Inkjet printing of pharmaceuticals

And the use of Raman spectroscopy for visualization and quality control

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Agenda

- About me
- Inkjet printing of pharmaceuticals
- Raman spectroscopy as Quality control
- Experiments
- Conclusions and further work

About me…

- **2015: Cand.scient.pharm, Dep. Of Pharmacy, Uni. Copenhagen**
- Subjects:
  - Hot-melt extrusion & 3D printing
  - Rheology of mixtures relevant in hot-melt extrusion

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journal homepage: www.jpharm

ELSEVIER

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Oscillatory Shear Rheology in Examining the Drug Interactions Relevant in Hot Melt Extrusion

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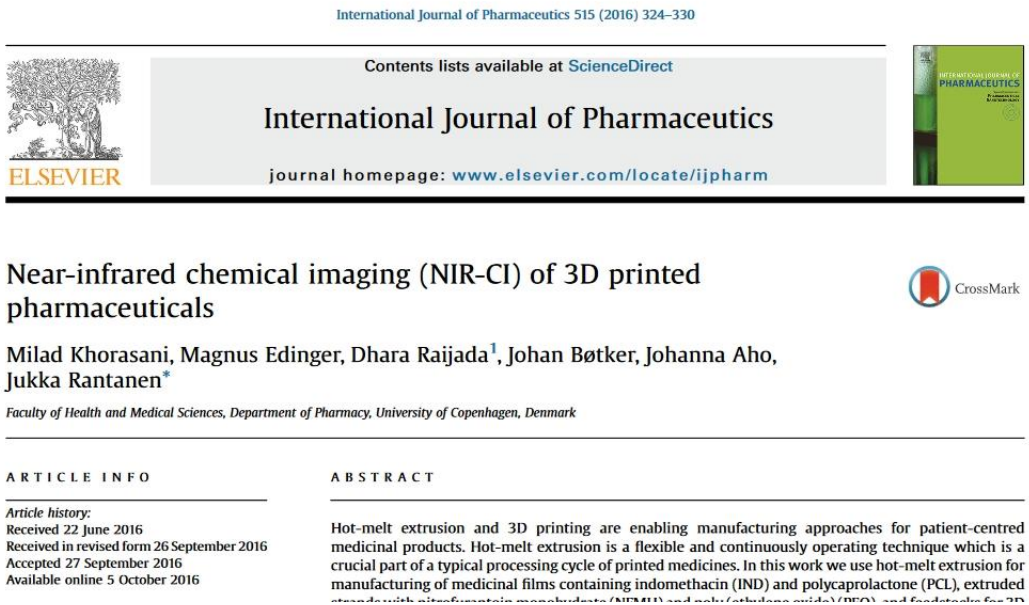
ABSTRACT

The flow properties of drug-polymer mixture
using techniques such as hot melt extrusion (
be used in laboratory scale HME were evalu
ibuprofen (IBU), or indomethacin (IND), an



International Journal of Pharmaceutics 515 (2016) 324–330

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journal homepage: www.elsevier.com/locate/ijpharm

ELSEVIER

Near-infrared chemical imaging (NIR-CI) of 3D printed pharmaceuticals

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ABSTRACT

Hot-melt extrusion and 3D printing are enabling manufacturing approaches for patient-centred medicinal products. Hot-melt extrusion is a flexible and continuously operating technique which is a crucial part of a typical processing cycle of printed medicines. In this work we use hot-melt extrusion for manufacturing of medicinal films containing indomethacin (IND) and polycaprolactone (PCL), extruded

About me…

- 2015: Cand.scient.pharm, Dep. Of Pharmacy, Uni. Copenhagen
- **2015-2018 Ph.d. student, Section of pharmaceutical technology and Engineering, Dep. Of Pharmacy, Uni Copenhagen**

"Flexible manufacturing of Inkjet-printed Dosage Forms"

Jukka Rantanen, Professor
Natalja Genina, Assist. Prof.
Daniel Bar-Shalom, Assoc. Prof.

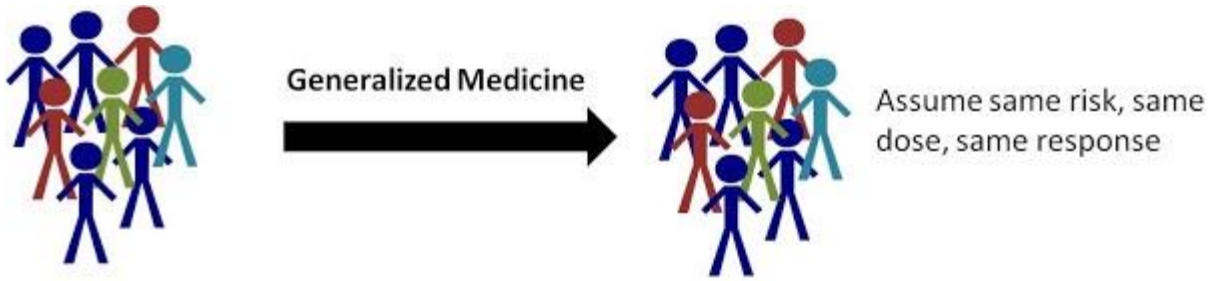
Visualization and Non-Destructive Quantification of Inkjet-Printed Pharmaceuticals on Different Substrates Using Raman Spectroscopy and Raman Chemical Imaging

Magnus Edinger, Daniel Bar-Shalom, Jukka Rantanen, Natalja Genina

Pharmaceutical Research, 2017 (in press)

Inkjet printing of pharmaceuticals

- One size fits all principle



Inkjet printing of pharmaceuticals

Dose flexibility

Combination doses

Manufacture on demand

"High throughput"

Control of properties of final dosage form

(faster dissolution, controlled delivery)

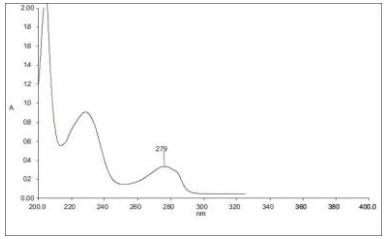
Personalized medicine

Low-dose APIs

Low output

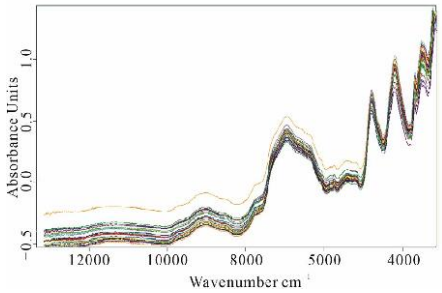
Quality control of inkjet-printed pharmaceuticals

API Content:



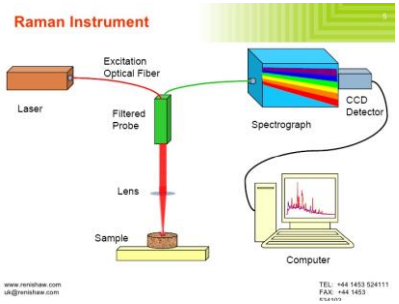
UV spectroscopy/HPLC (destructive)

Non-destructive:



Near-infrared spectroscopy

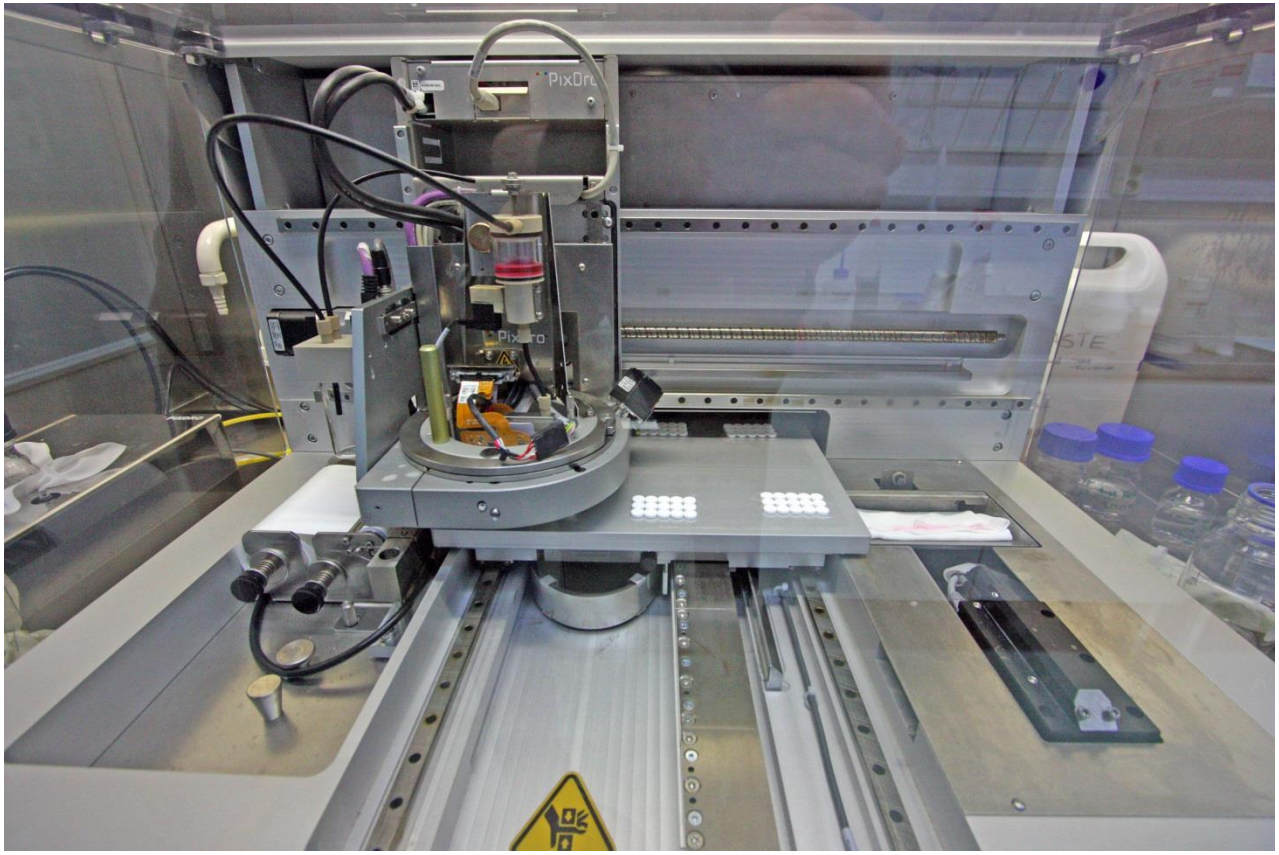
Raman spectroscopy



Raman chemical imaging

Equipment

- PixDro LP50 (Meyer Burger Technologies)*



* Åbo Akademi, Niklas Sandler

Inkjet Printing

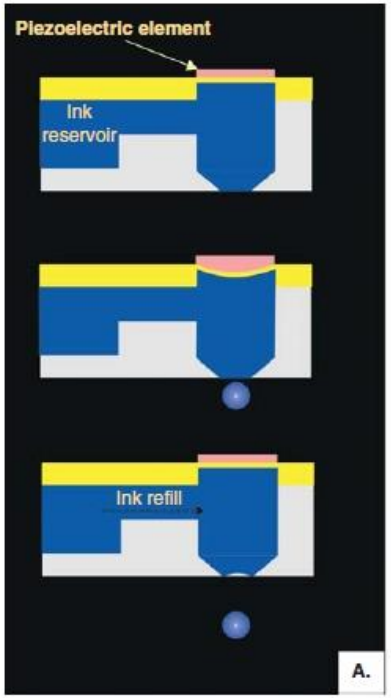
- **Ink base**: non-toxic and not too volatile.

