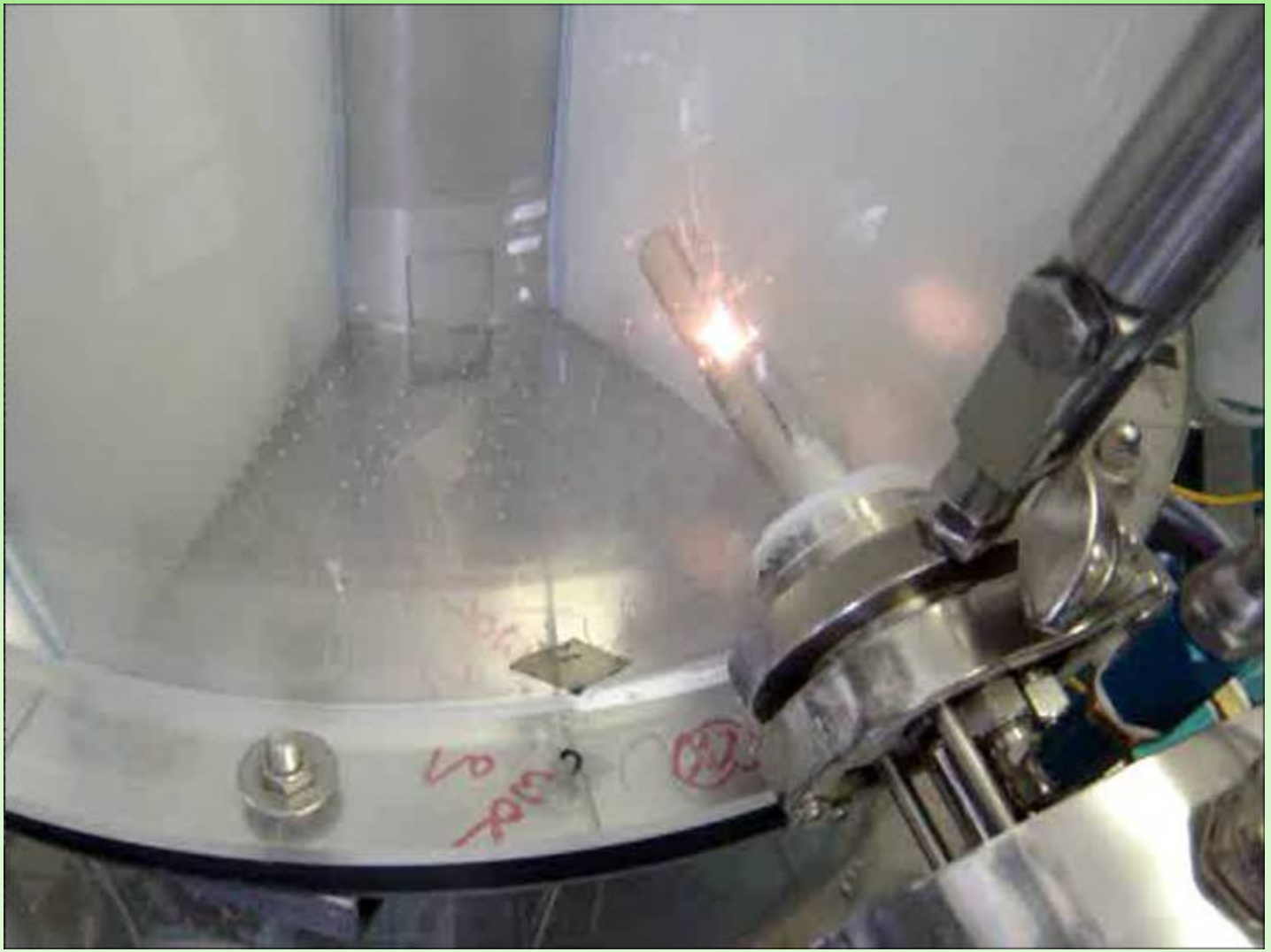
PAT solutions for pharmaceutical industry

Alexey L. Pomerantsev



Semenov Institute of Chemical Physics

Russian chemometric society

Content

- Introduction
- Case study 1: Incoming Inspection
- Case study 2: Process Control
- Case study 3: Outcoming Inspection

Process Analytical Technology

PAT is a syste and controlling
manufacturing ts (i.e., during
processing) of ce attributes of
raw and in-proc s, with the goal
of ensuring fina

Guidance for Indust e Pharmaceutical
Development, Manu
Pharmaceutical CG

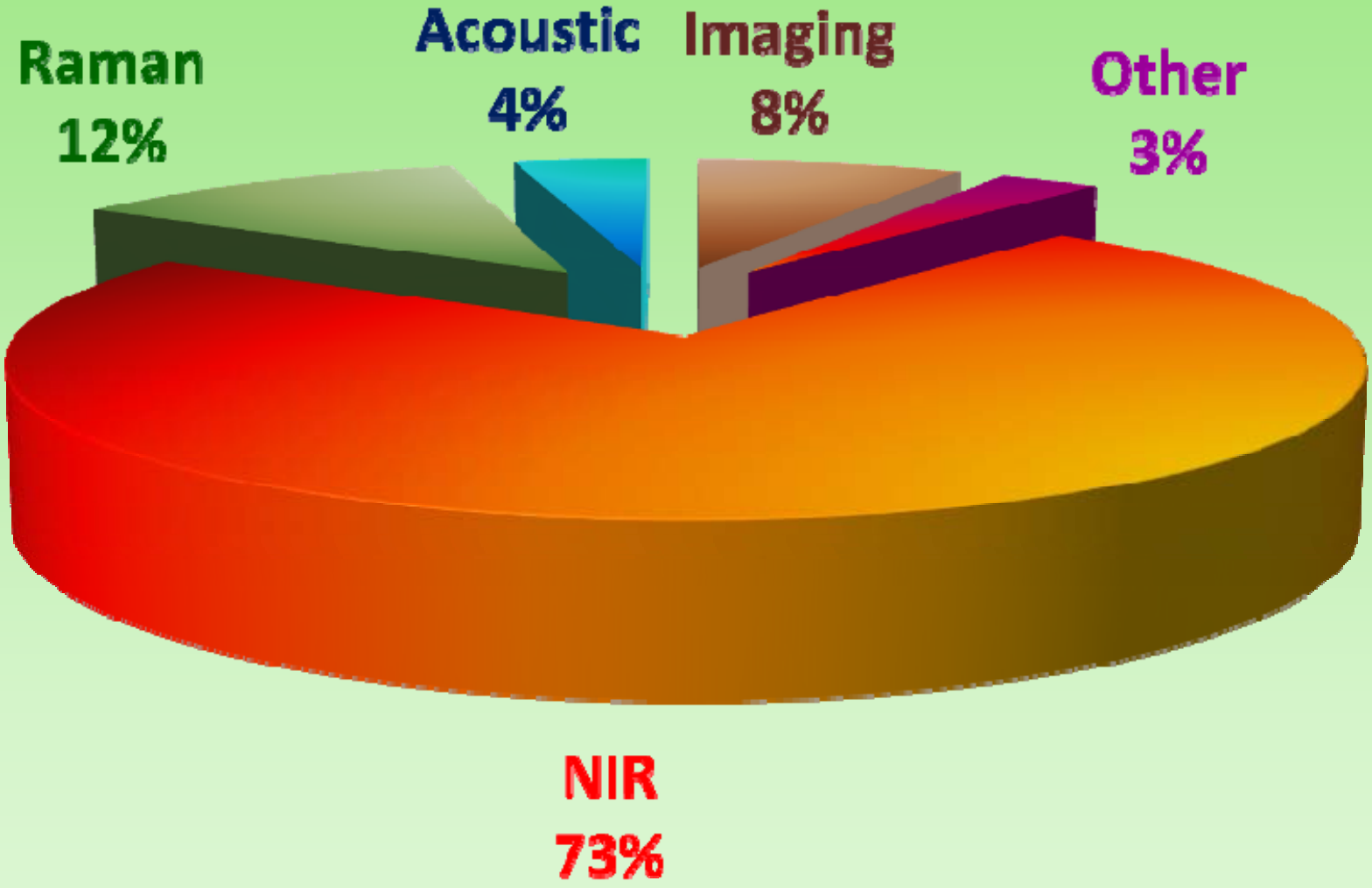
Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

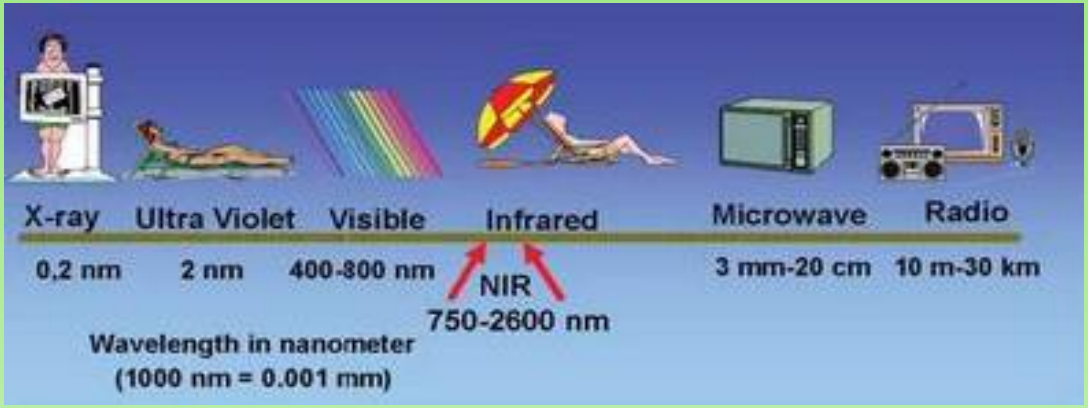
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

