*, 96(10):2703–2709, October 2007d.
doi:10.1002/Jps.20908.