- Examples: Ethanol, water,
- Polyethylene glycols,
- Polypropylene glycols

- API soluble in ink base

- **Substrates**
- Any form – tablet, film, foam, etc

- Any pharmaceutically approved excipient



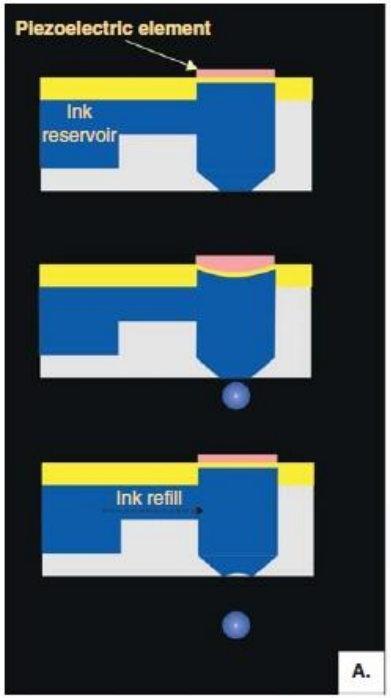
Kolakovic et al. Exp. Opin. On Drug Del. 2013 10(12)

Inkjet Printing

API Content

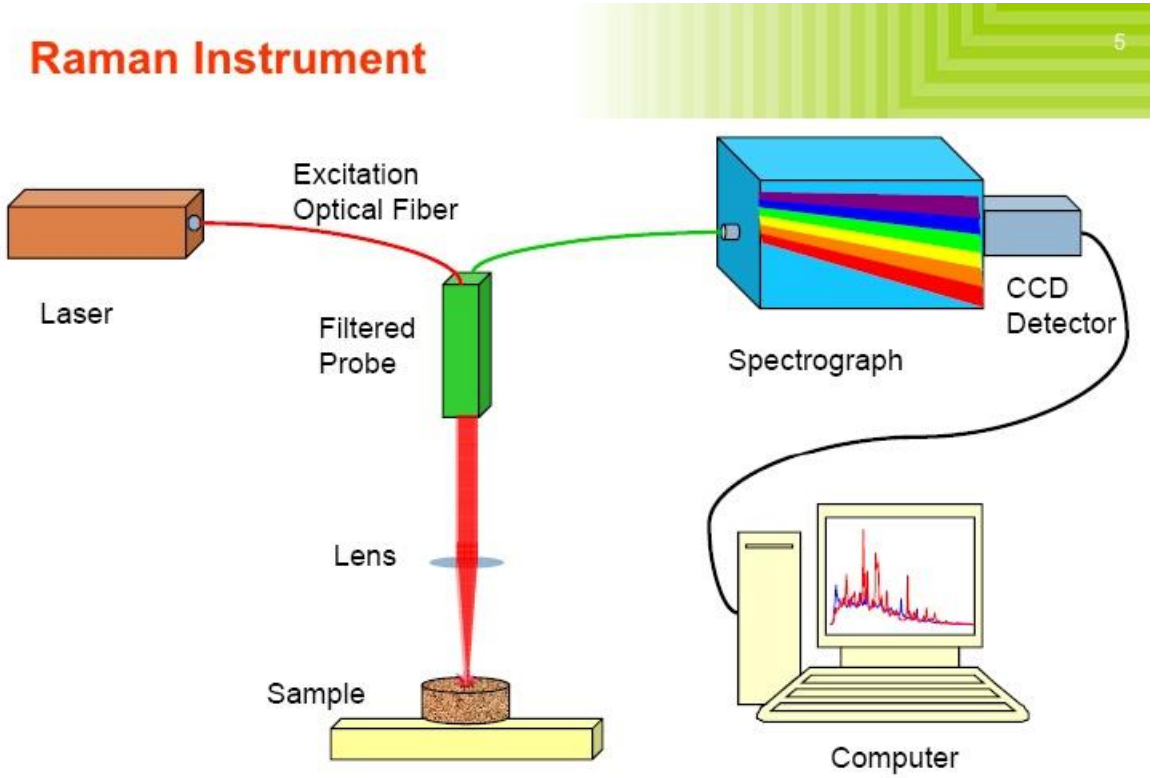
- Concentration 160 mg/mL
- Droplet size 62 pl
- Dots per inch (DPI) 450 (max)
- Area -
- Layers -

= 0.31 mg API/layer/cm^2



Kolakovic et al. Exp. Opin. On Drug Del. 2013 10(12)

Raman spectroscopy

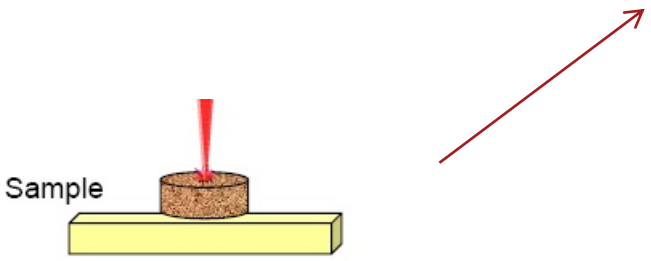


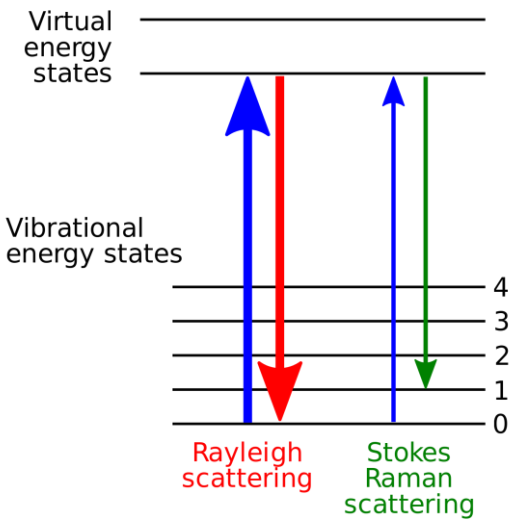
Tong Zhang presentation, Renishaw UK PLC

Raman spectroscopy

Inelastic scattering

- Relies on shift in photon wavelength after absorbance in molecular bonds

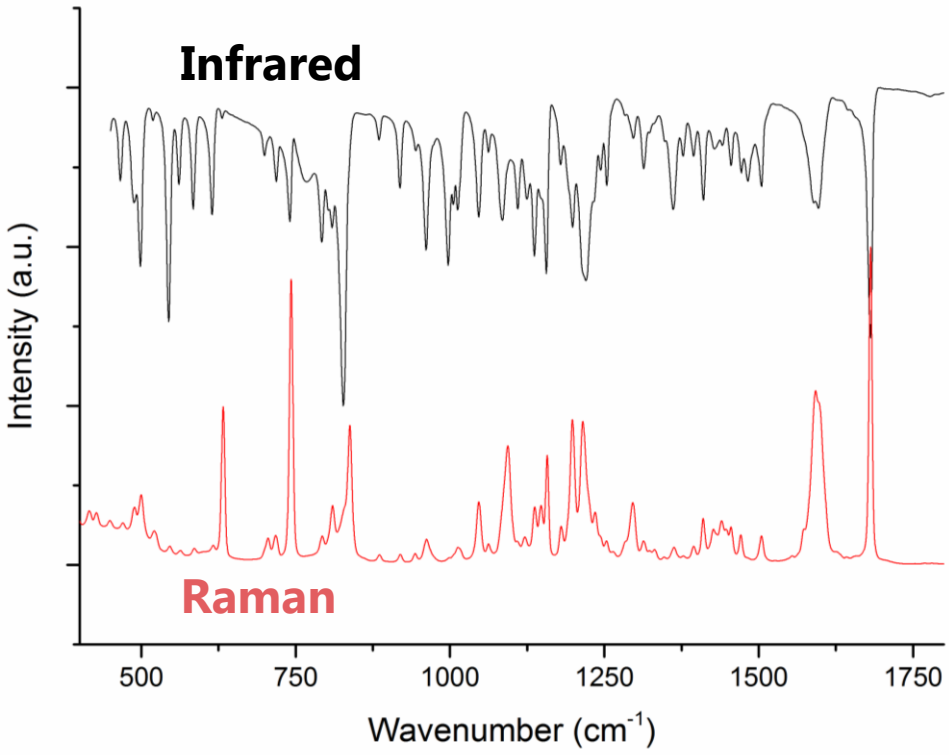




Tong Zhang presentation, Renishaw UK PLC
Wikipedia, Raman spectroscopy

Raman spectroscopy vs. IR spectroscopy

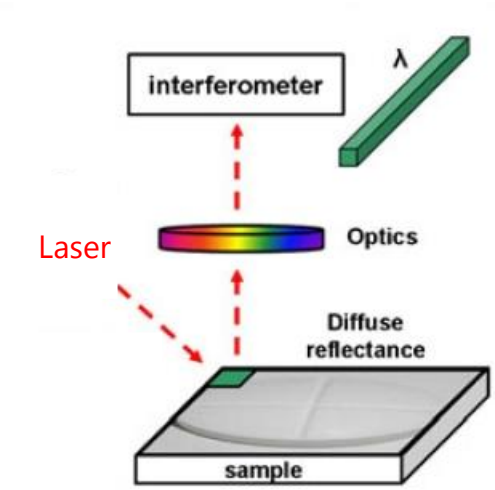
- Haloperidol

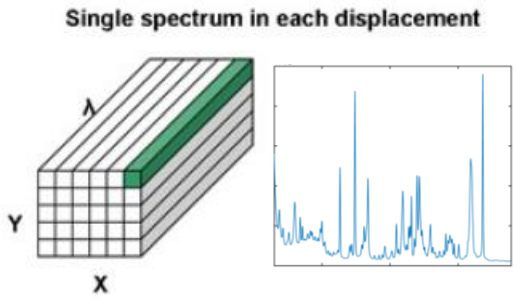


- IR: measures change in dipole moment of molecular bonds.
- Raman: Measures polarizability of molecular bonds