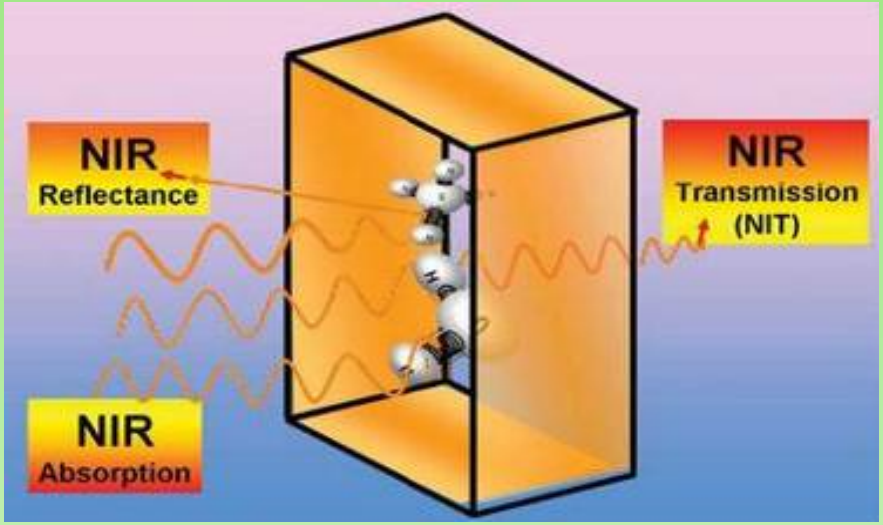
Pharmaceutical CGMPs
September 2004

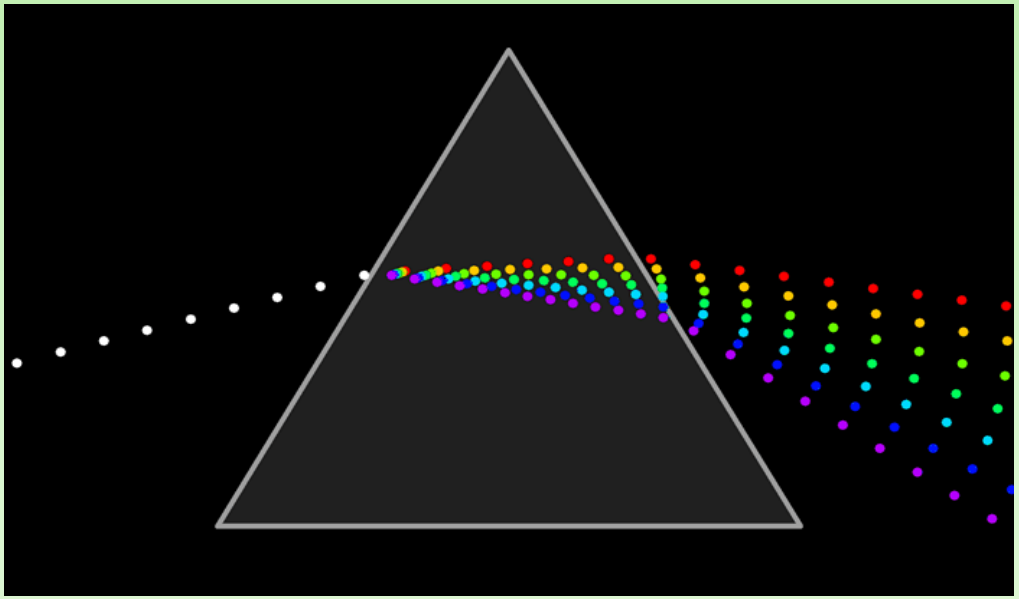
PAT Instruments

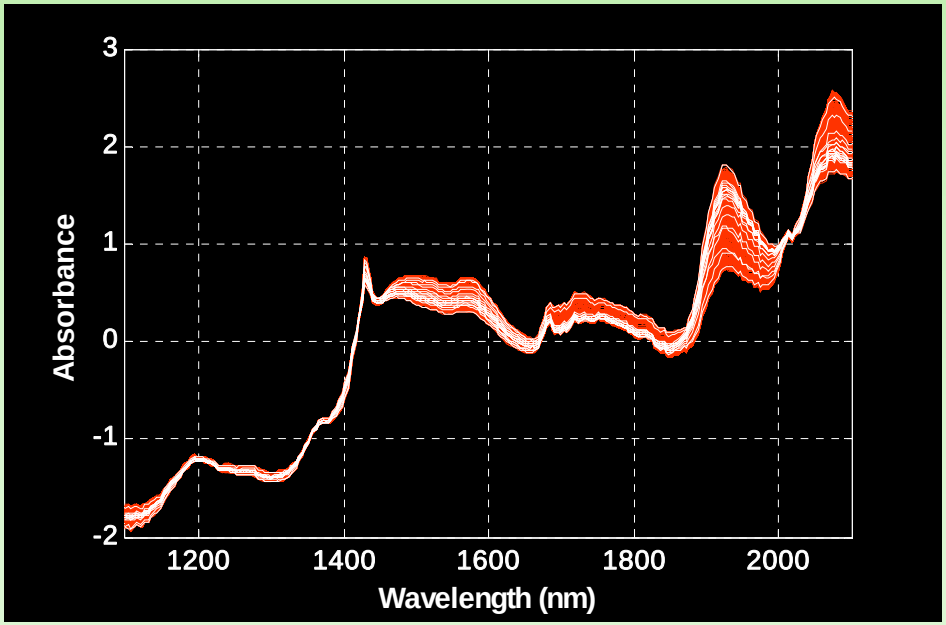


Near Infra Red spectroscopy









Generic PAT Solutions

Substance **Process** **Product**

Incoming inspection

Process control

Outcoming inspection

Case study 1: Incoming Inspection

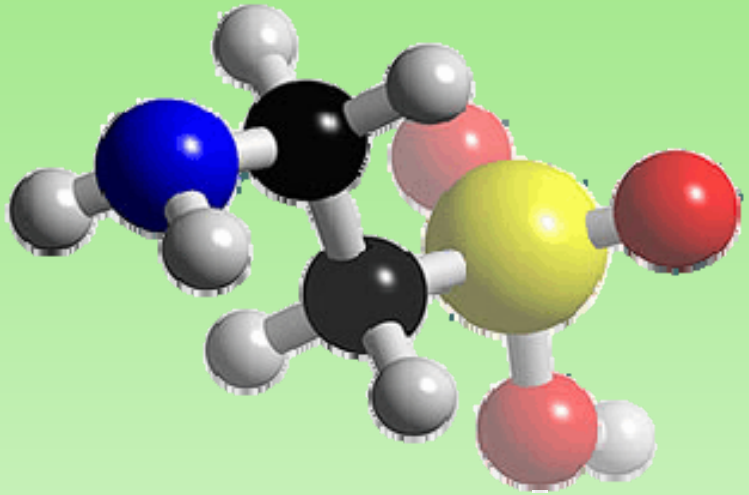
To design a quick and simple routine procedure for recognition the perfect raw pharmaceutical substances directly in a warehouse

The goal

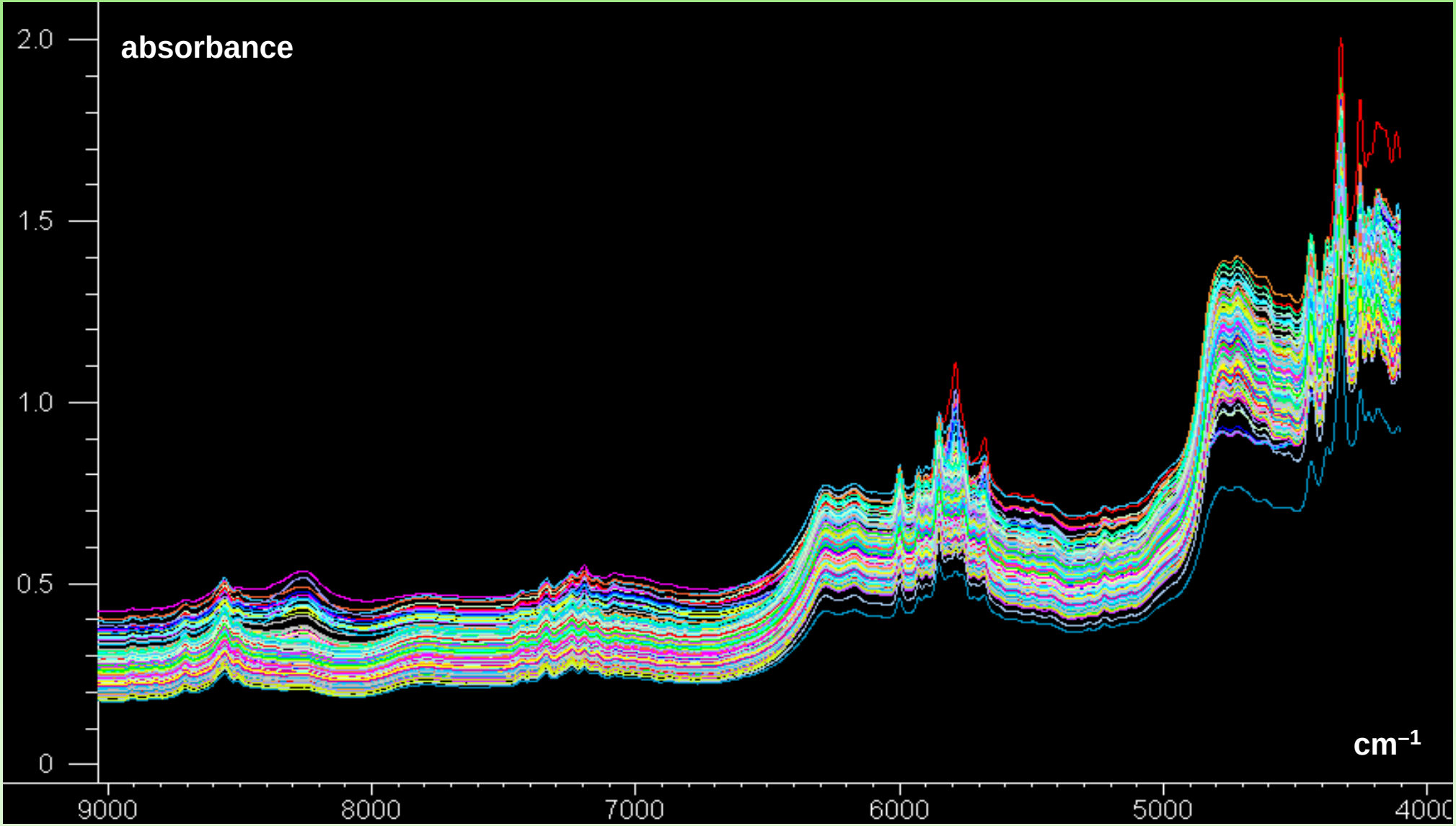
Material: Taurine, a non-essential sulfur-containing amino acid

Data: NIR spectra measured in 4100 -10000 cm^{-1} region, resolution 2 cm^{-1}

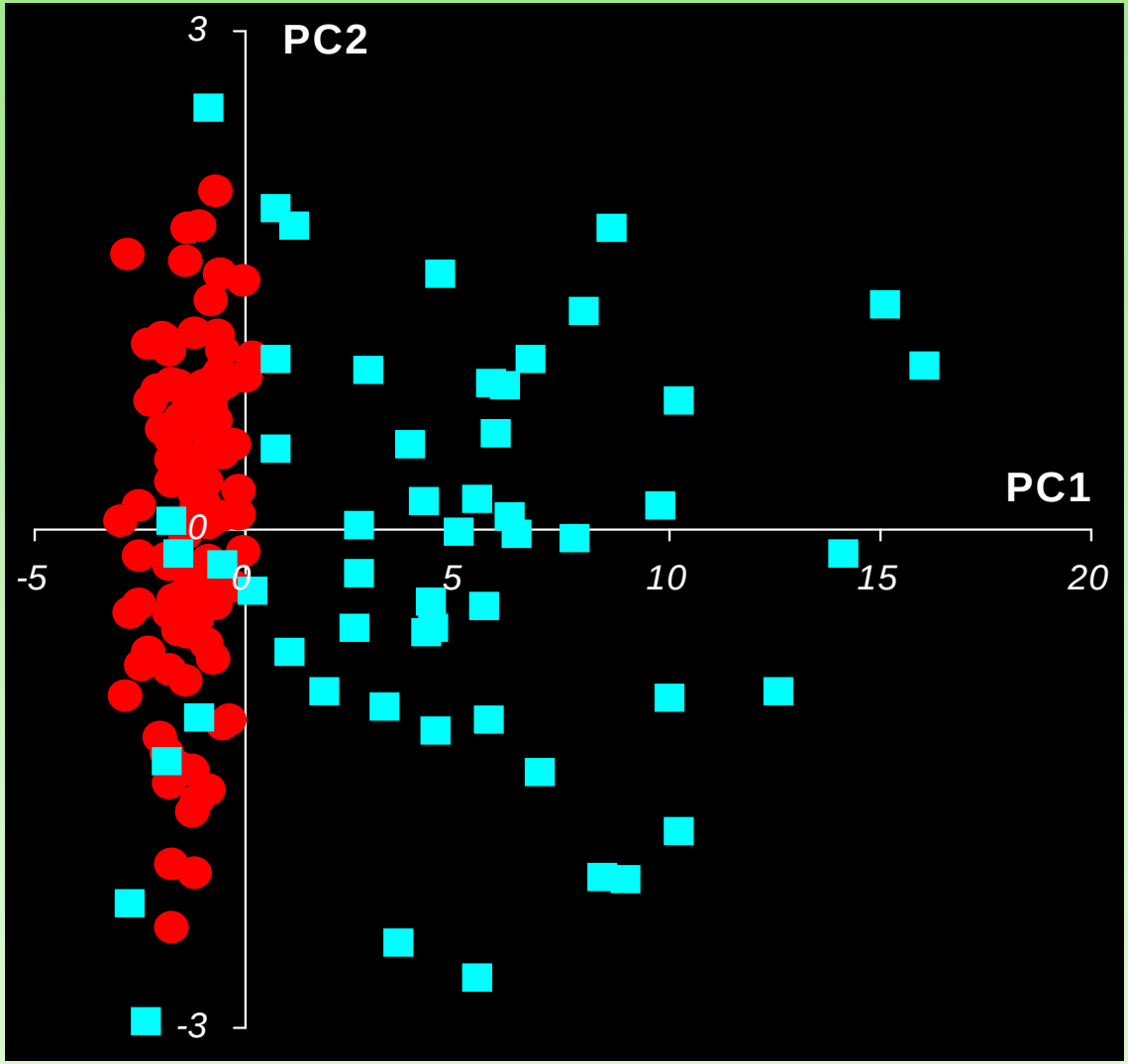
Substance: in the closed PE bags, 82 drums measured 3 times, totally: 246 spectra



Spectra



Explorative analysis

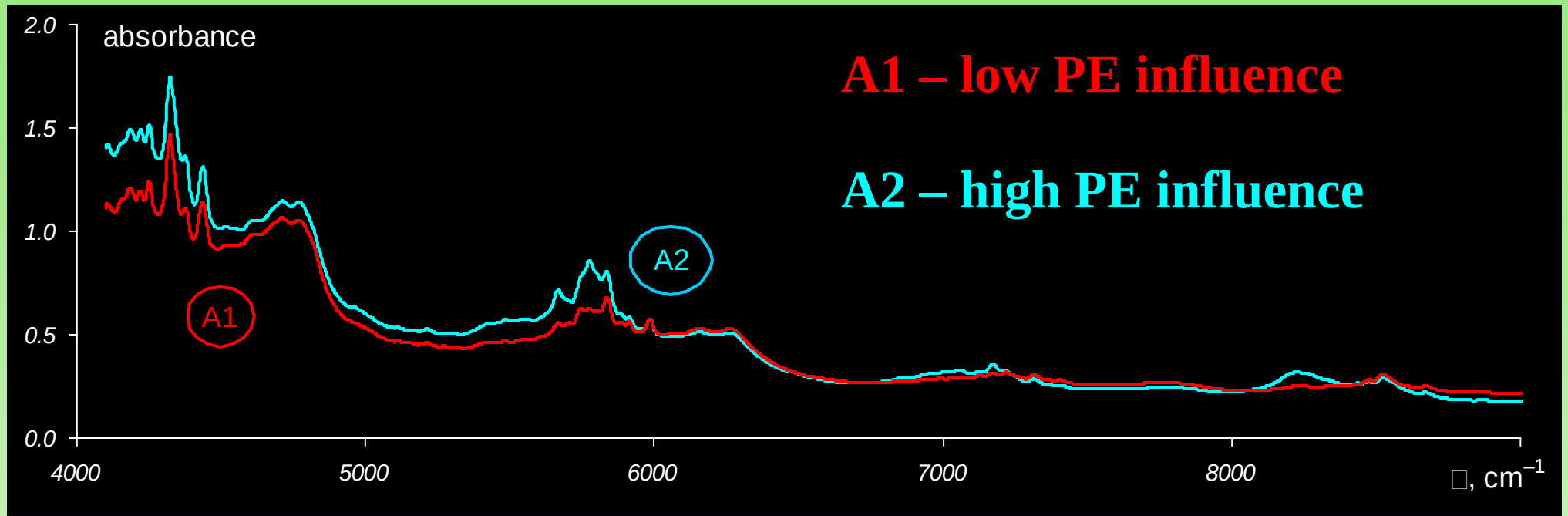


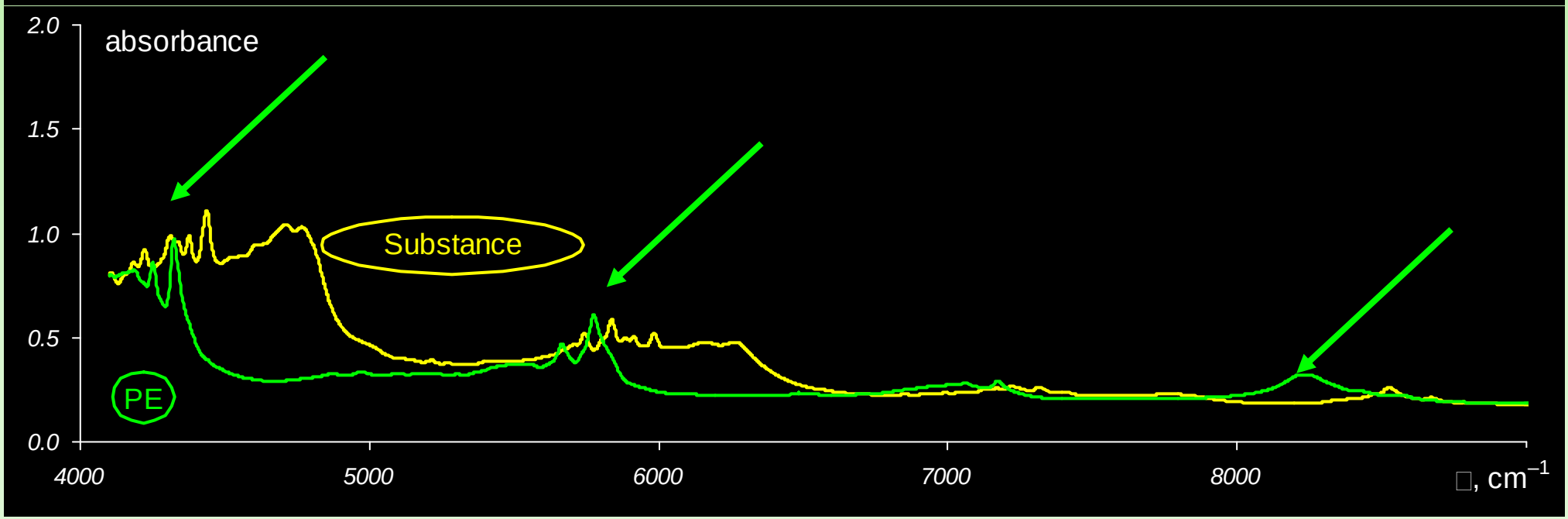
The problem:

60 points of 246 are outliers.