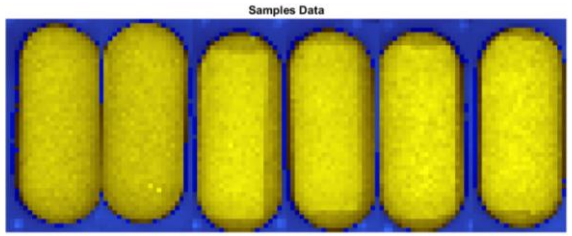
Raman chemical imaging

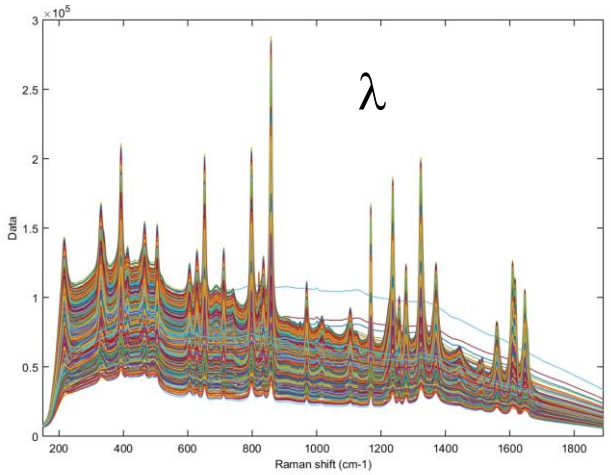
- Extension to Raman spectroscopy





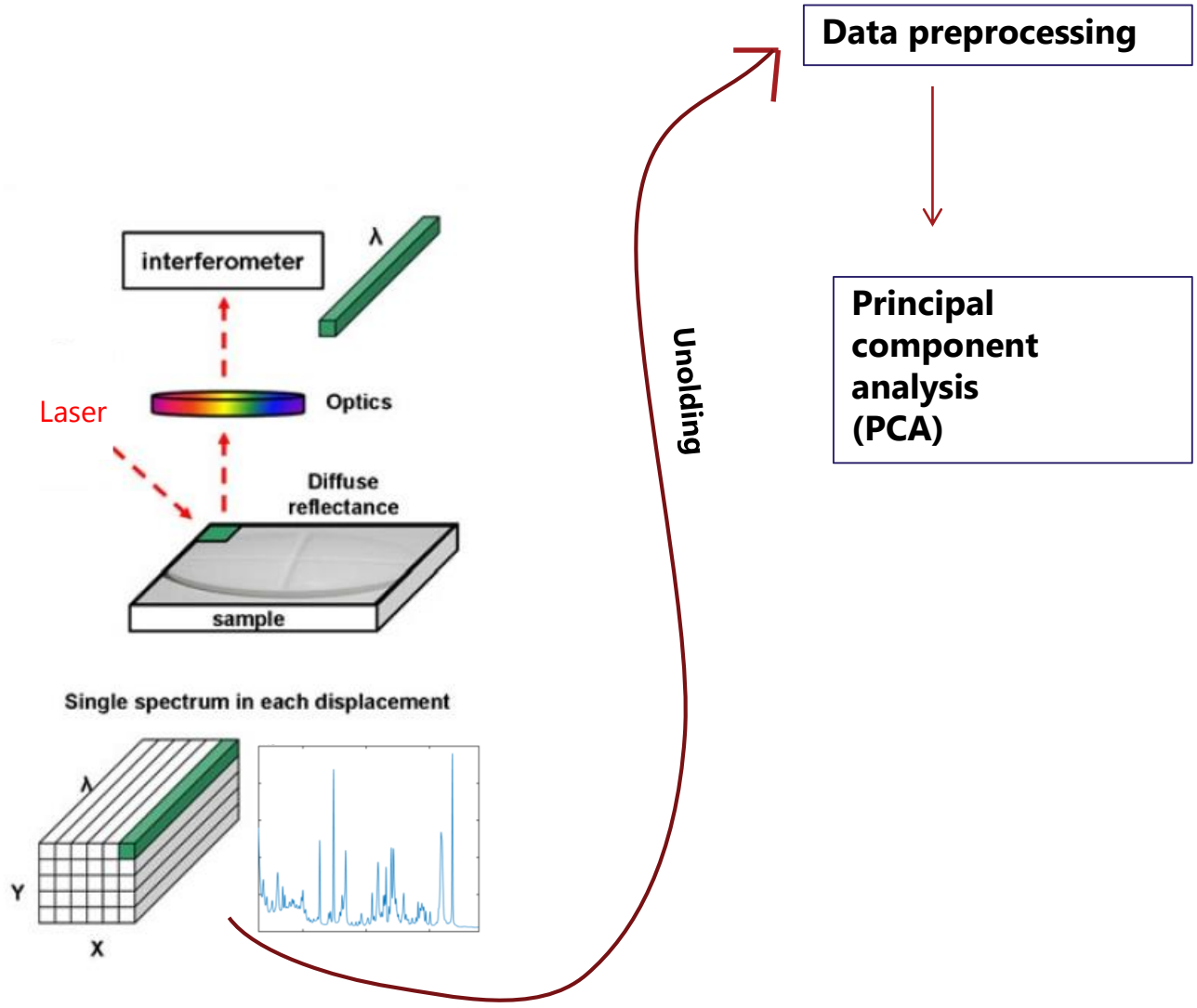
X * Y





JM Amigo, Anal Bioanal Chem, 2010 (398)

Raman chemical imaging

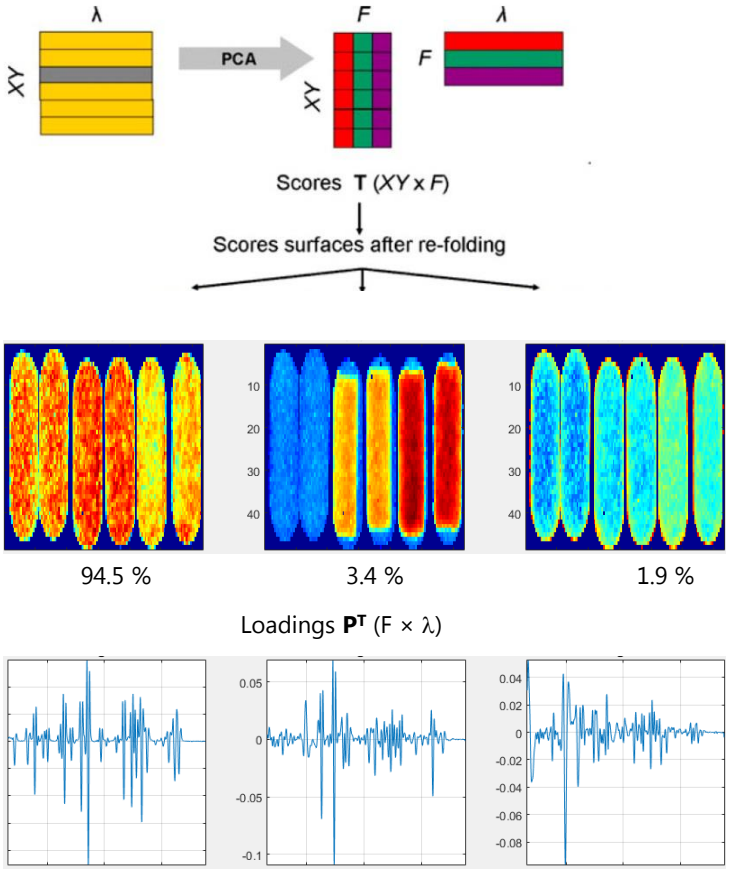


JM Amigo, Anal Bioanal Chem, 2010 (398)

Raman chemical imaging

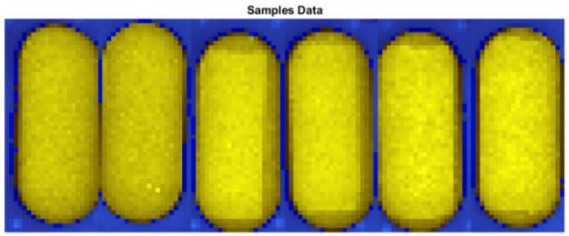
Principal component analysis

- Method for visualizing patterns in datasets
- Decomposes data into **sources of greatest variation**
- Scores plot
- Loadings plot
- %

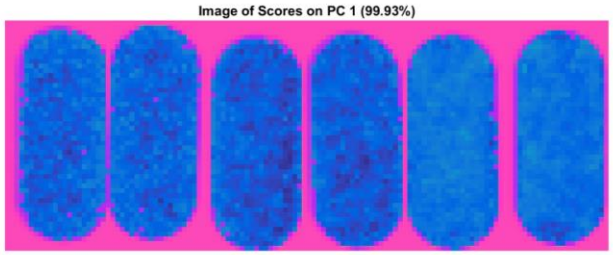


Data preprocessing

Raw sample data



Masking

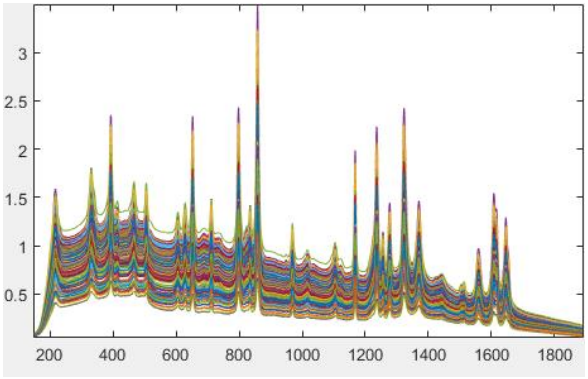


Done in order to remove

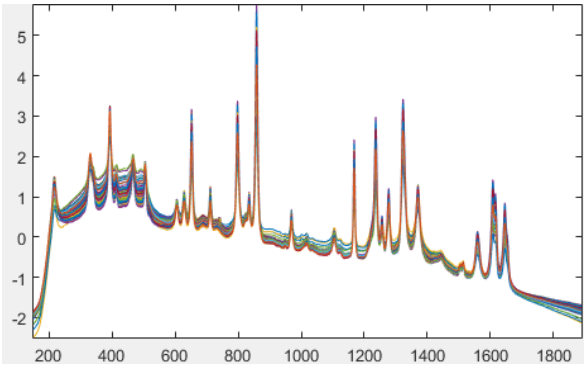
Background
Noise
Scattering
Etc.

Data preprocessing

Raw spectral data (1008 spectra)

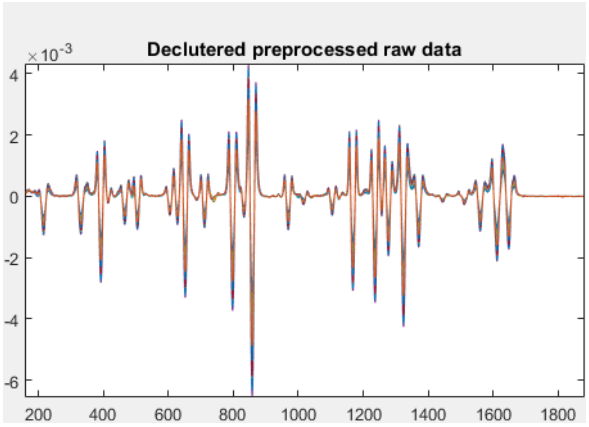


Standard Normal Variate Transformation



Savitzky-Golay smoothing

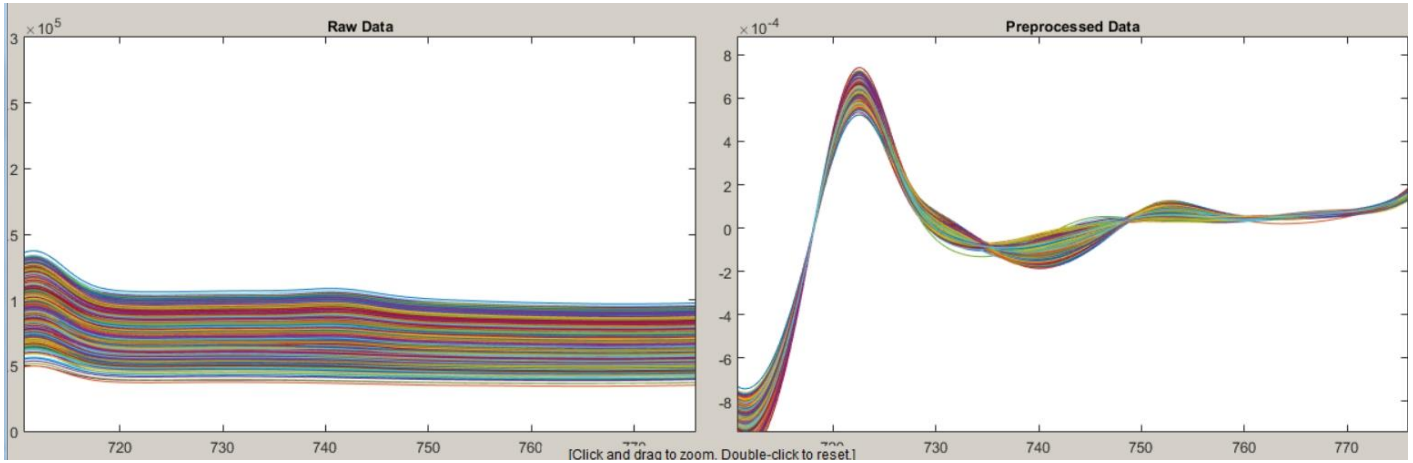
81 point window,
2nd order polynomial,
2nd derivative



Data preprocessing

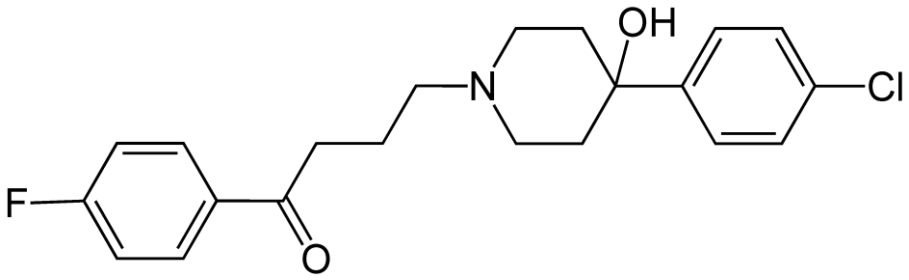
Why do preprocessing?

- Removing noise
- Removing baseline variation
- Enhancing subtle differences between spectra:



Materials and Methods

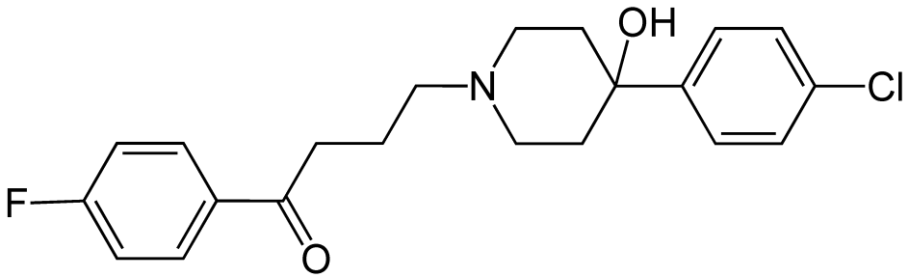
- **API**: Haloperidol



- Antipsychotic
- (Schizophrenia and psychosis treatment)
- 0.5 – 5 mg dose
- Adverse effects common
- Low aqueous solubility
- **Highly soluble in lactic acid**

Materials and Methods

- **Ink base:**

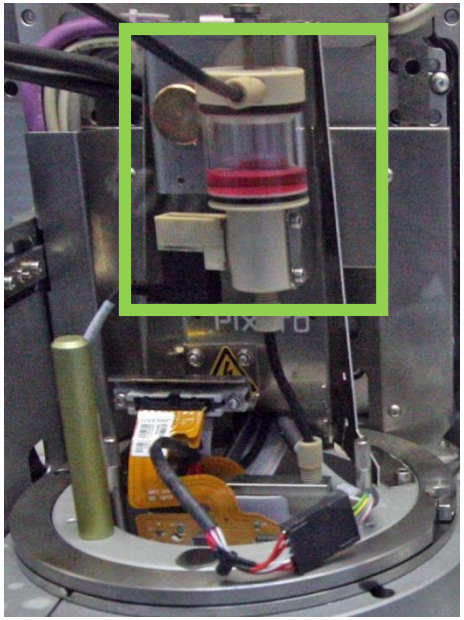


- Haloperidol

- Lactic acid 14%
- Ethanol 86%

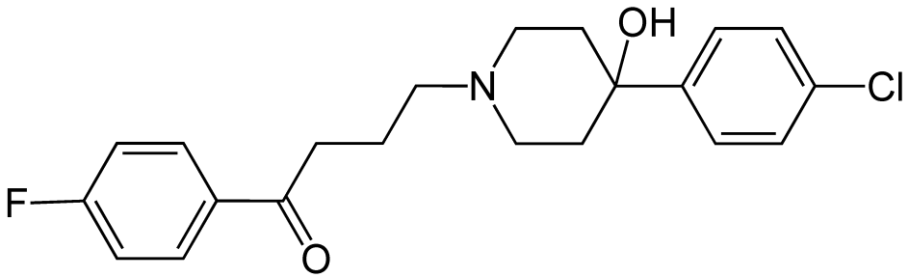
- Erythrosine for coloring

- Final concentration of Haloperidol: 160 mg/mL



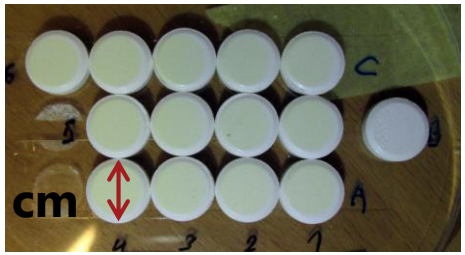
Materials and Methods

- **API**: Haloperidol



- **Substrates:**

- Calcium hydrogen phosphate (CaHPD) compacts
  - Commonly used tablet filler
  - Weak Raman scatterer

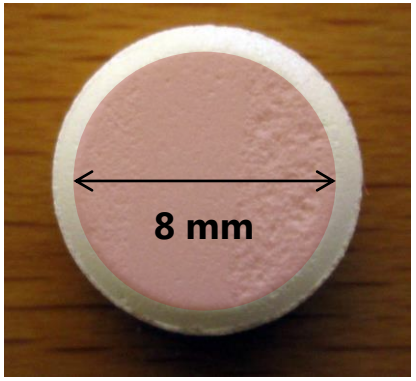


- Uncoated commercial paracetamol tablets (500 mg)
  - Go-to OTC analgesic
  - Strong Raman scatterer

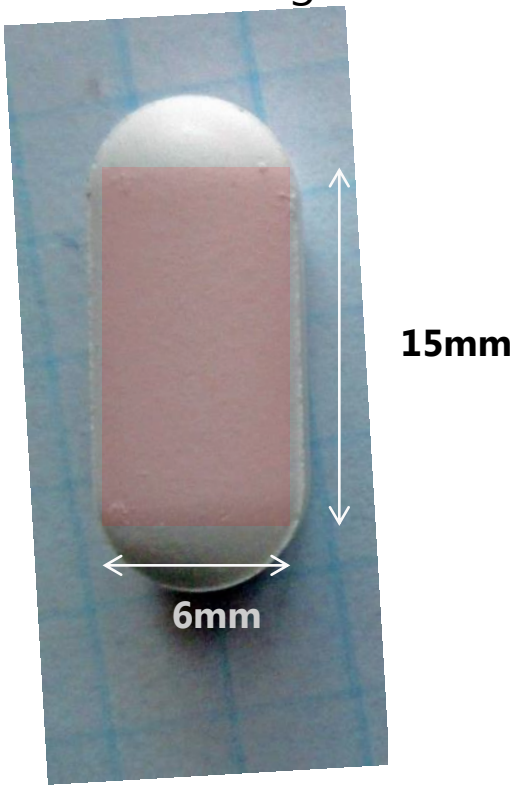
Materials and Methods

- Printing on substrates

1	2	5	10 layers
0.16	0.3	0.8	1.6 mg

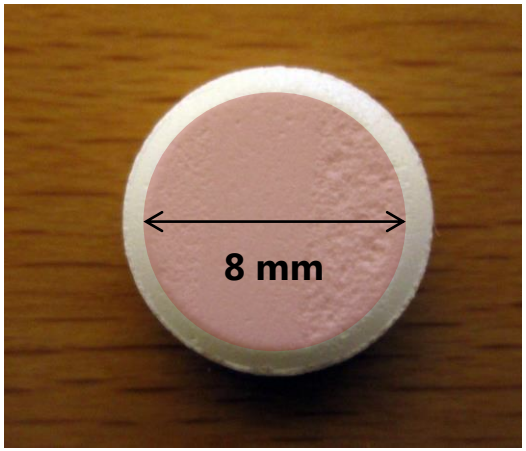


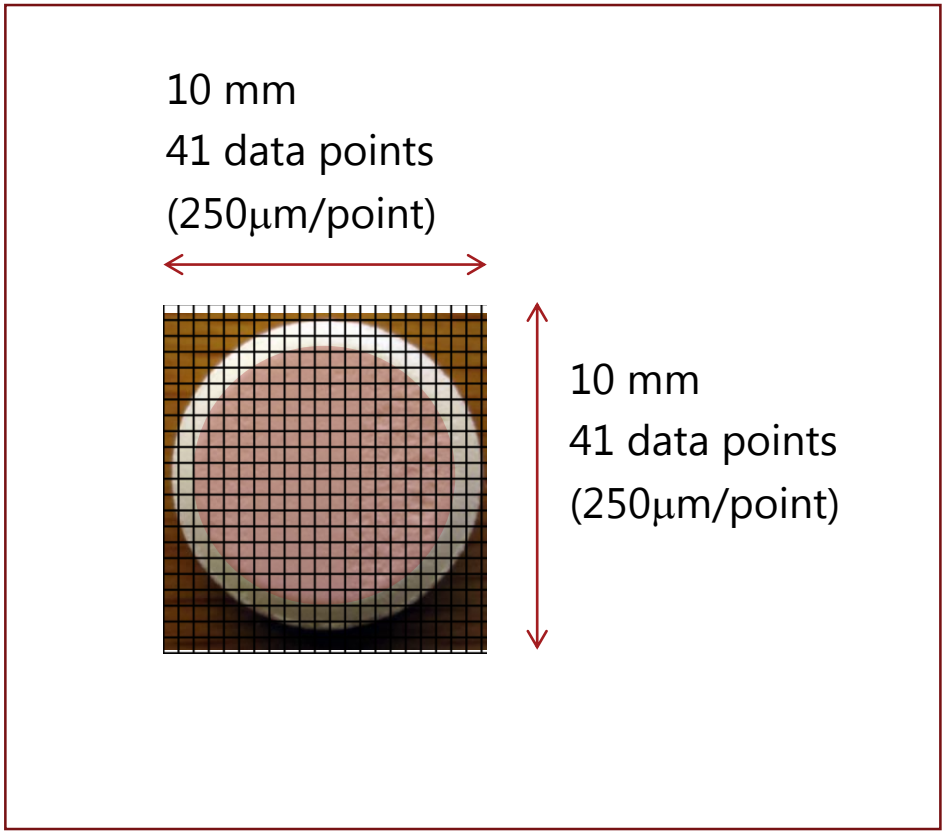
5 and 10 layers
1.4 – 2.8 mg



Raman chemical imaging

- CaHPD tablets
- 1, 2, 5 and 10 layers



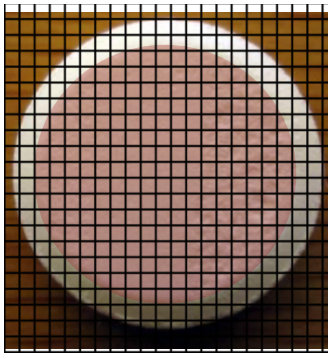


Raman chemical imaging

- CaHPD tablets
- 1, 2, 5 and 10 layers

9 seconds/point
1681 points
4.2 hours/analysis

10 mm
41 data points
(250µm/point)