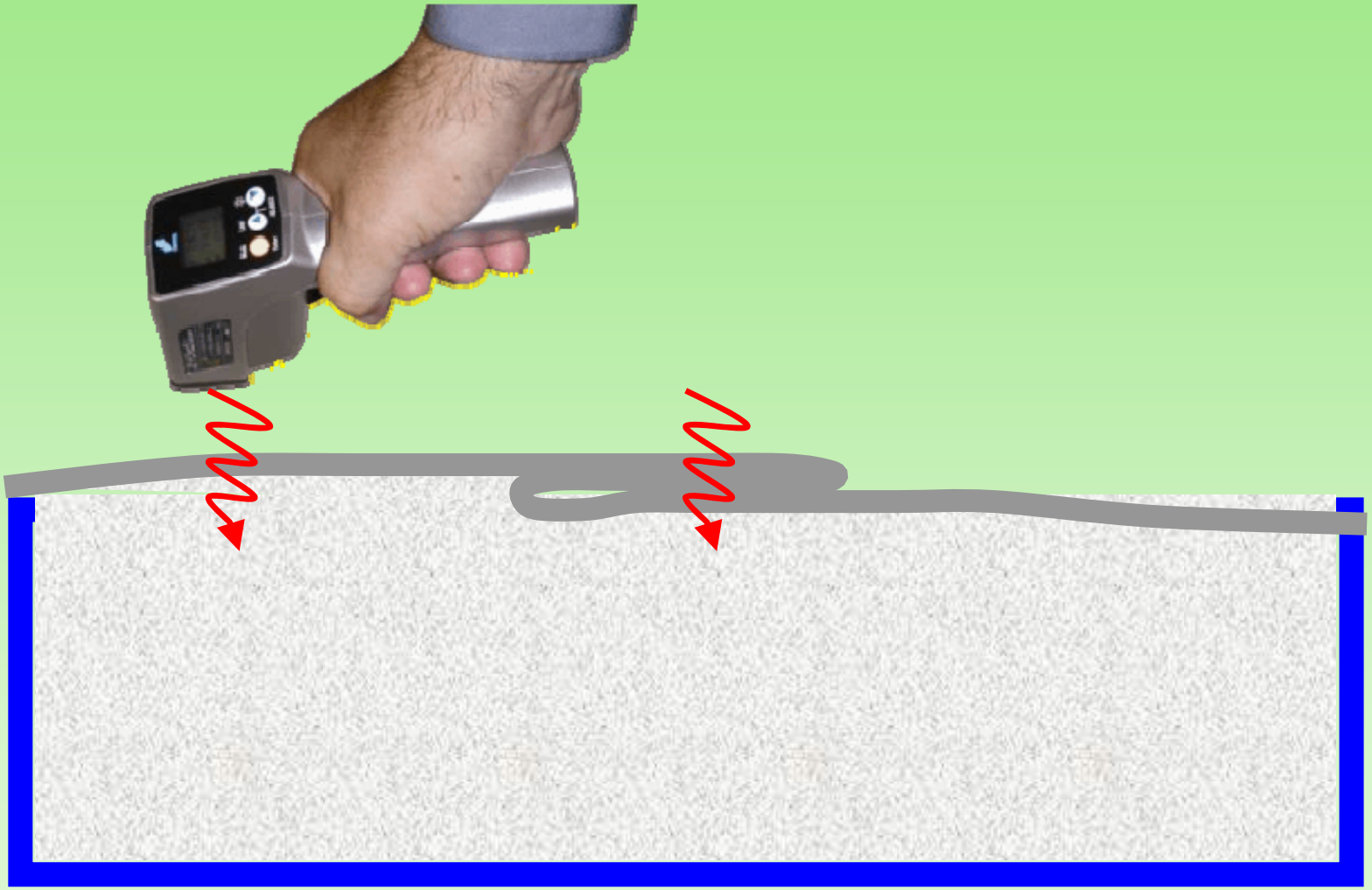
Are they fakes?

Reason of failure

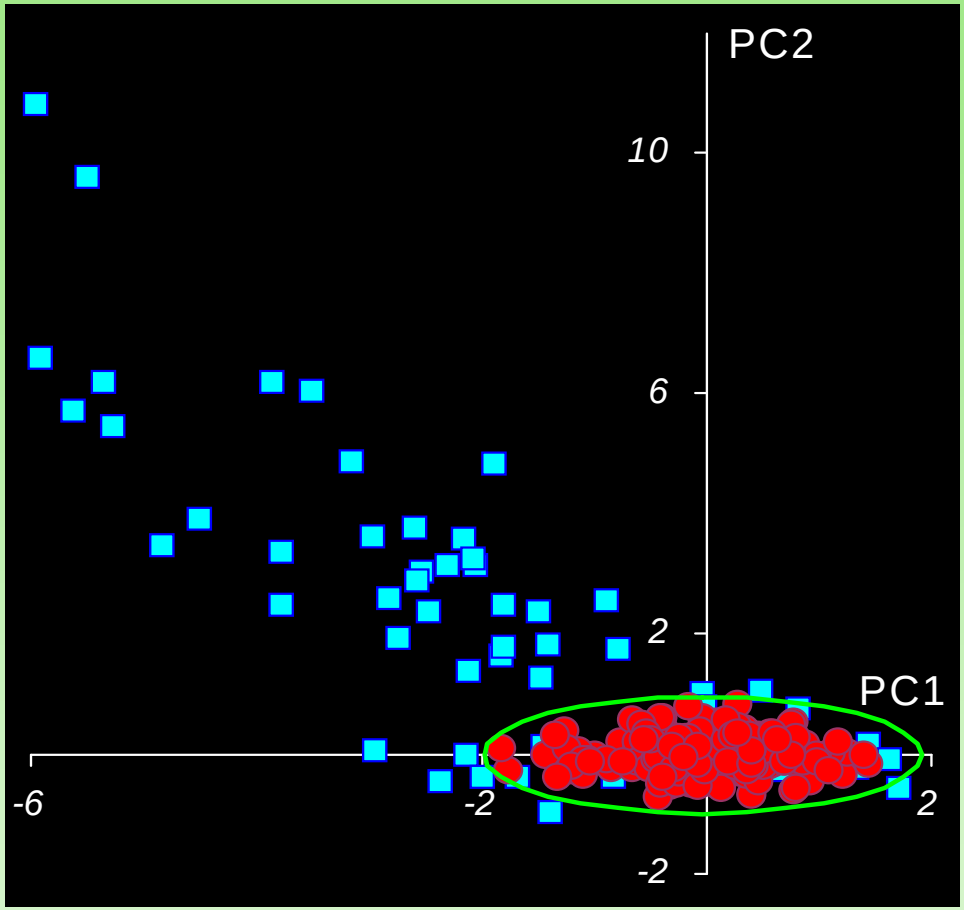


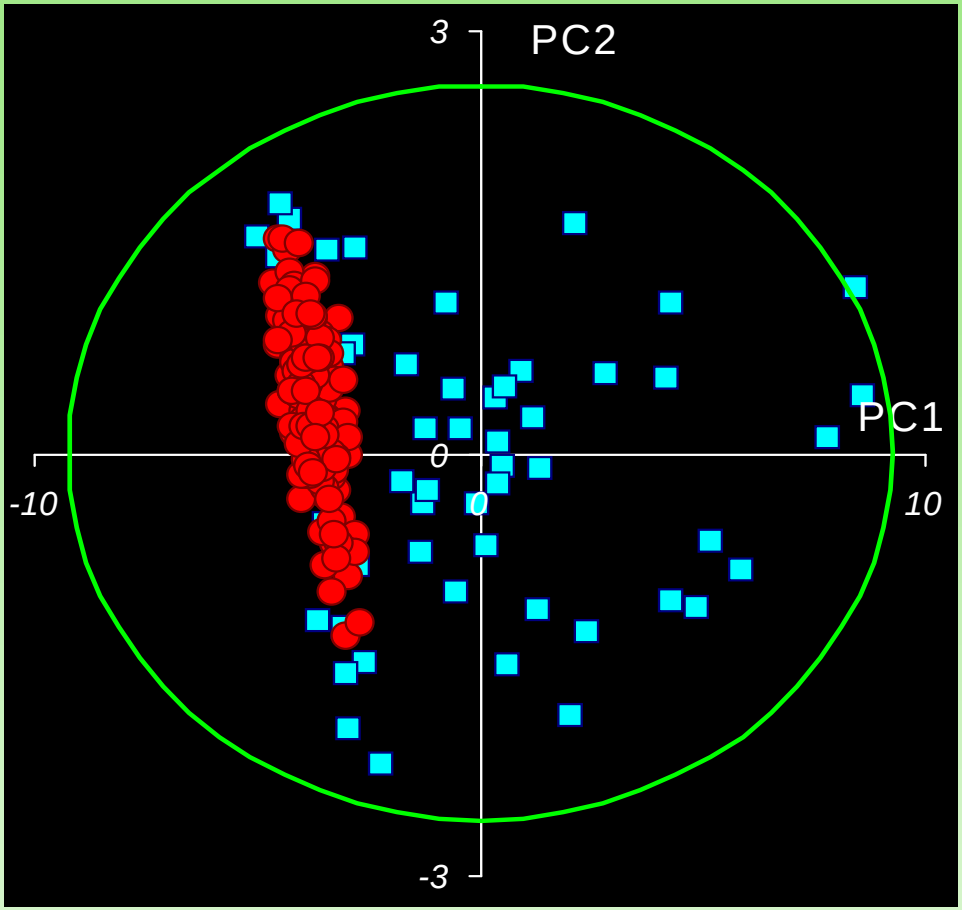


Probe position effect



Two PCA models





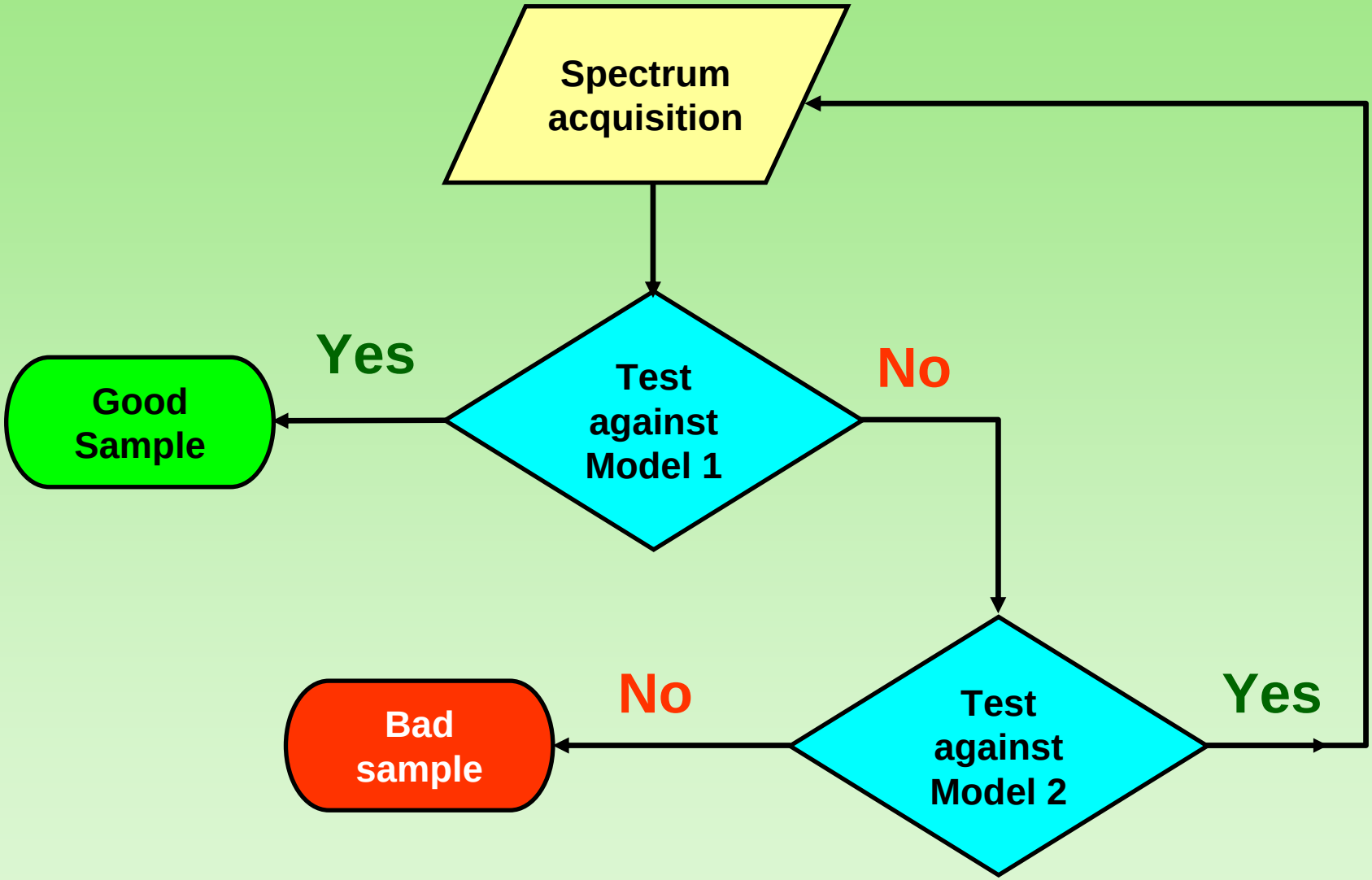
Model 1

Dots are the training samples (Group 1)
Squares are the test samples (Group 2)