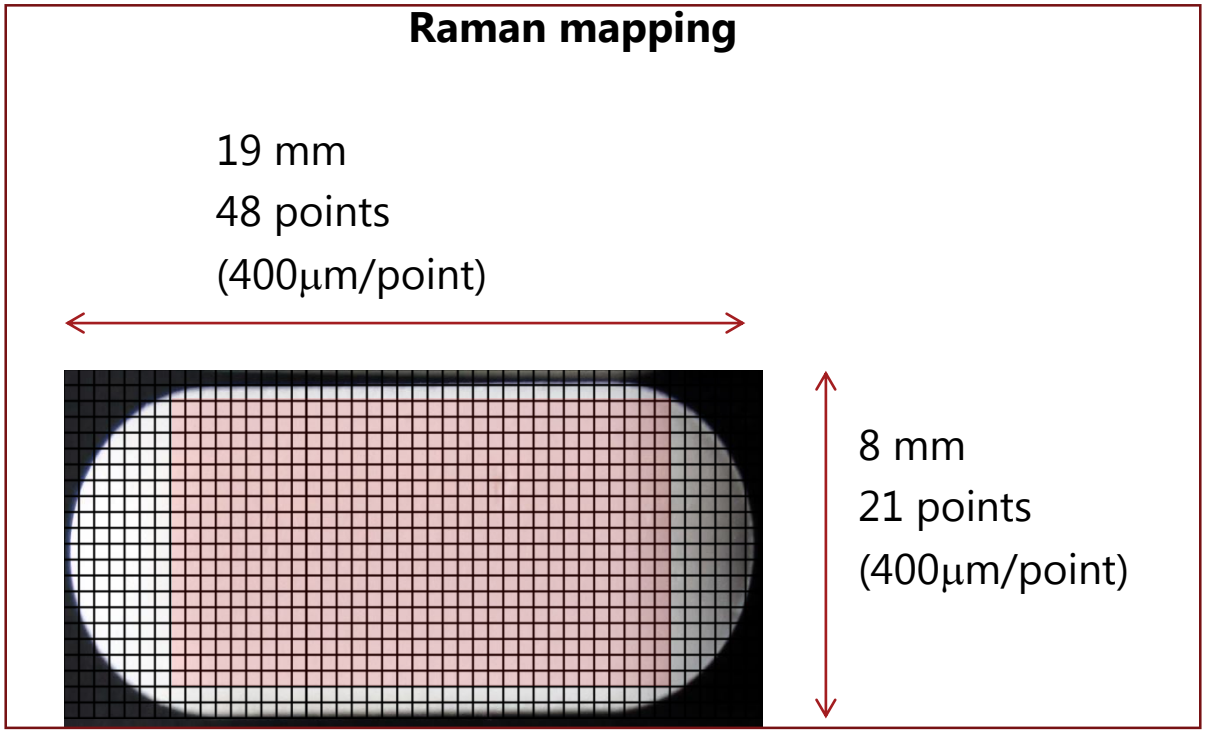


10 mm
41 data points
(250µm/point)

Raman chemical imaging

- Paracetamol tablets
- 5 and 10 layers

0.28 mg/layer



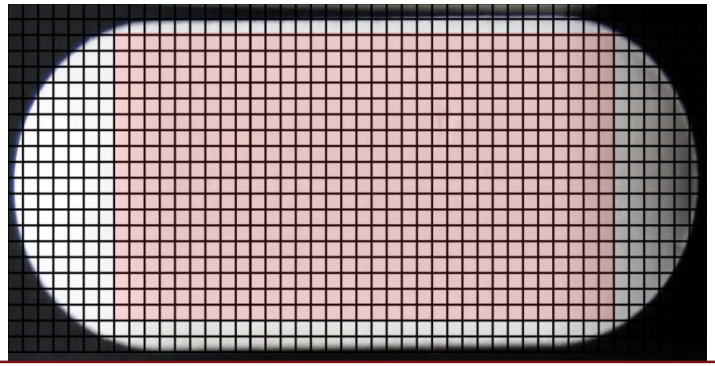
Raman chemical imaging

- Paracetamol tablets
- 5 and 10 layers

10 seconds/point
1008 points
2.8 hours/analysis

Raman mapping

19 mm
48 points
(400µm/point)

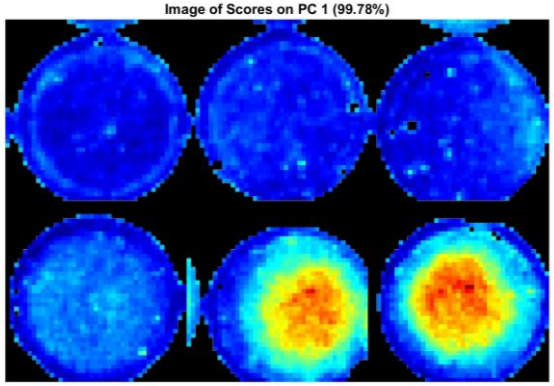


8 mm
21 points
(400µm/point)

Results – Raman chemical imaging CaHPD tablets

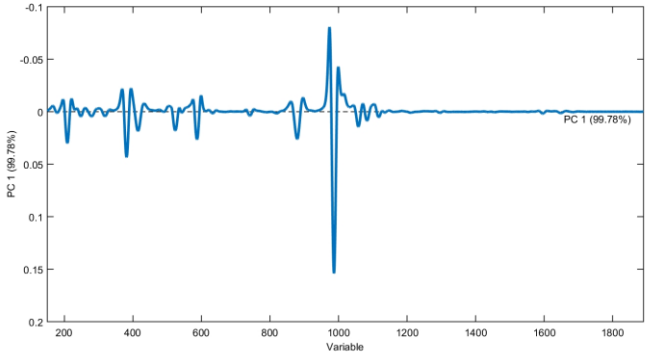
Pure tablet 1 Layer 2 layers

5 layers 10 layers 10 layers



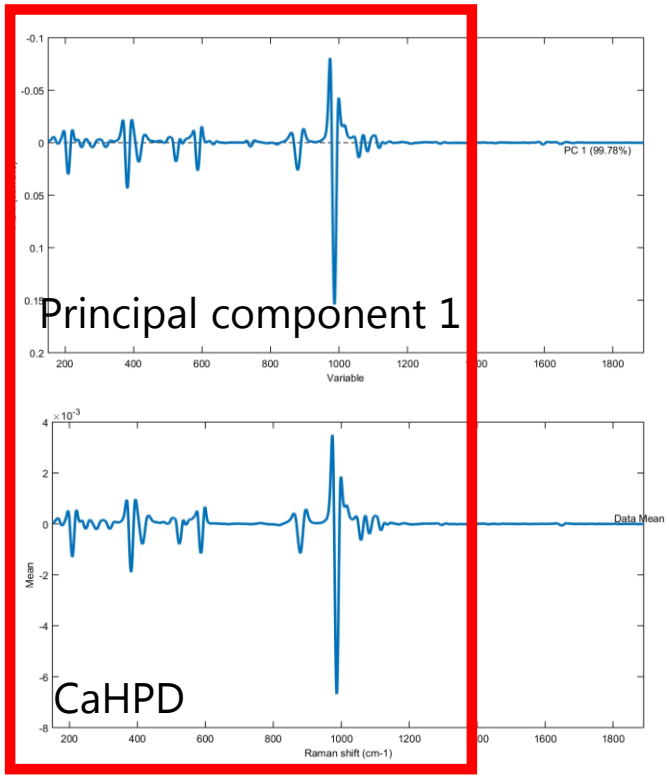
Principal component 1

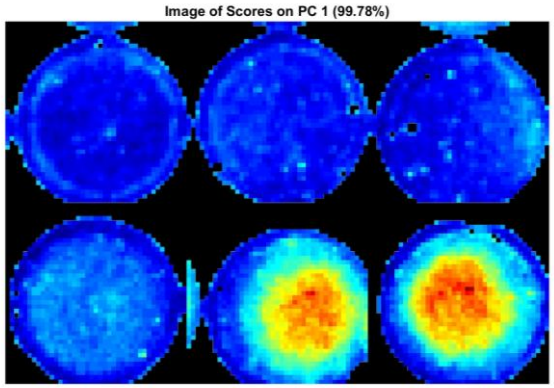
99.8 %



Edinger, M. et al, Pharm Res. 2017, (in press)

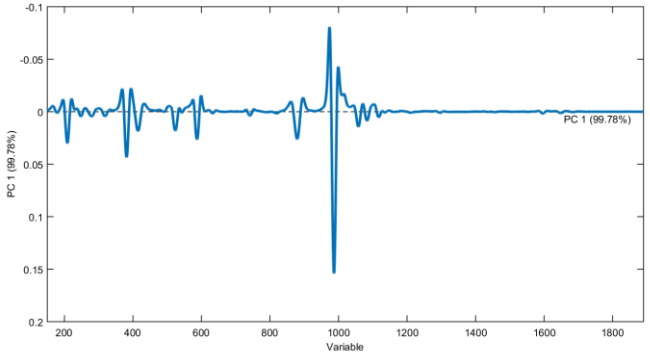
Results – Raman mapping CaHPD tablets





Principal component 1

99.8 %

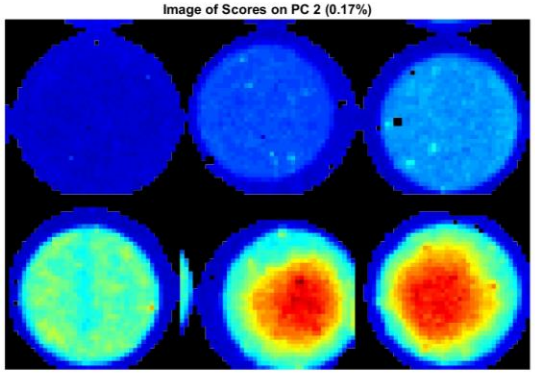


Edinger, M. et al, Pharm Res. 2017, (in press)