Model 2

Squares are the training samples (Group 1)
Dots are the test samples (Group 2)

Routine testing procedure



Case study conclusions

- Probing robust method
- Qualitative trihotomy analysis: yes / no / try again
- 100 % inspection (≤ 3 trials)

Details

ANALYTICA CHIMICA ACTA 642 (2009) 222–227

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

Quality control of packed raw materials in pharmaceutical industry

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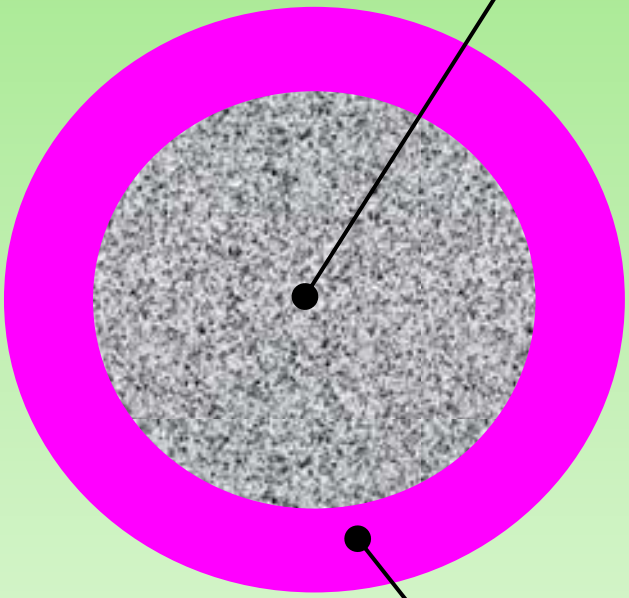
Case study 2: Process Control

To predict the drug release profiles during a running pellet coating process from the in-line near infrared (NIR) measurements

Objects: Pellets



Sugar +API

Coating: Acryl EZE

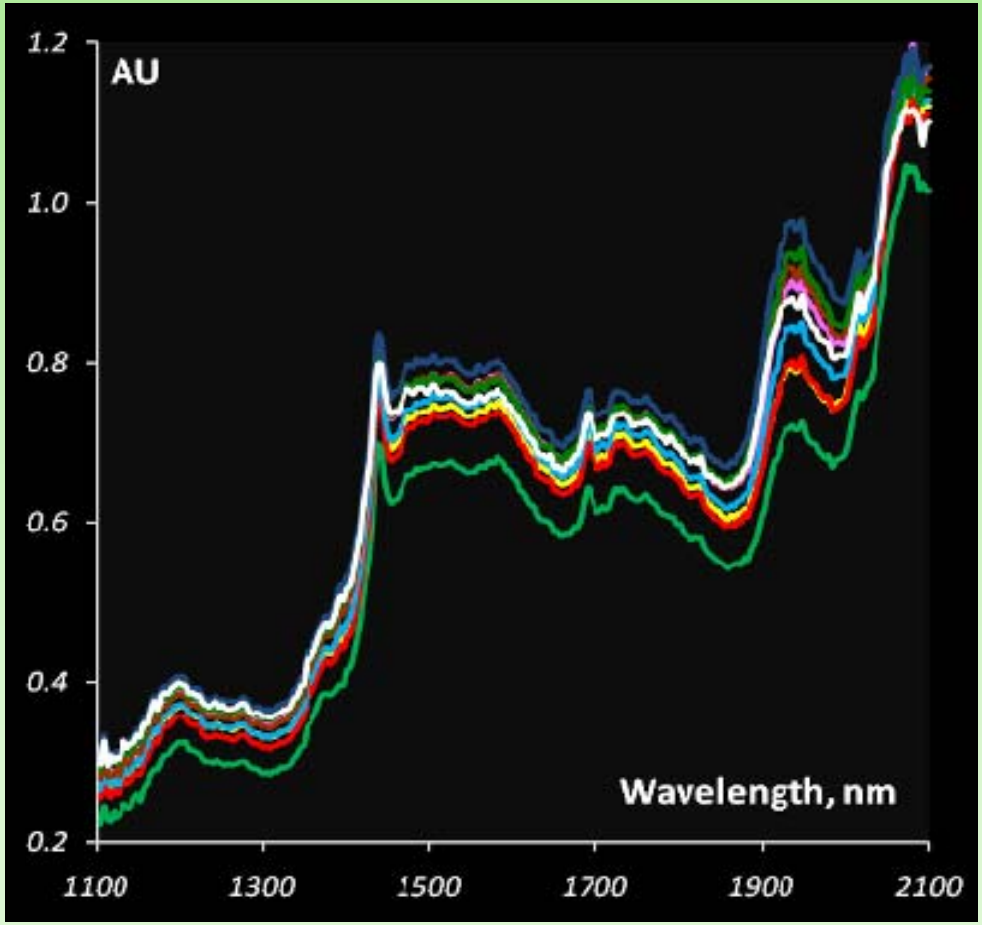
Fluid bed coating

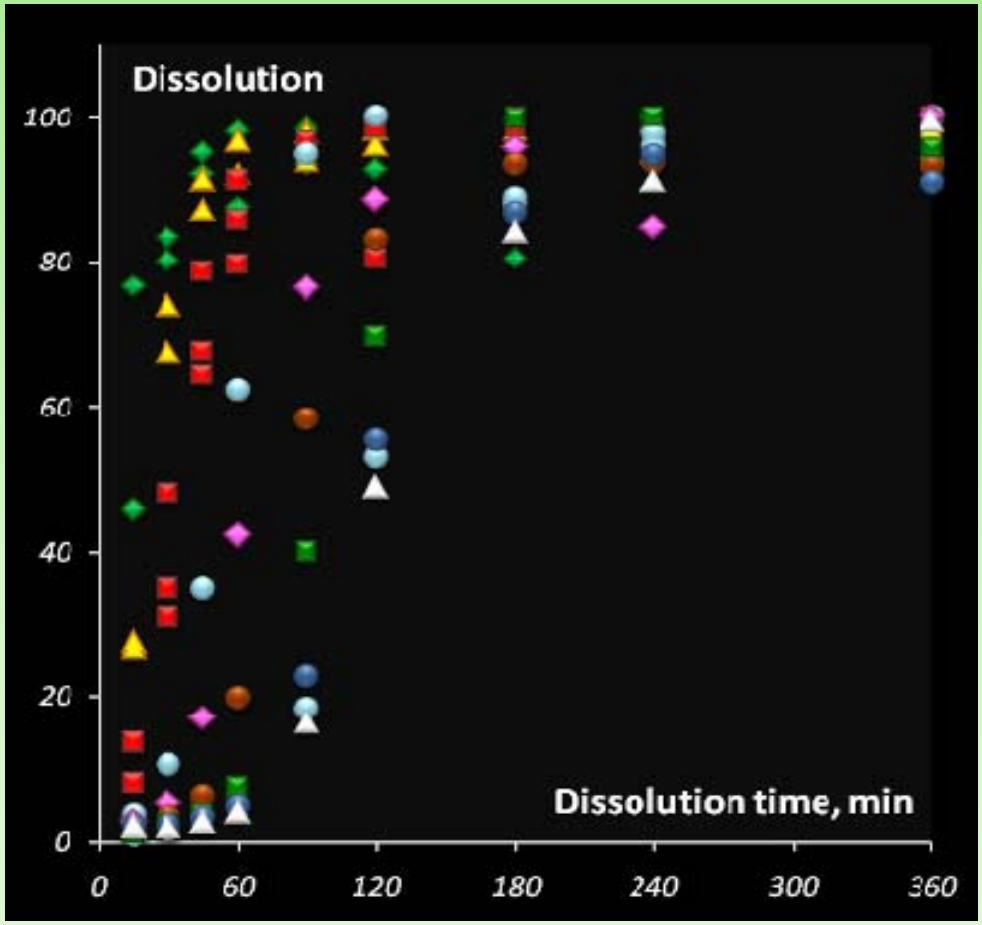
Experiment

NIR Spectra

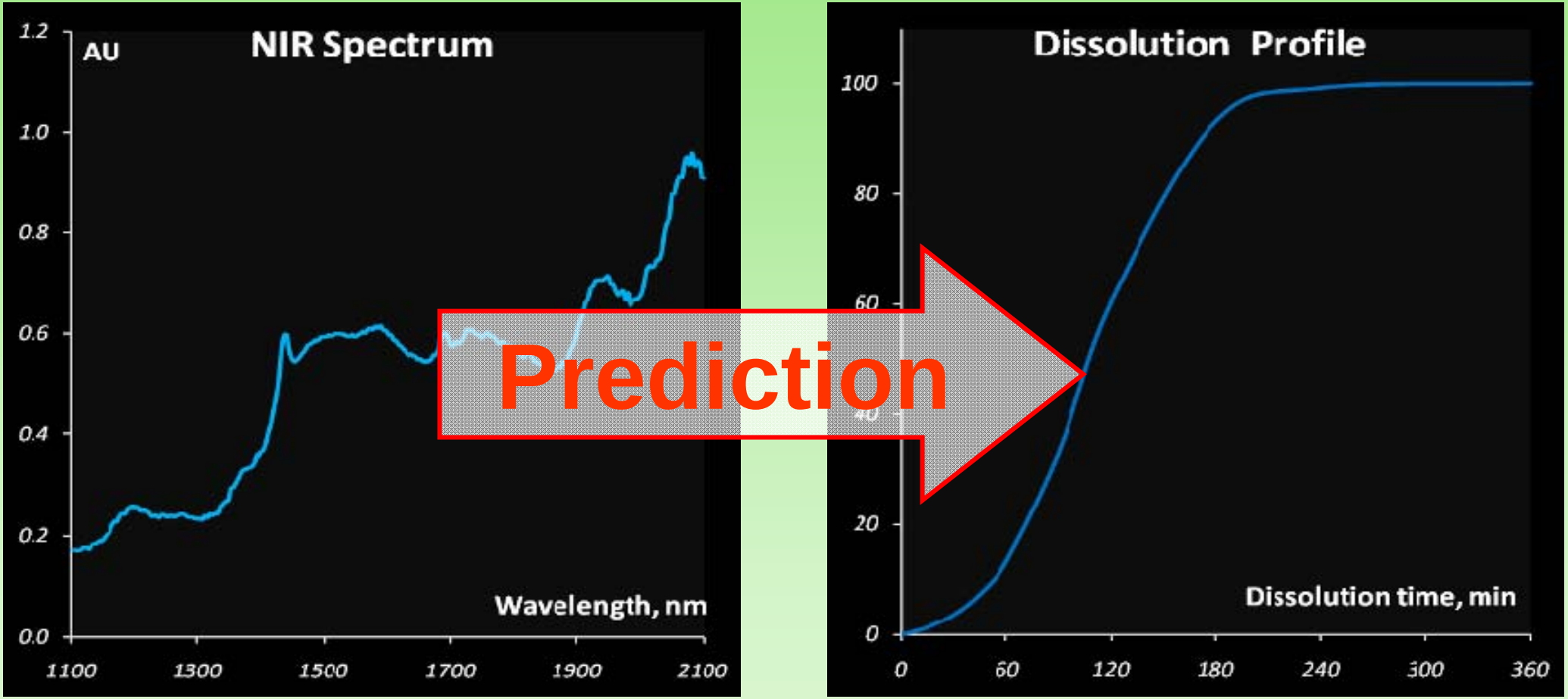
Dissolution Profiles

***t* = 105**





Our goal

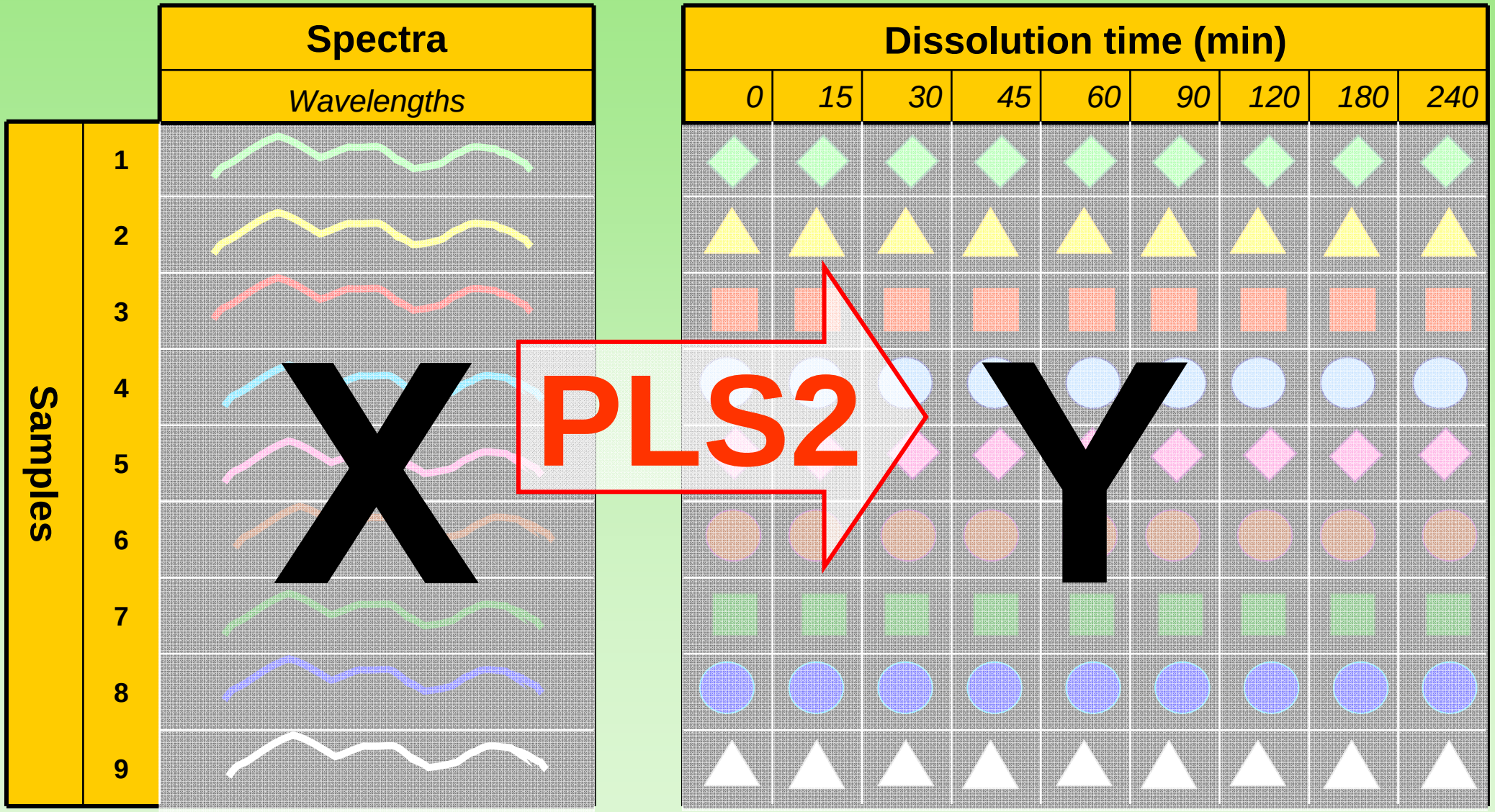

NIR Spectrum
AU
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1100
1300
1500
1700
1900
2100
Wavelength, nm
Prediction
Dissolution Profile
100
80
60
20
0
0
60
120
180
240
300
360
Dissolution time, min