Results – Raman mapping CaHPD tablets

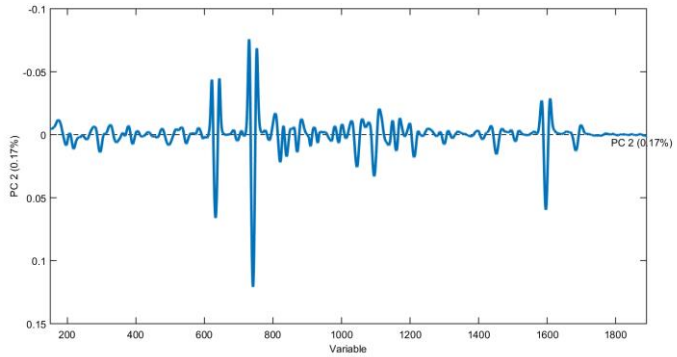
Pure tablet 1 Layer 2 layers

5 layers 10 layers 10 layers



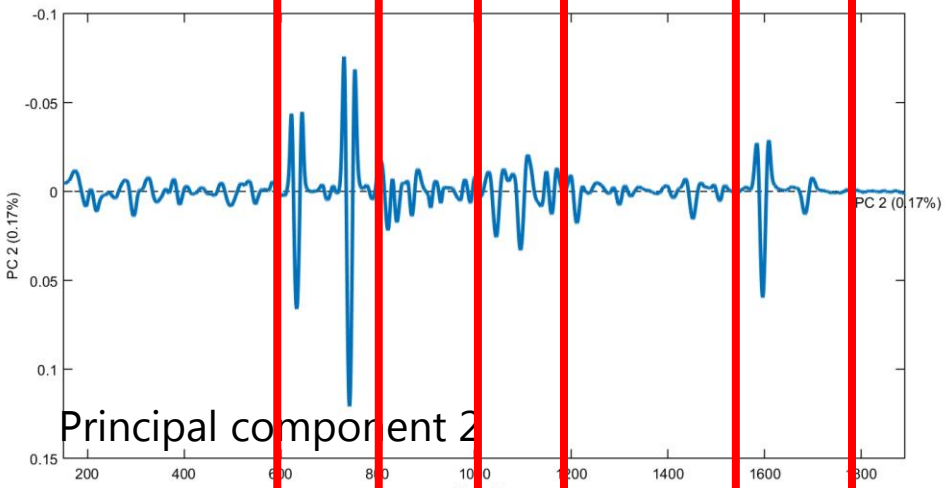
Principal component 2

0.17 %

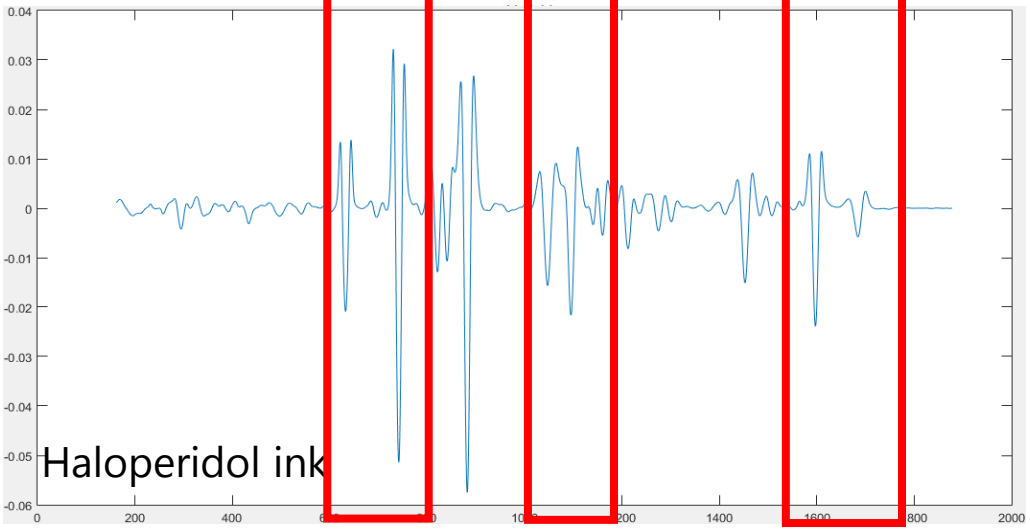


Edinger, M. et al, Pharm Res. 2017, (in press)

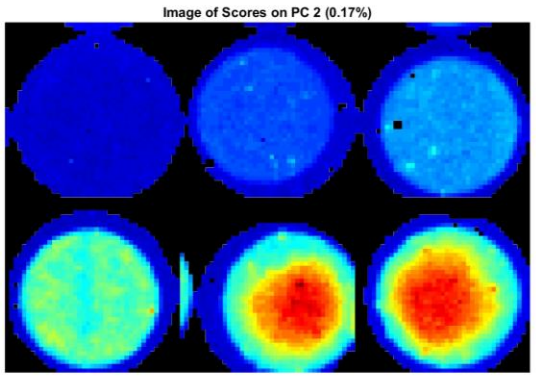
Results – Raman mapping CaHPD tablets



Principal component 2

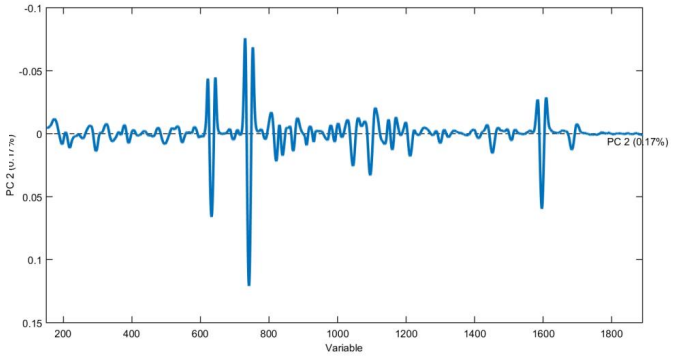


Haloperidol ink



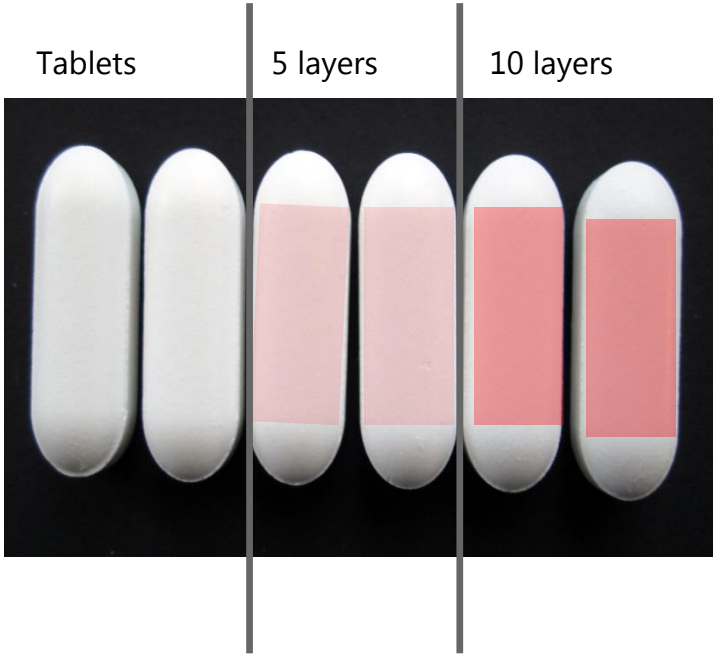
Principal component 2

0.17 %

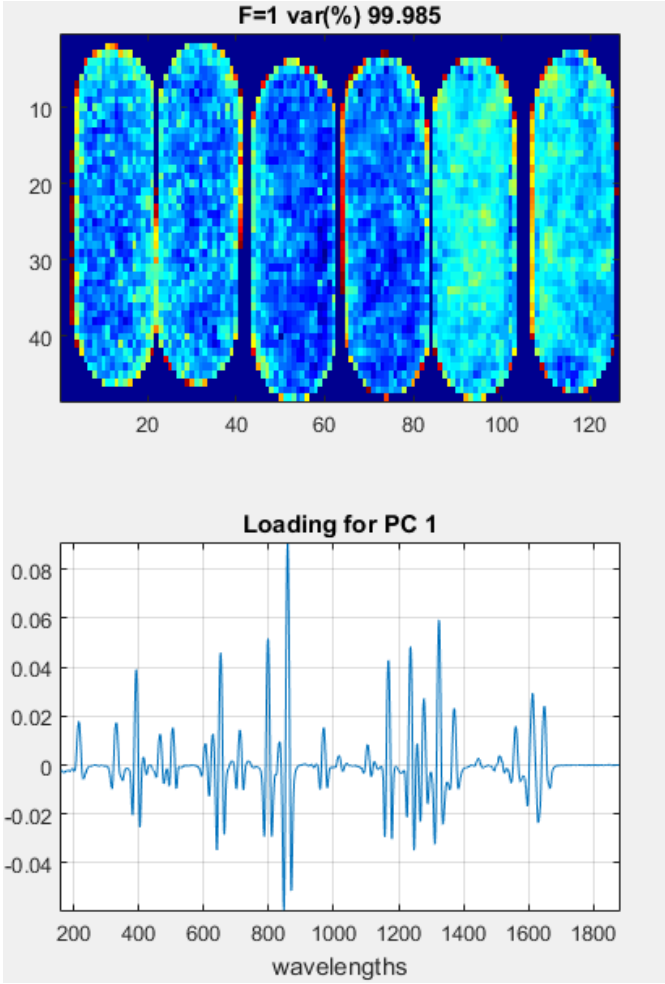


Edinger, M. et al, Pharm Res. 2017, (in press)

Results – Raman chemical imaging



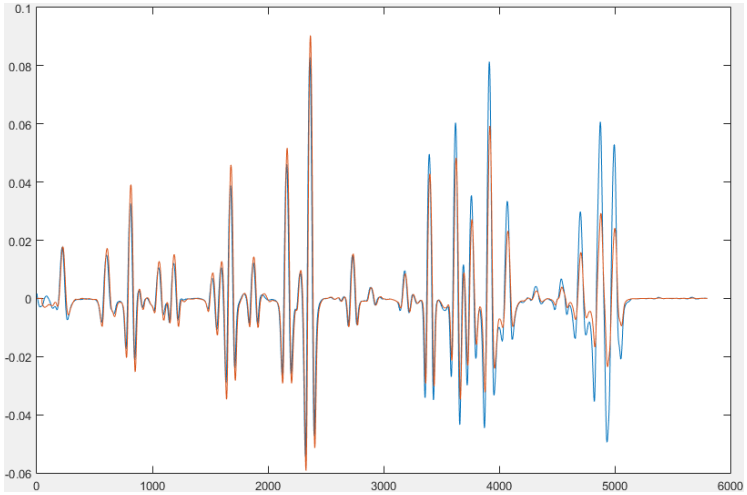
Principal component 1



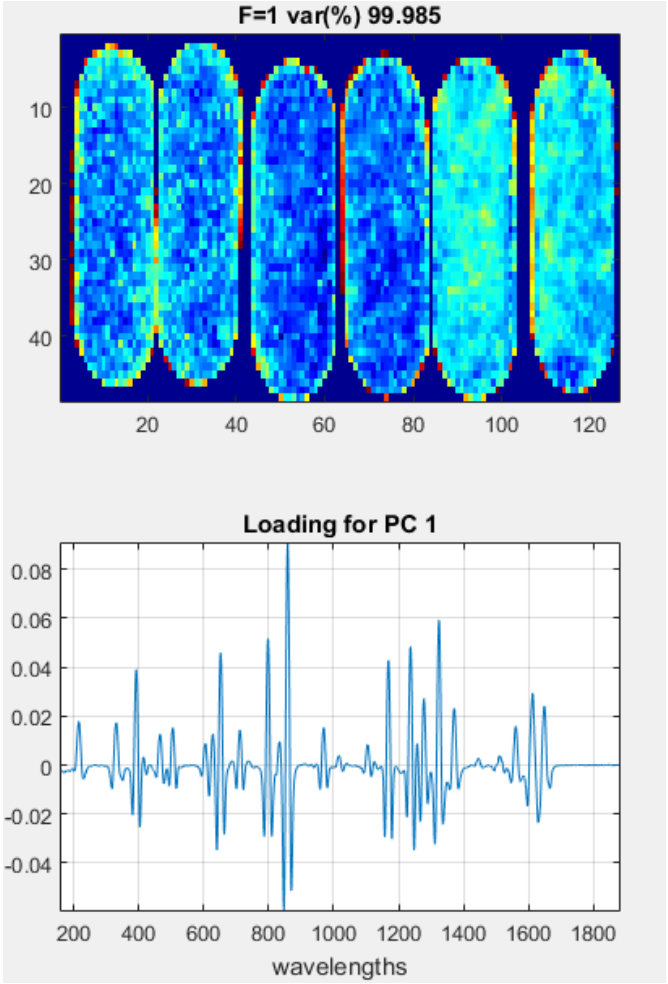
Edinger, M. et al, Pharm Res. 2017, (in press)

Results – Raman chemical imaging

- Paracetamol tablet



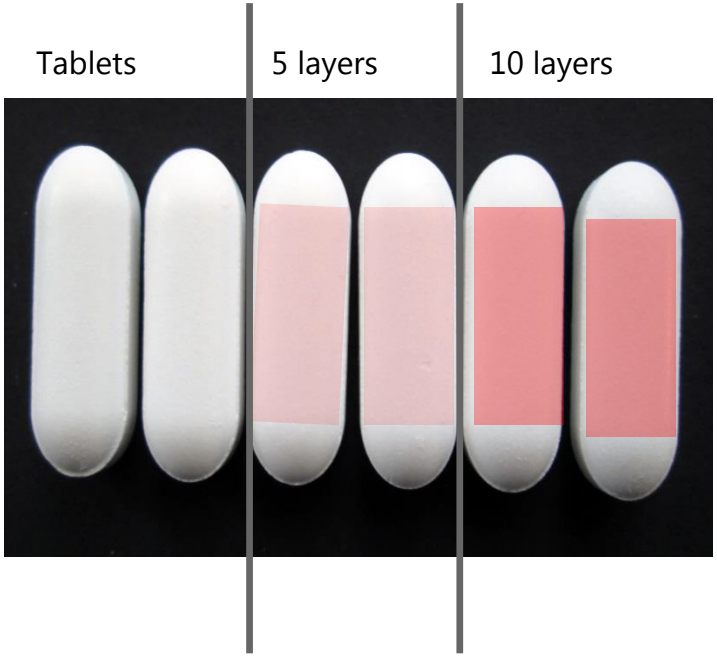
Principal component 1



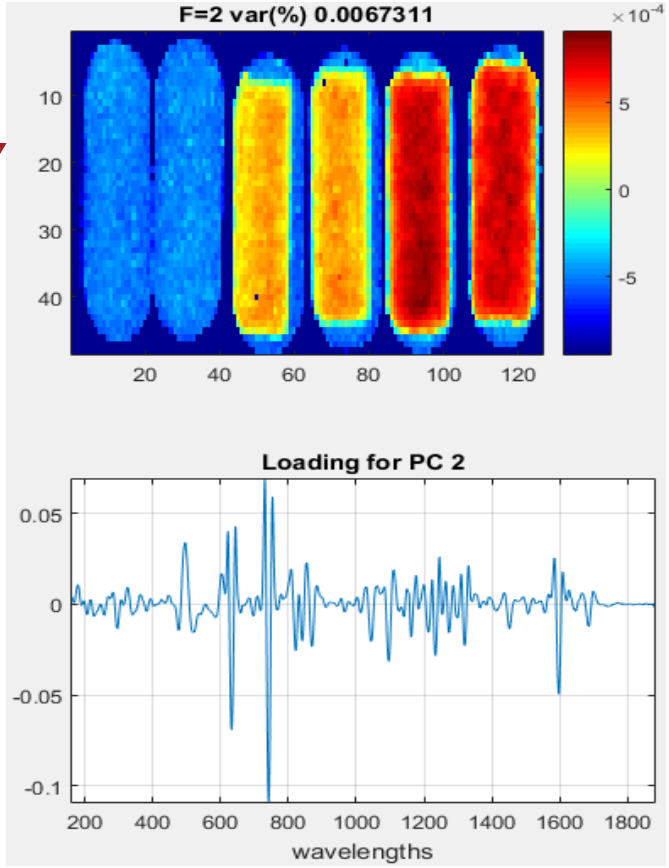
Edinger, M. et al, Pharm Res. 2017, (in press)

Results – Raman chemical imaging

- Principal component 2

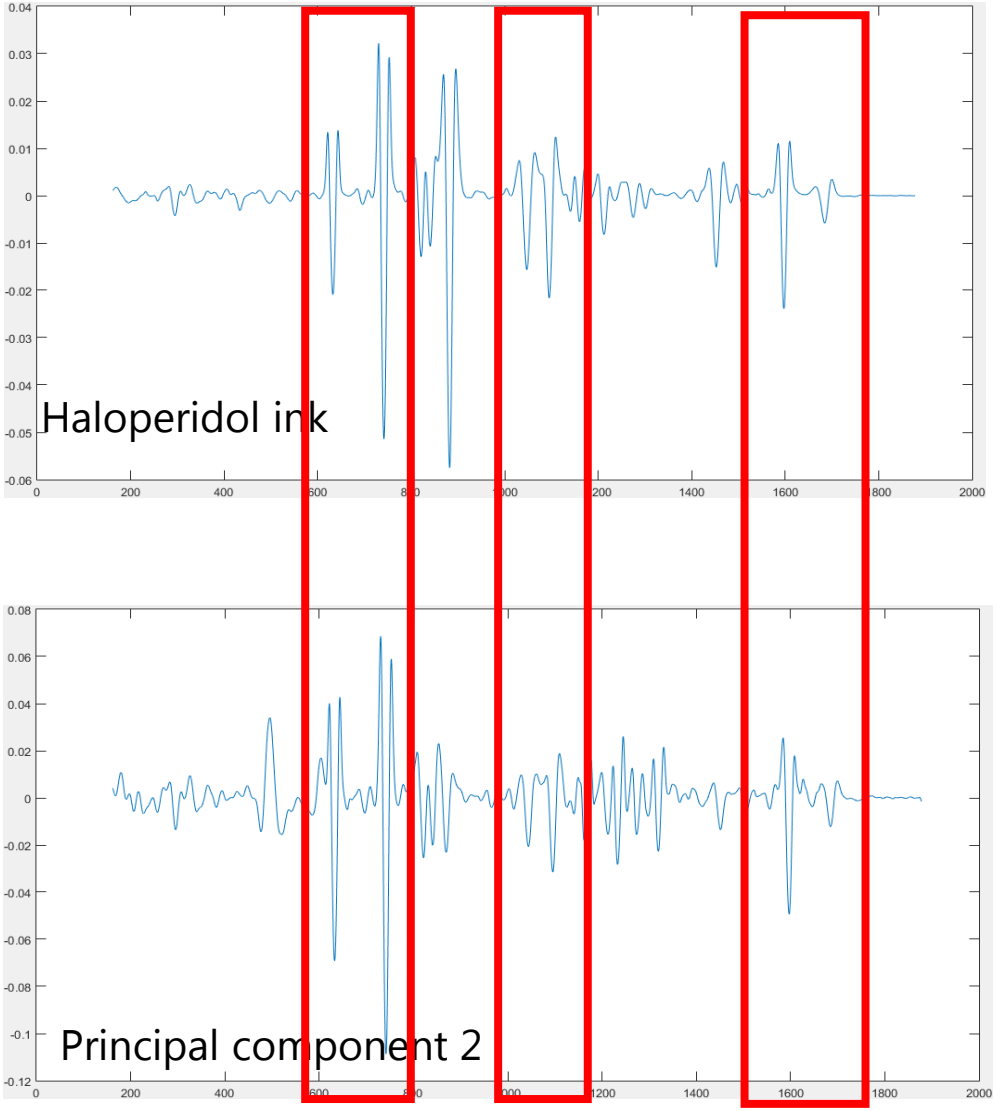


Principal component 2



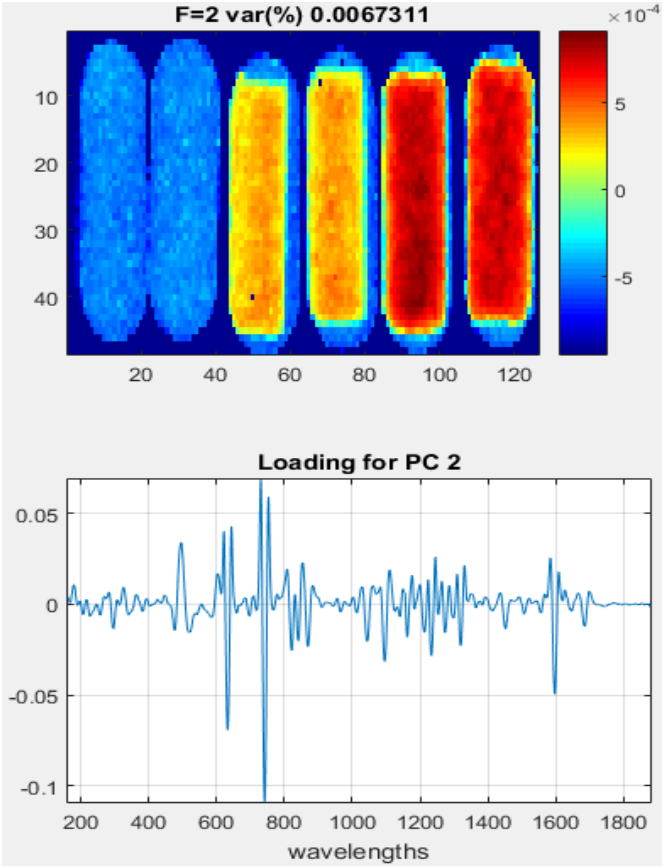
Edinger, M. et al, Pharm Res. 2017, (in press)

Results – Raman mapping



Edinger, M. et al, Pharm Res. 2017, (in press)

Principal component 2

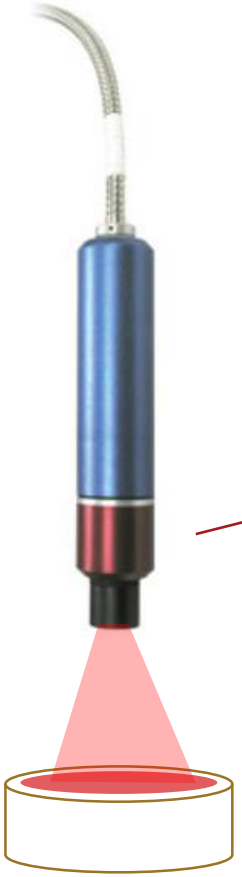


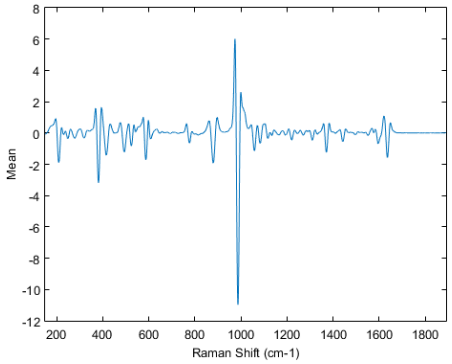
PBP World Meeting 2016

Results – Raman mapping

- Possible to visualize API on inkjet printed samples.
- LONG analysis time
- Is it possible to shorten analysis time and get quantitative data?

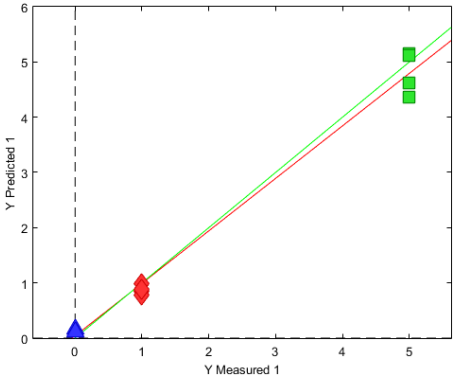
Quantification of haloperidol using Raman spectroscopy?





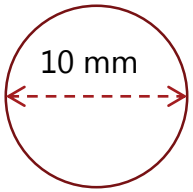
UV/HPLC

PLS algorithm

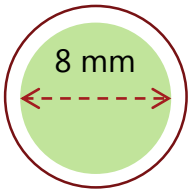


Quantification of haloperidol using Raman spectroscopy?