Data overview

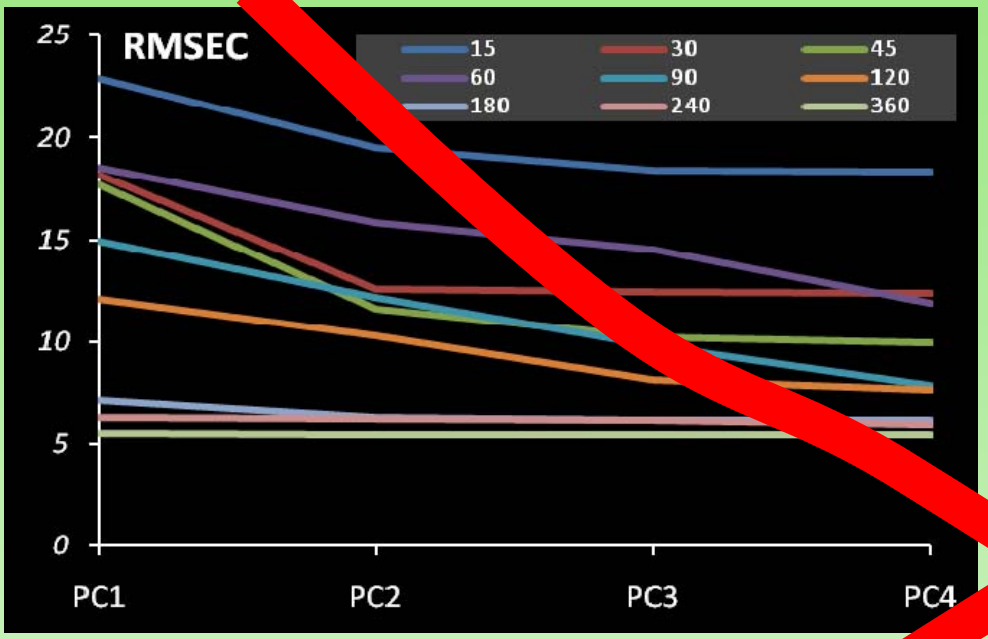
Batches	Samples 1	2	3	4	5	6	7	8	9
W1	25	44	62	82	99	117	136	154	171
W2	22	37	52	67	81	98	110	124	142
W3	18	30	41	52	62	73	85	97	114
W4	19	36	52	67	83	98	114	129	137
W5	18	31	42	51	61	71	79	89	105
W6	39	70	98	127	156	188	215	246	260
W7	19	34	48	64	79	95	111	125	140
Y1	21	40	59	77	96	115	133	152	168
Y2	20	30	43	55	67	82	92	105	121
Y3	24	46	70	89	111	133	155	176	191
Y4	26	50	74	98	122	150	171	194	209
Y5	18	31	42	52	63	73	83	94	110
Y6	19	34	49	64	79	94	109	124	140

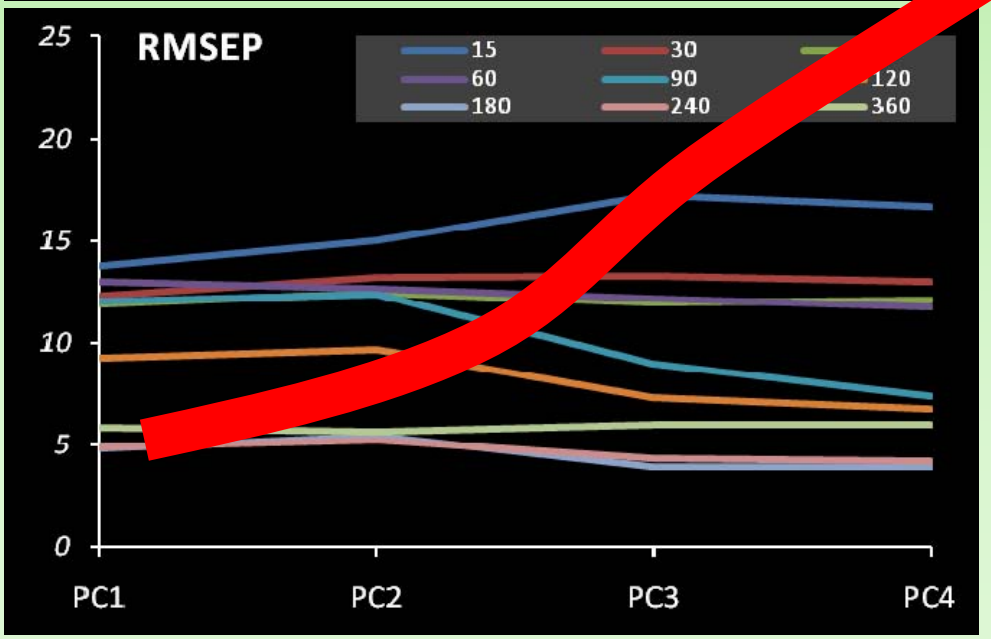
Process time, min

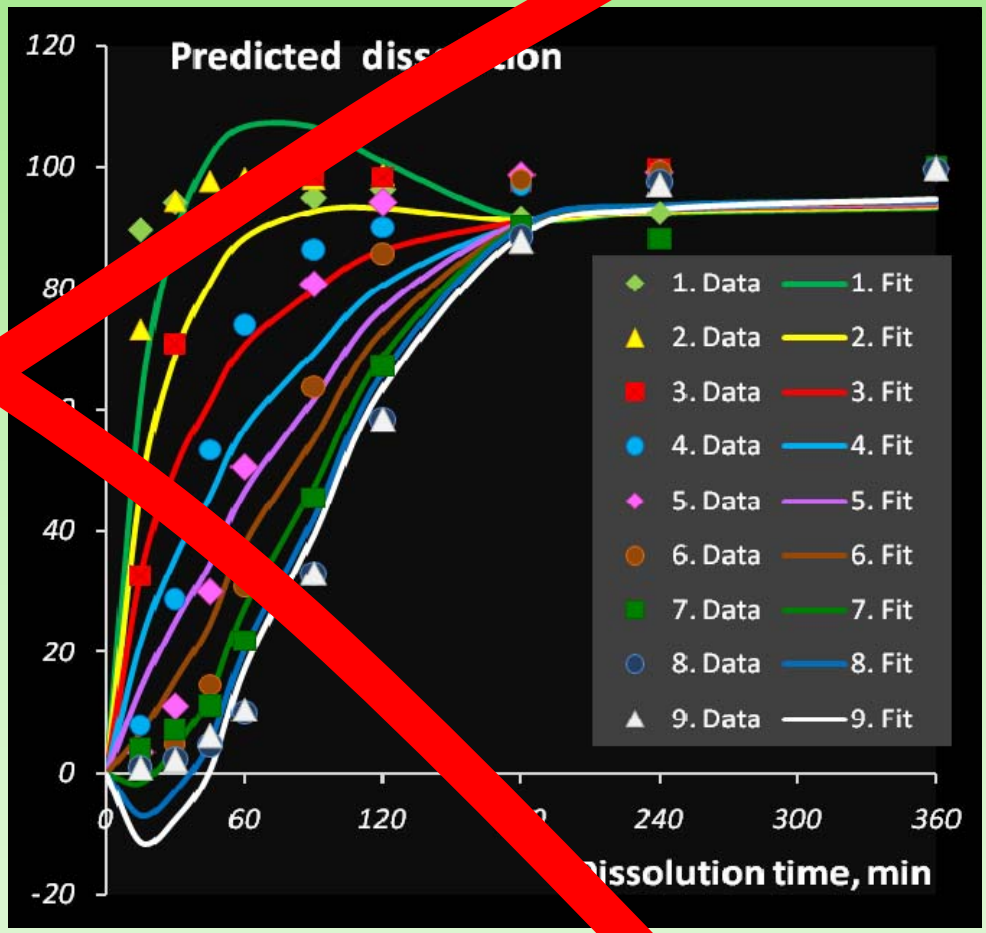
Conventional approach



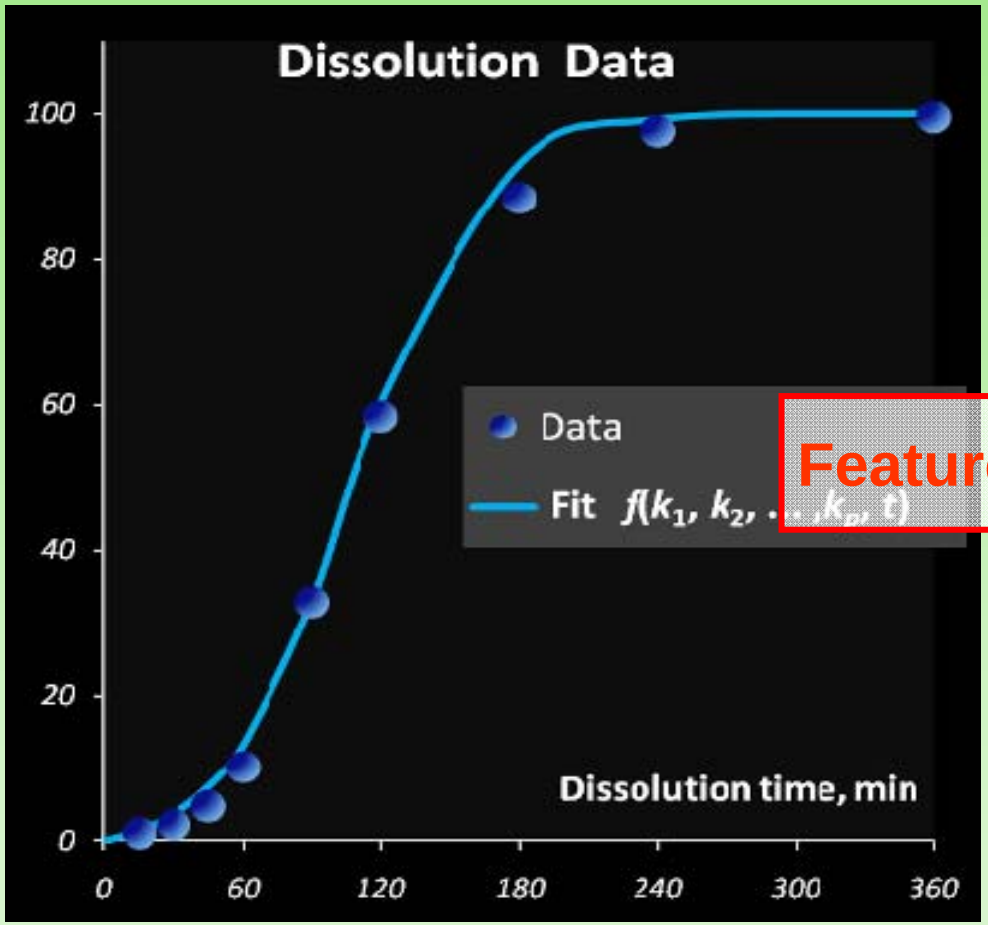
PLS2 results







Kinetic approach



Features extraction

Samples	k_1	k_2	...	k_p
1	3.56	0.10	...	0.33
2	4.03	0.09	...	0.66
3	4.99	0.10	...	0.98
4	6.13	0.15	...	1.28
5	6.84	0.1	...	1.62
6	7.81	0.2	...	1.93
7	8.66	0.30	...	2.23
8	9.49	0.33	...	2.54
9	9.82	0.35	...	2.54

Y

Autocatalysis

$$\varphi(t,m,k) = 100k\,\frac{\exp[(m+k)t]-1}{m+k\exp[(m+k)t]}$$

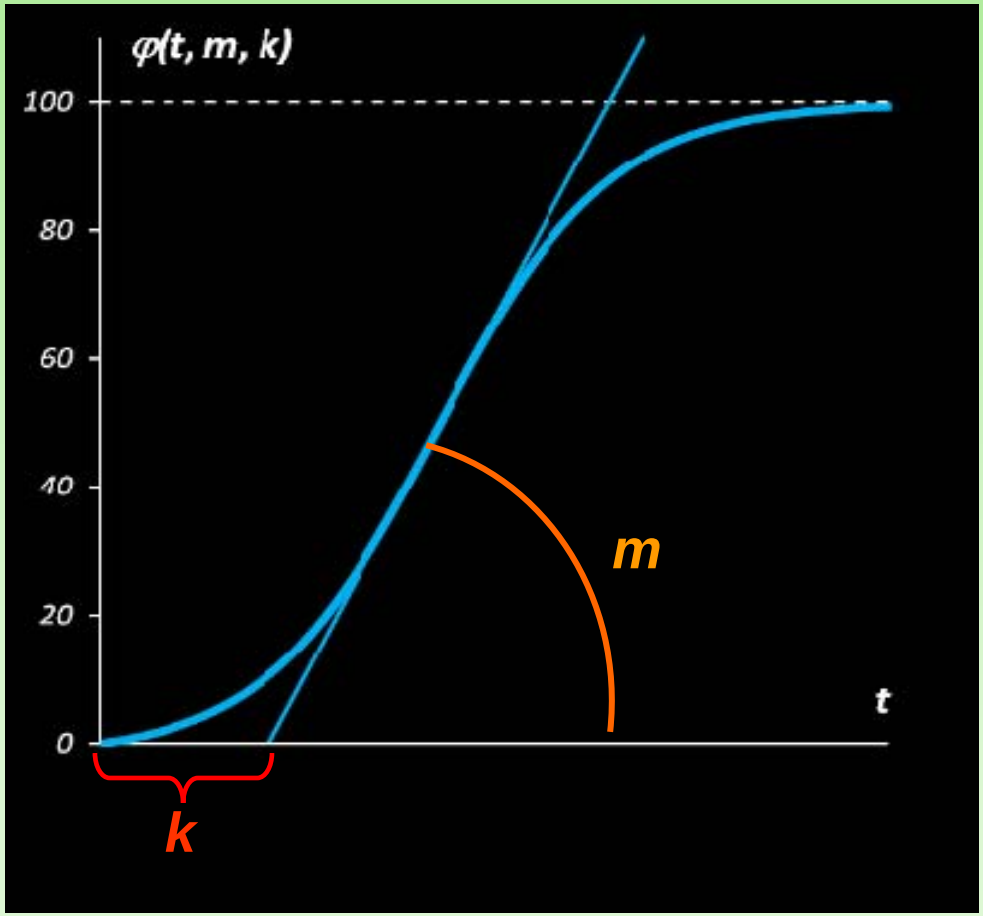
$$\mathrm{A} + \mathrm{B} \xrightarrow{m} 2\mathrm{B}$$