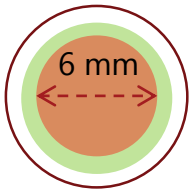
- CaHPD compacts



Tablet

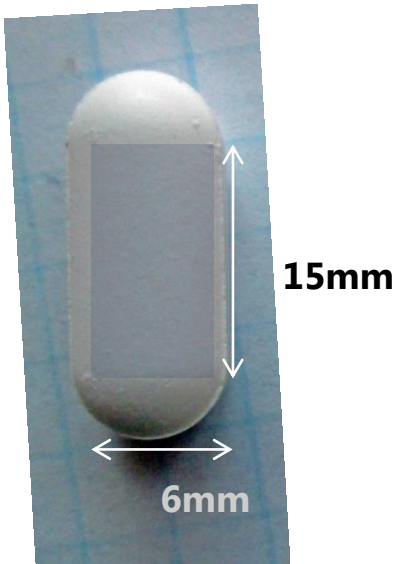


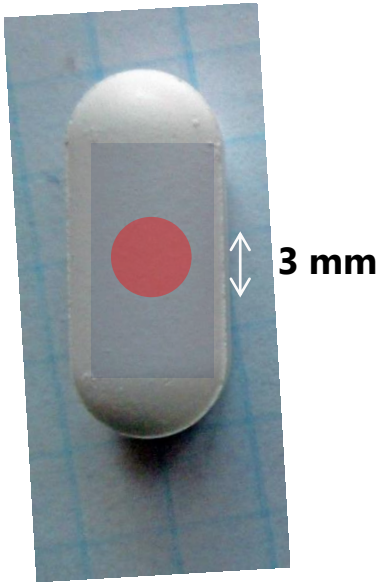
Printed area



Area of analysis

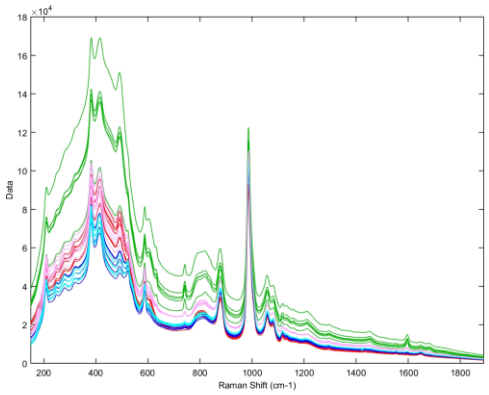
- Paracetamol tablets





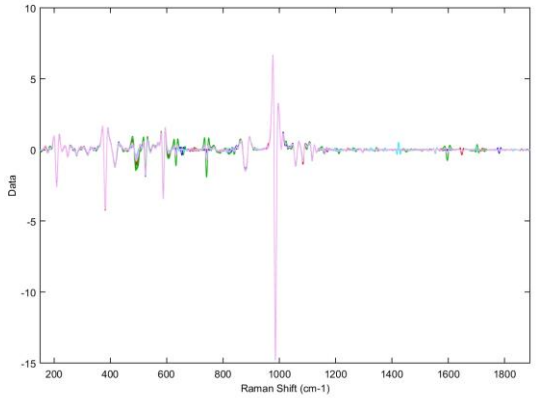
Preprocessing

CaHPM compacts
Raw spectra



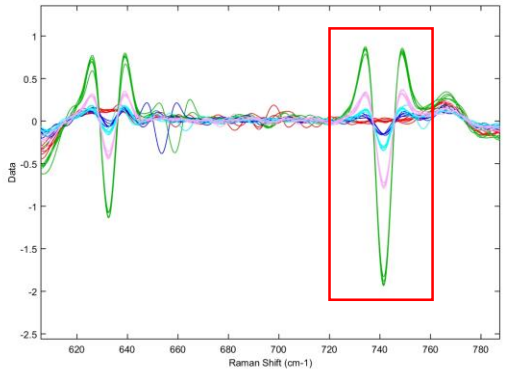
0 layers
1 layer
2 layers
5 layers
10 layers

Preprocessing



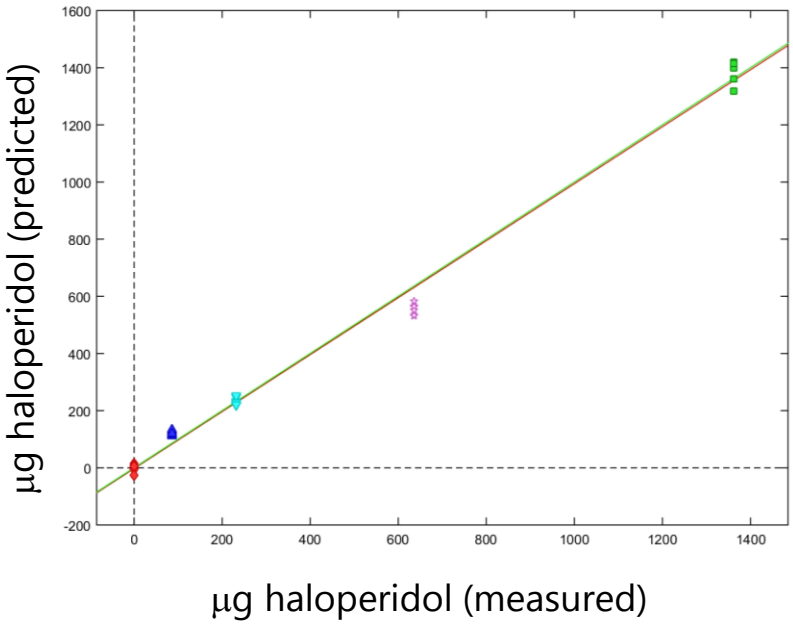
Spectral

selection

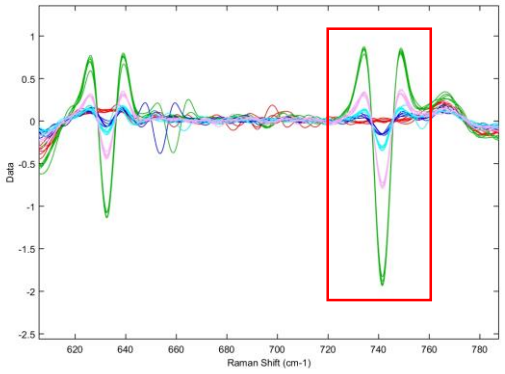


PLS modeling – CaHPM compacts

- Correlating to HPLC data

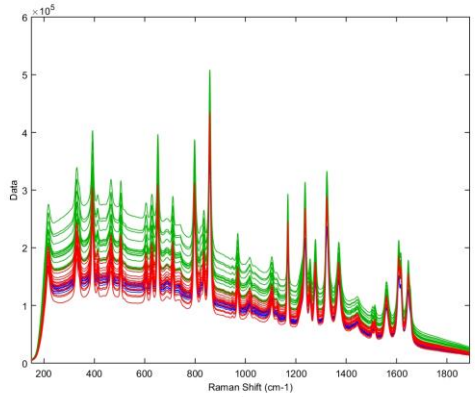


R^2 = 0.99
RMSEP = 80 µg



Preprocessing

CaHPM compacts
Raw spectra



0 layers
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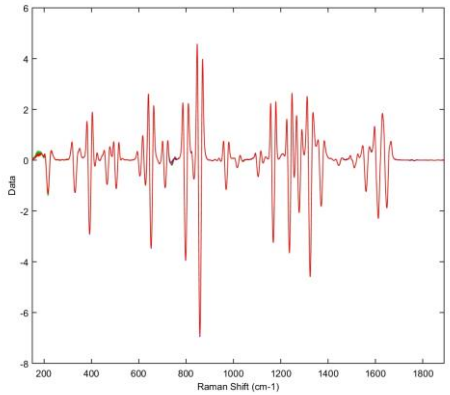
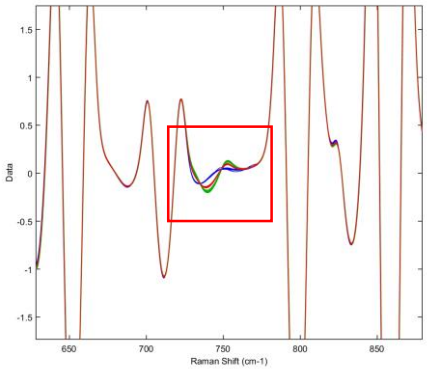
Preprocessing



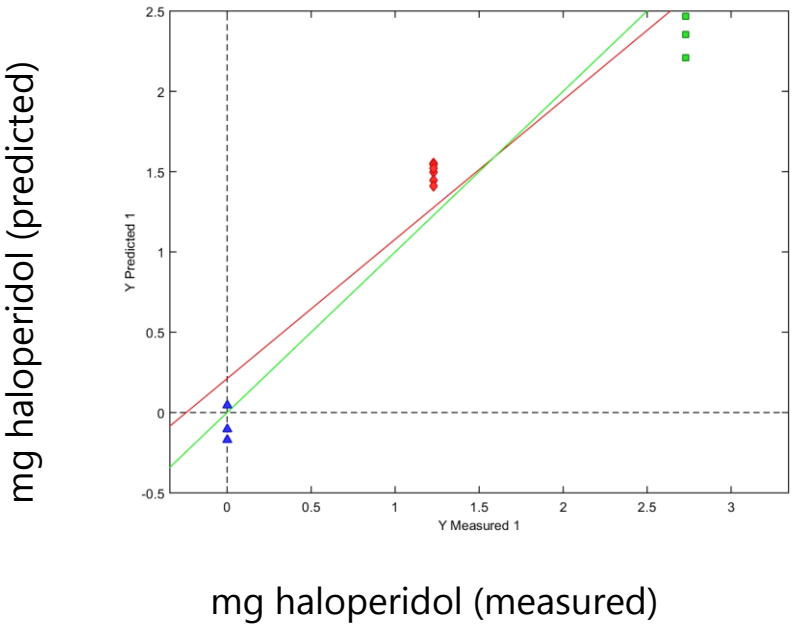
Spectral

selection

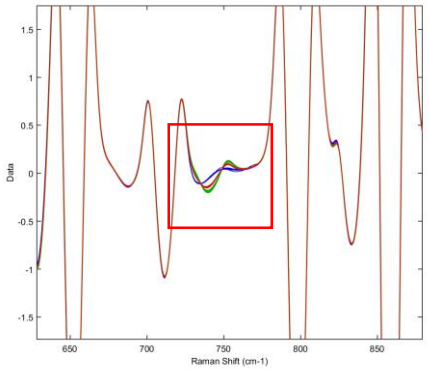


PLS modeling – Paracetamol tablets

- Correlating to HPLC data



R^2 = 0.90
RMSEP = 0.2 mg



Conclusions

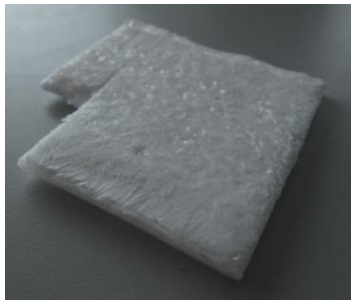
- It is possible to use Raman chemical imaging to visualize inkjet printed pharmaceuticals even on strongly Raman scattering substrates

- It is possible to non-destructively quantify inkjet printed pharmaceuticals using Raman spectroscopy and PLS modeling.
  - Lower accuracy on strong Raman scatterers
  - Penetration depth of ink and Raman laser

Future work

- Implementation of transmission Raman spectroscopy methods for API quantification

- Development of substrates optimized for inkjet printing of pharmaceuticals



  - Printing APIs as their own quality control – QR codes

Thanks to…

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