$$\mathrm{A} \xrightarrow{k} \mathrm{B}$$

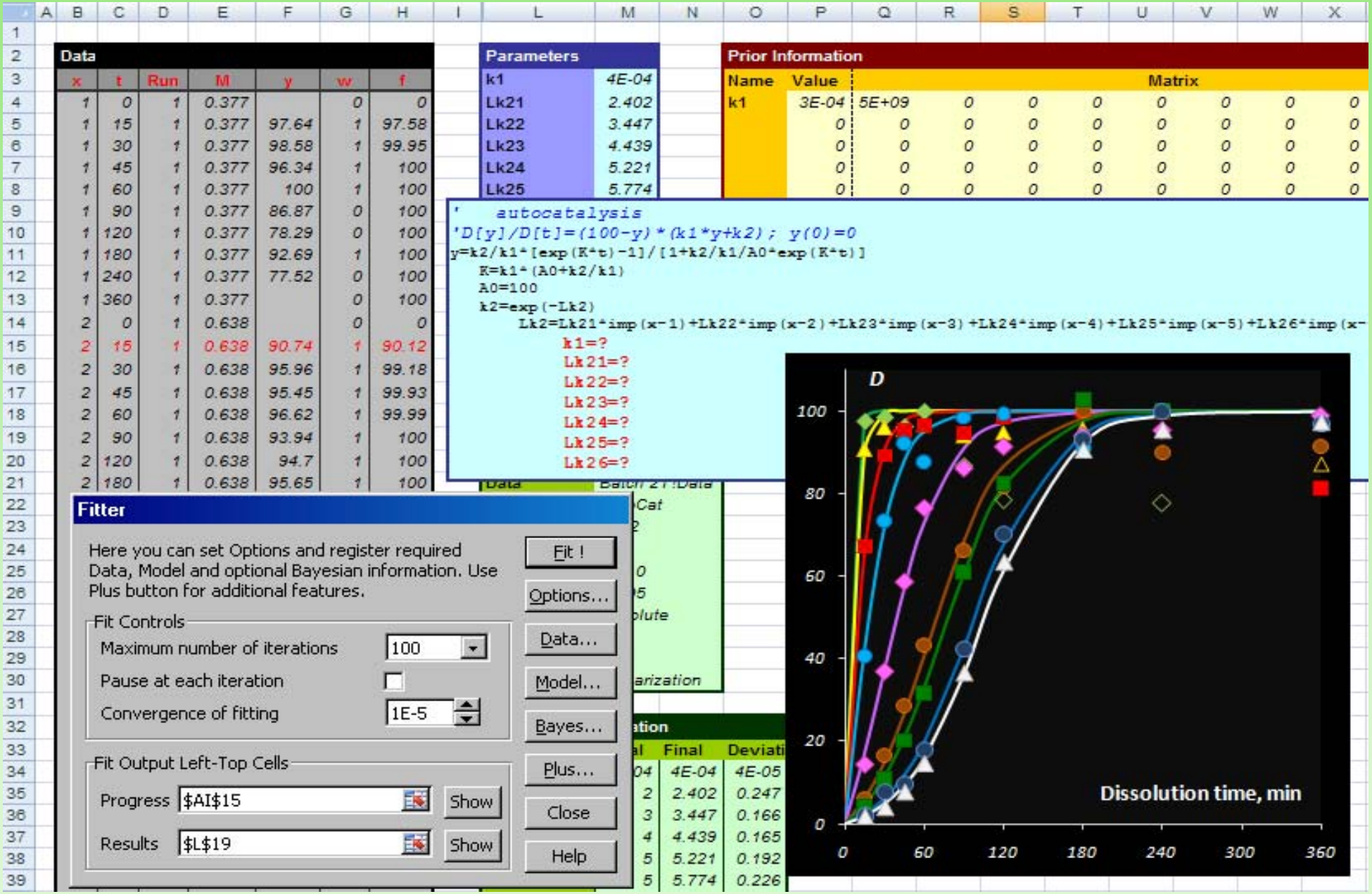
$$[\mathrm{A}]+[\mathrm{B}] = 100$$

$$[\mathrm{B}](0) = 0$$

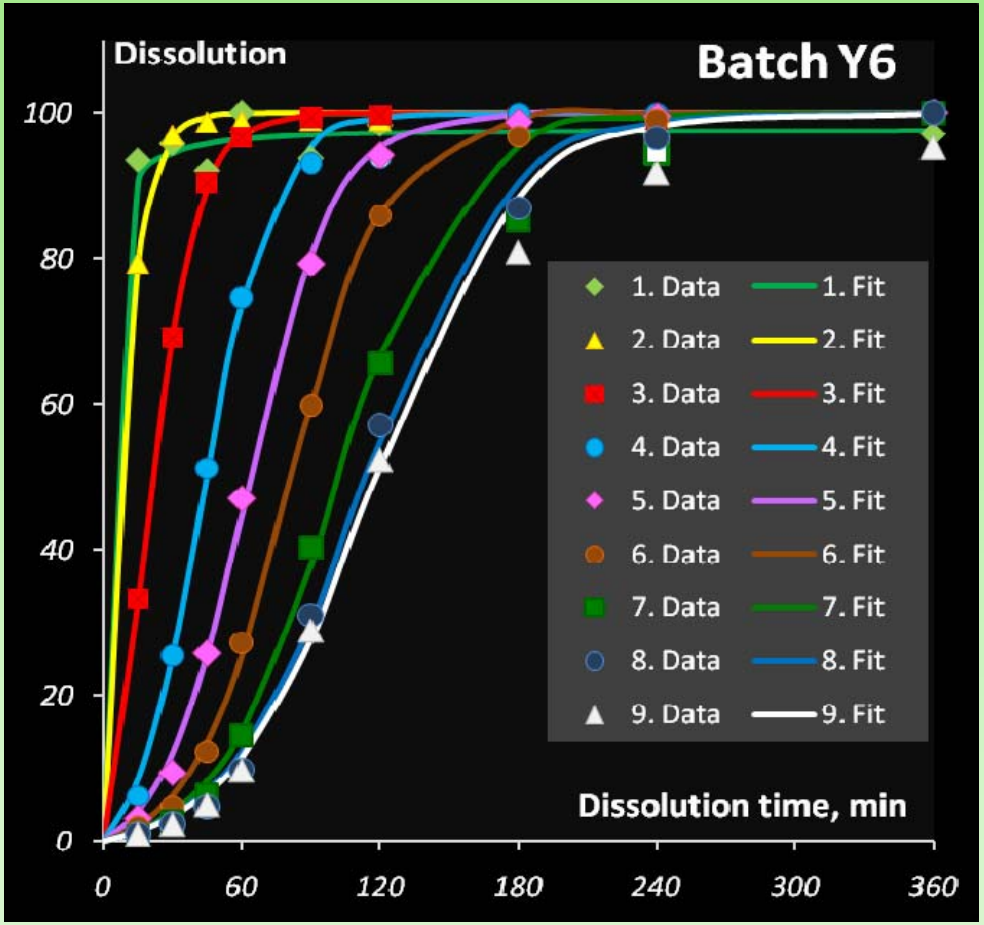
$$\varphi = [\mathrm{B}]$$

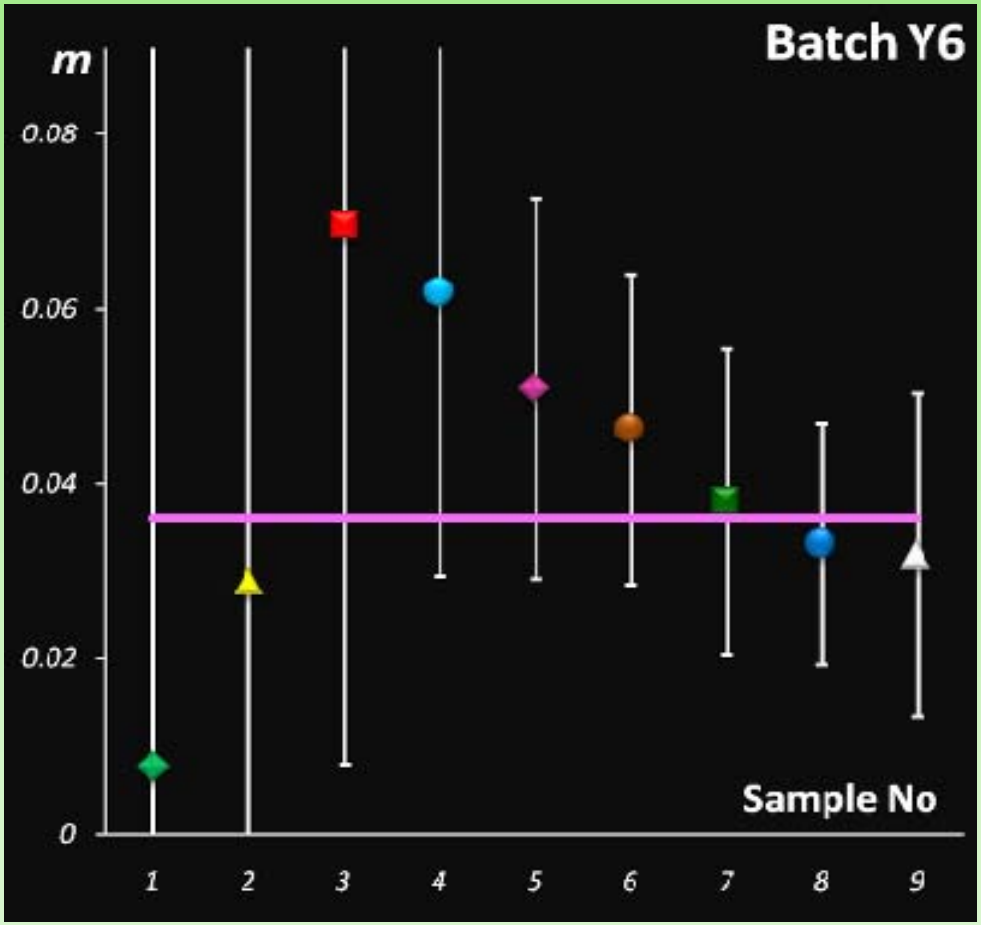


Fitter software

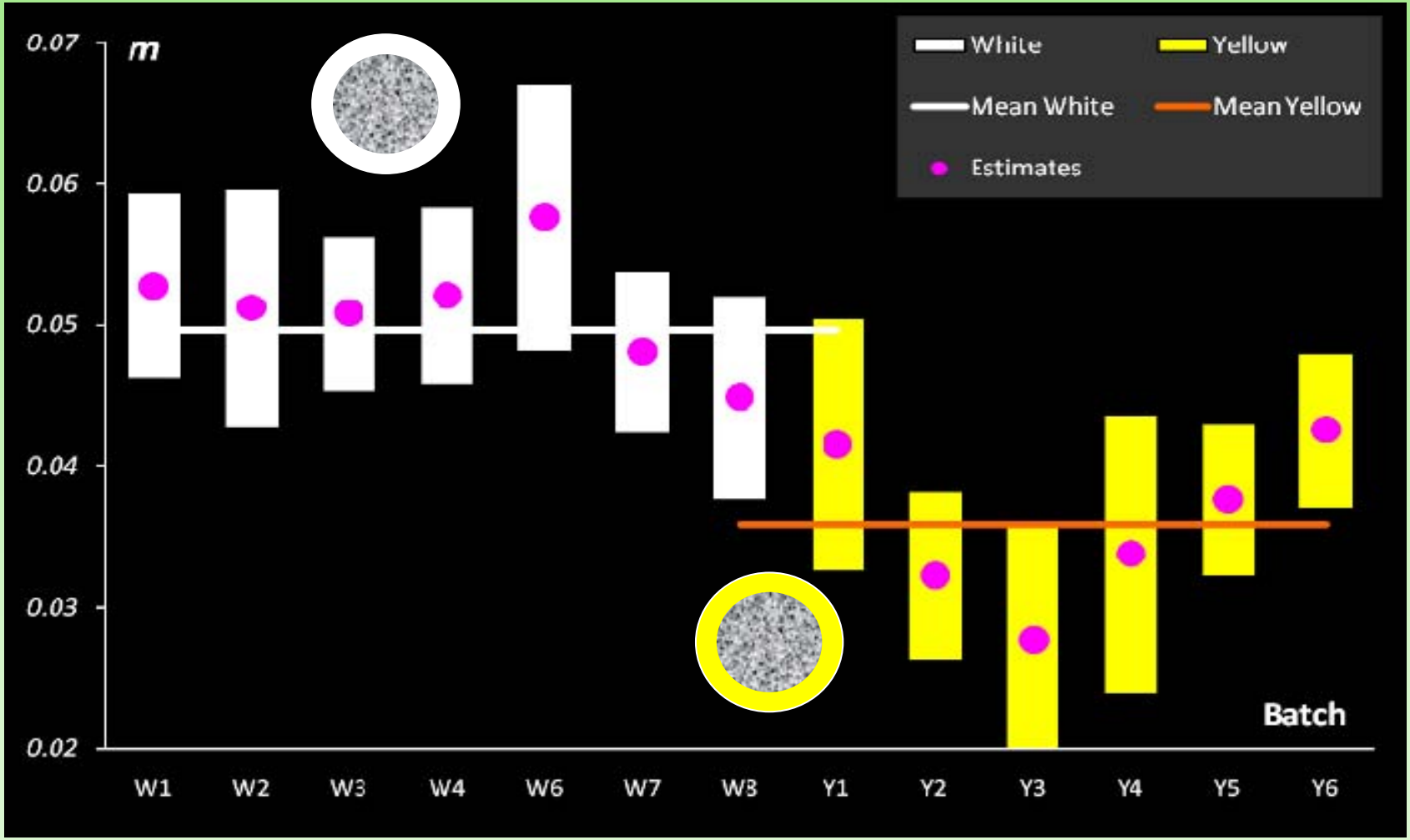


Parameter *m* is common within a batch

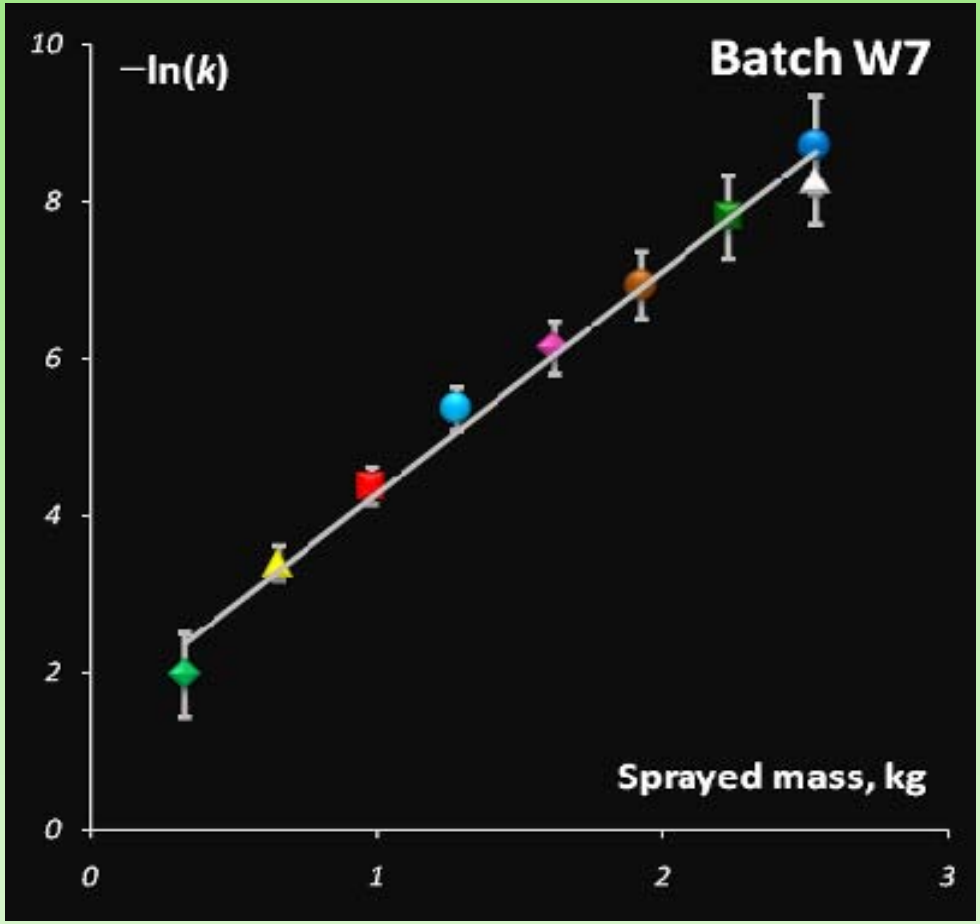


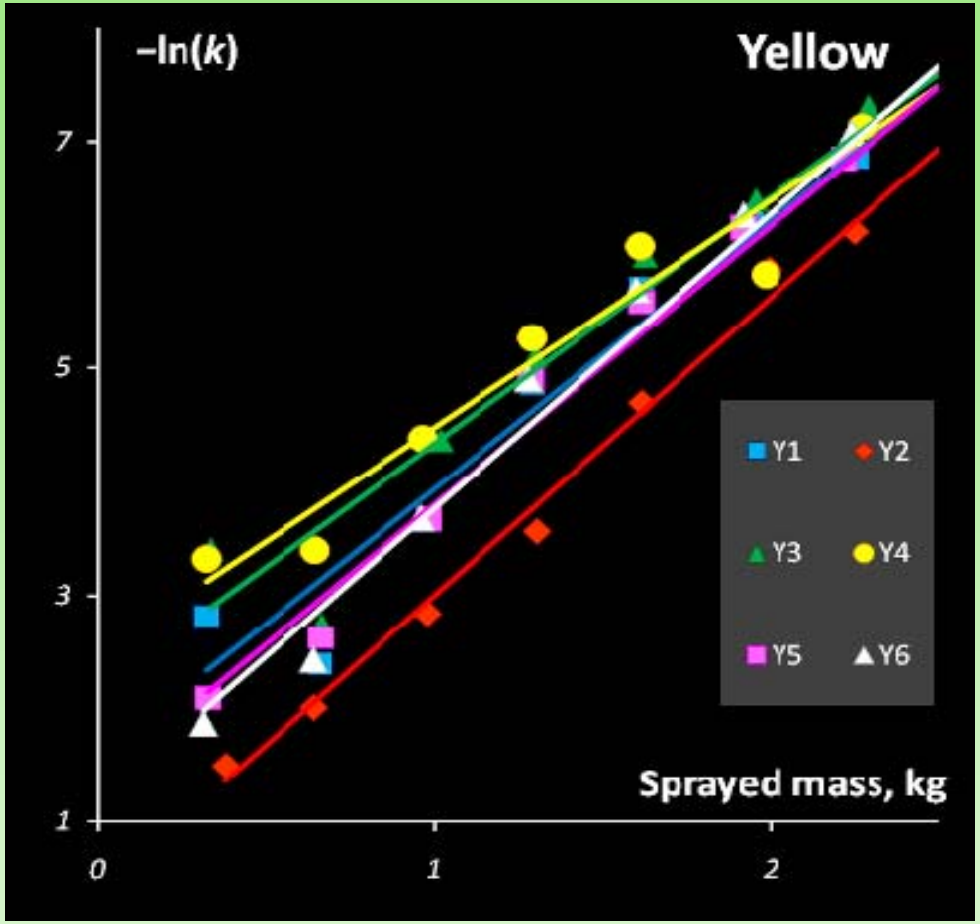


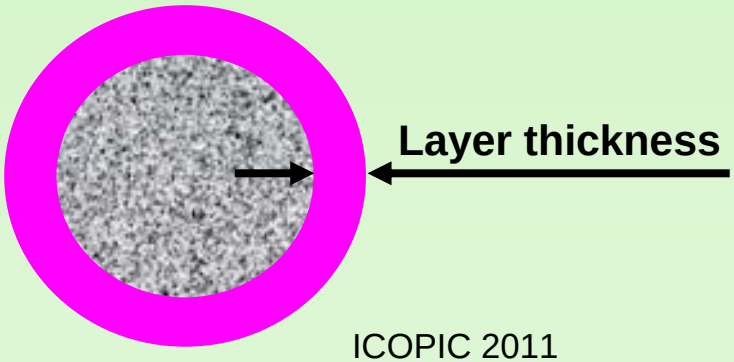
Parameter *m* and the layer grade



Parameter *k* and the layer thickness







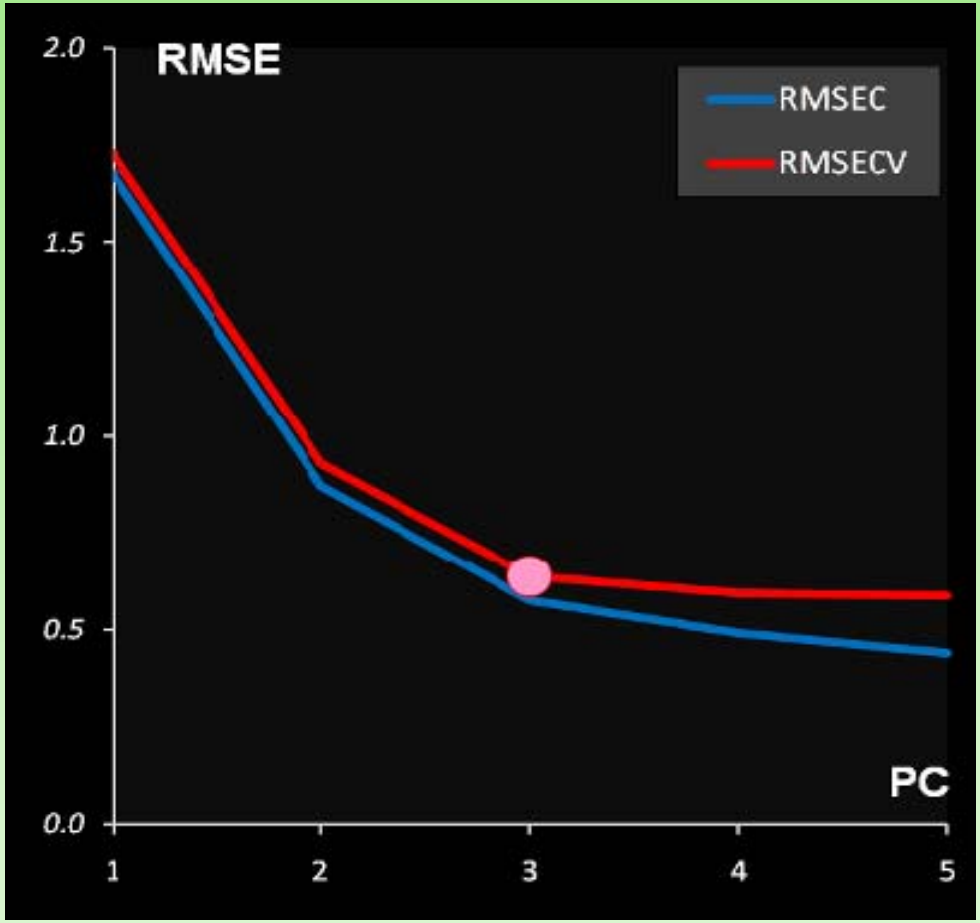
Intermediate conclusions

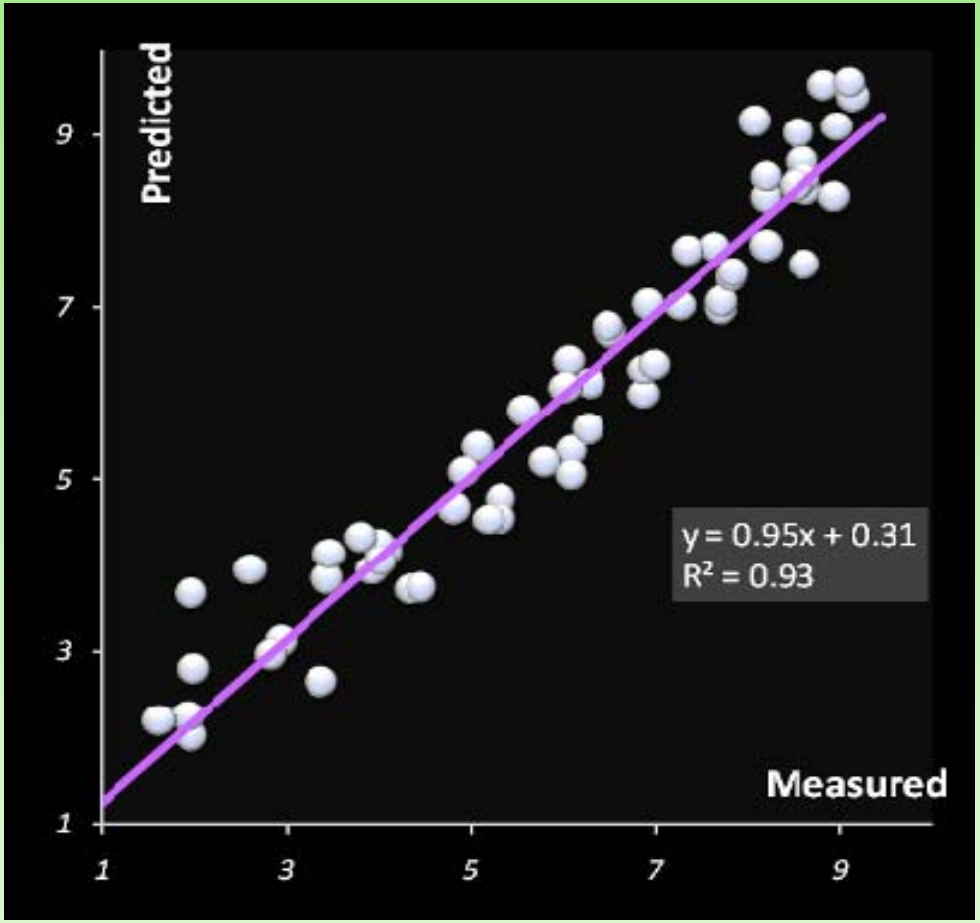
parameter *m*
reflects the material grade

parameter *k*
depends on the layer thickness

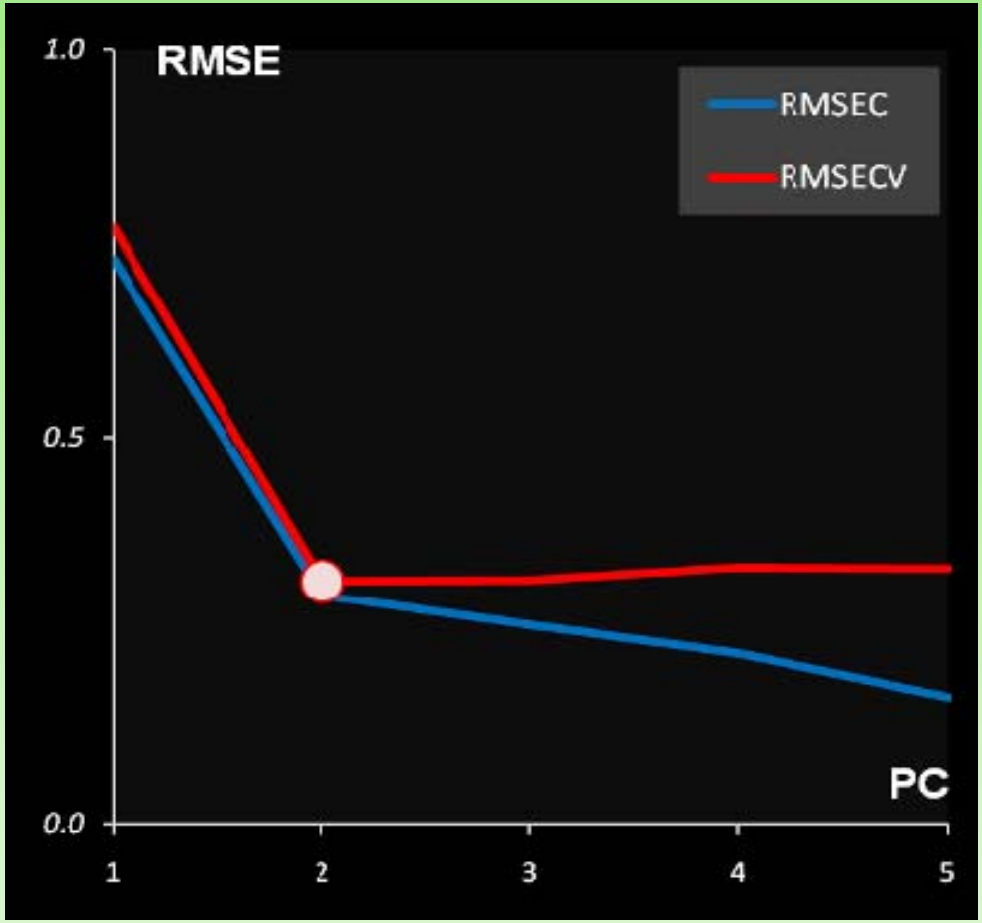
parameter *k*
keeps track of batch variations

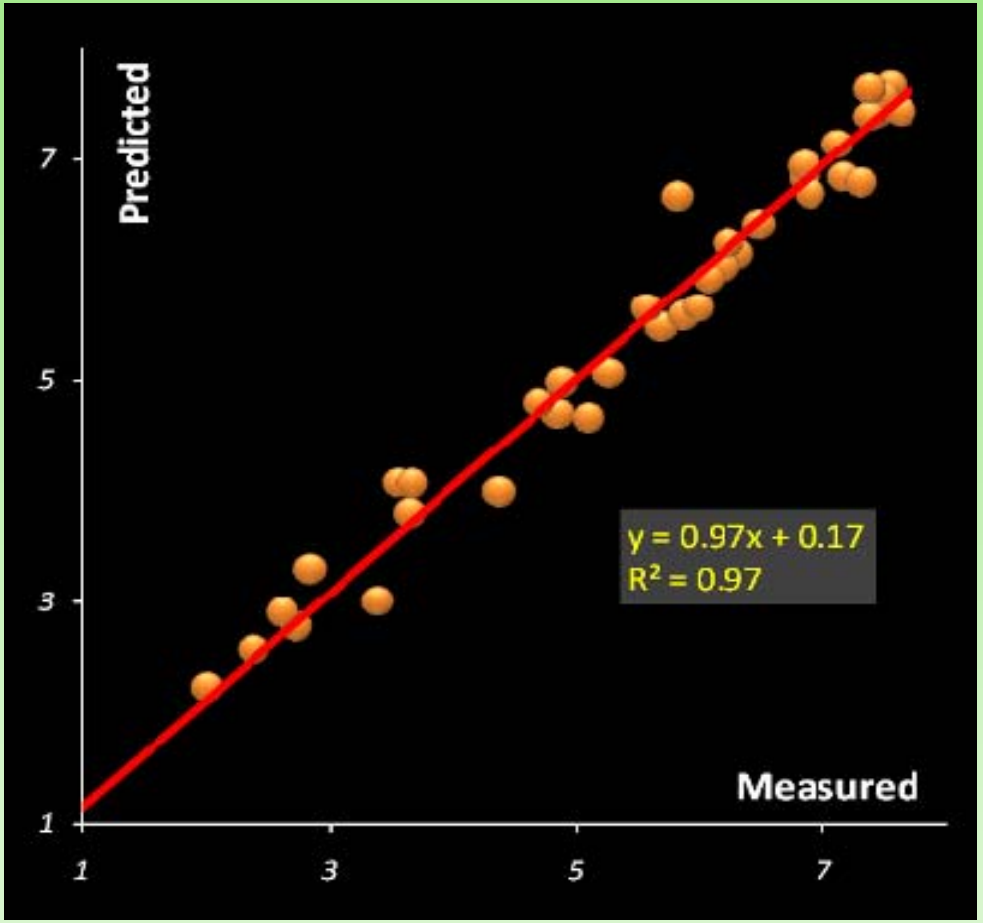
Prediction of *k*: NLR – NIR (White subset)



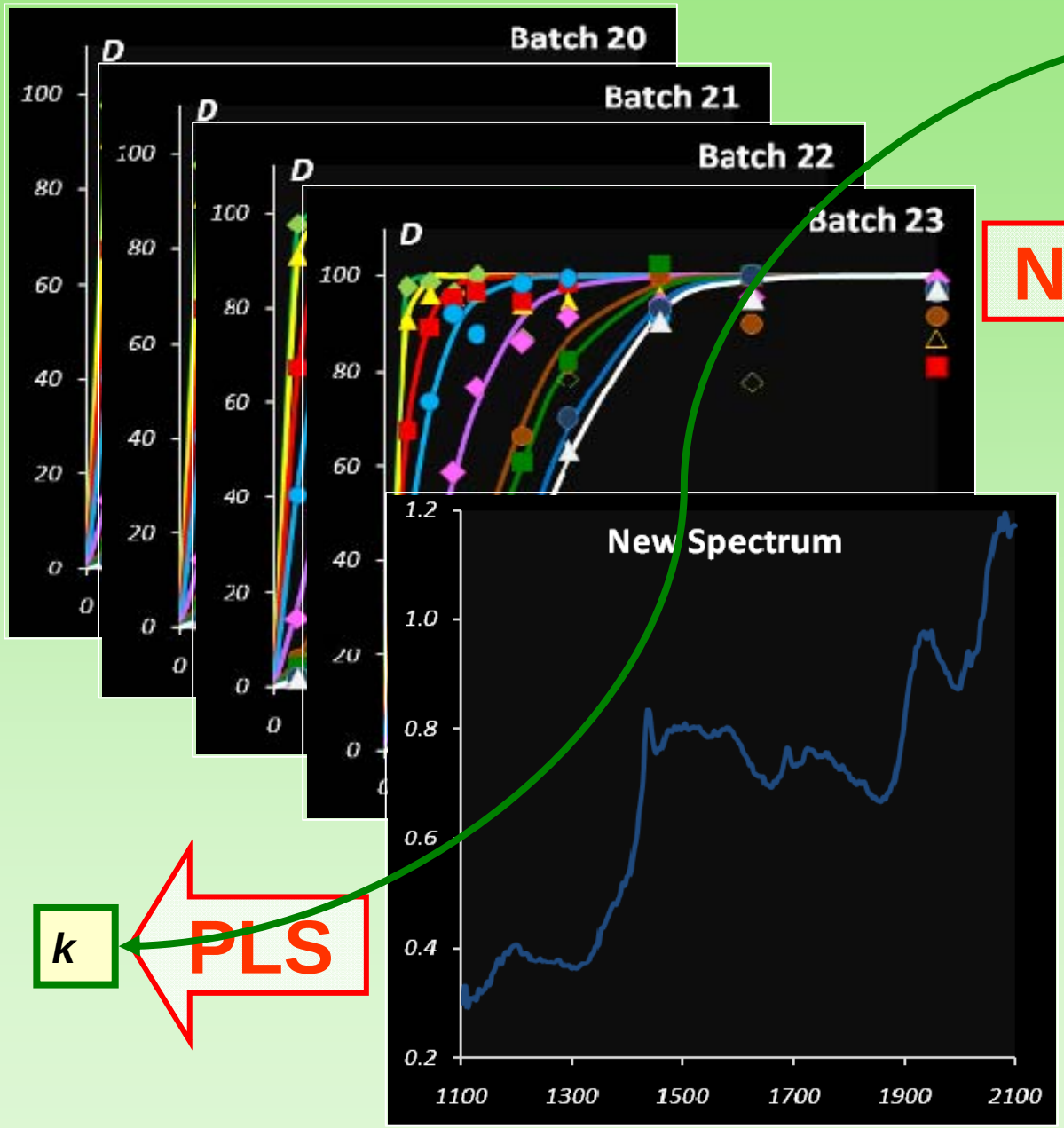


Prediction of *k*: NLR – NIR (Yellow subset)





Prediction technique



k

PLS

NLR

m common for the grade

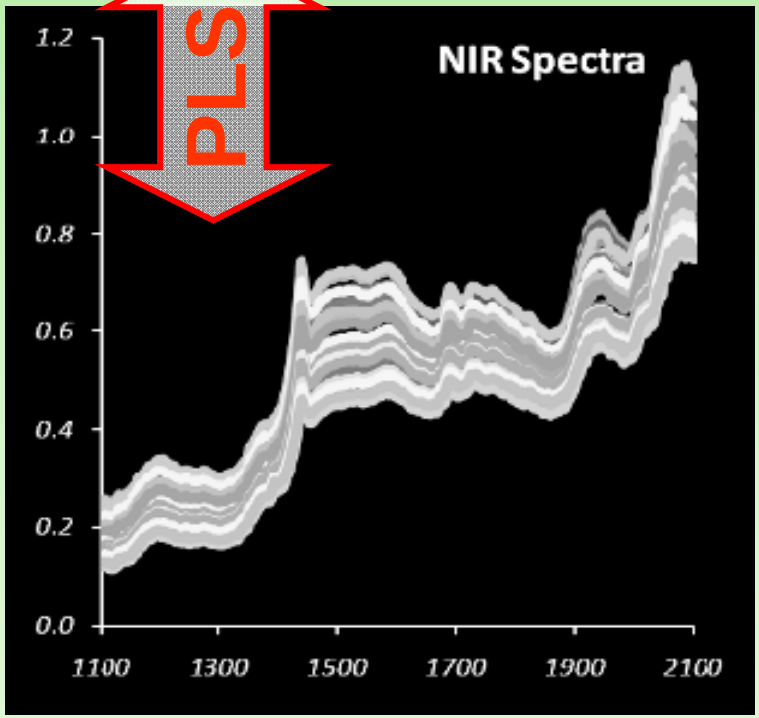
k_{11} , ... , k_{19} : for batch 1

k_{21} , ... , k_{29} : for batch 2

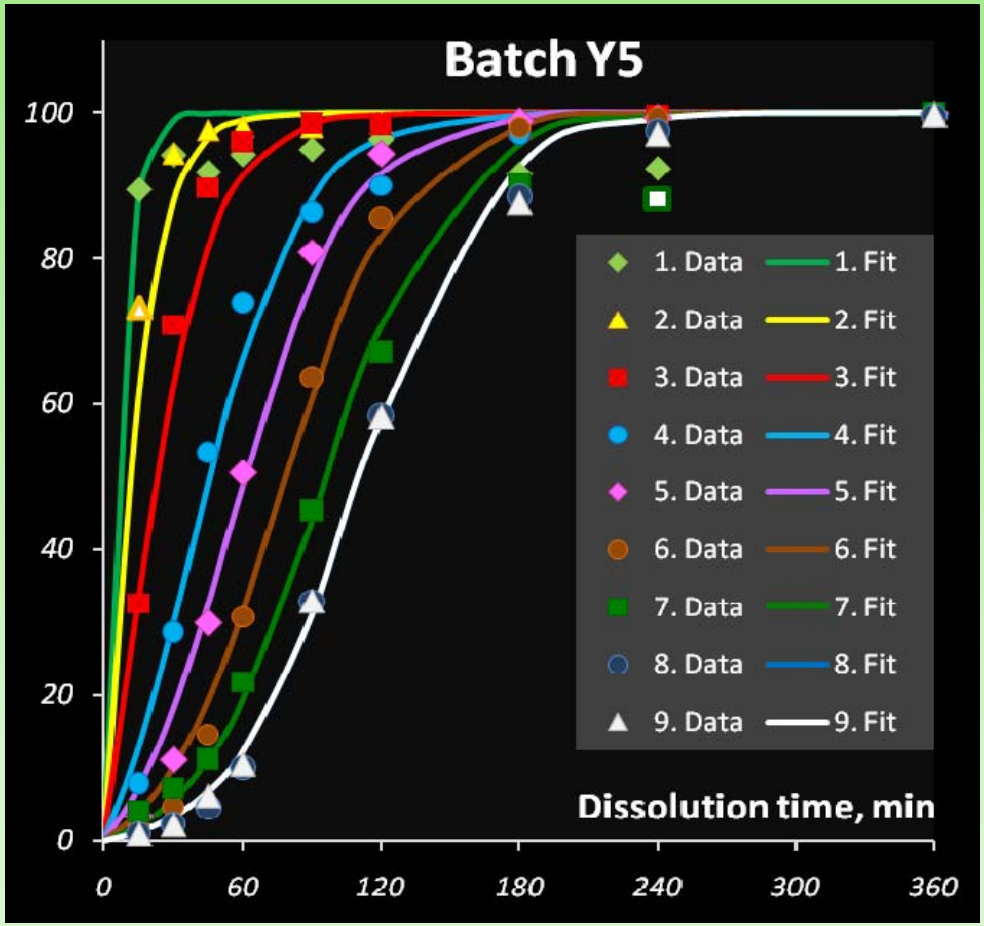
k_{31} , ... , k_{39} : for batch 3

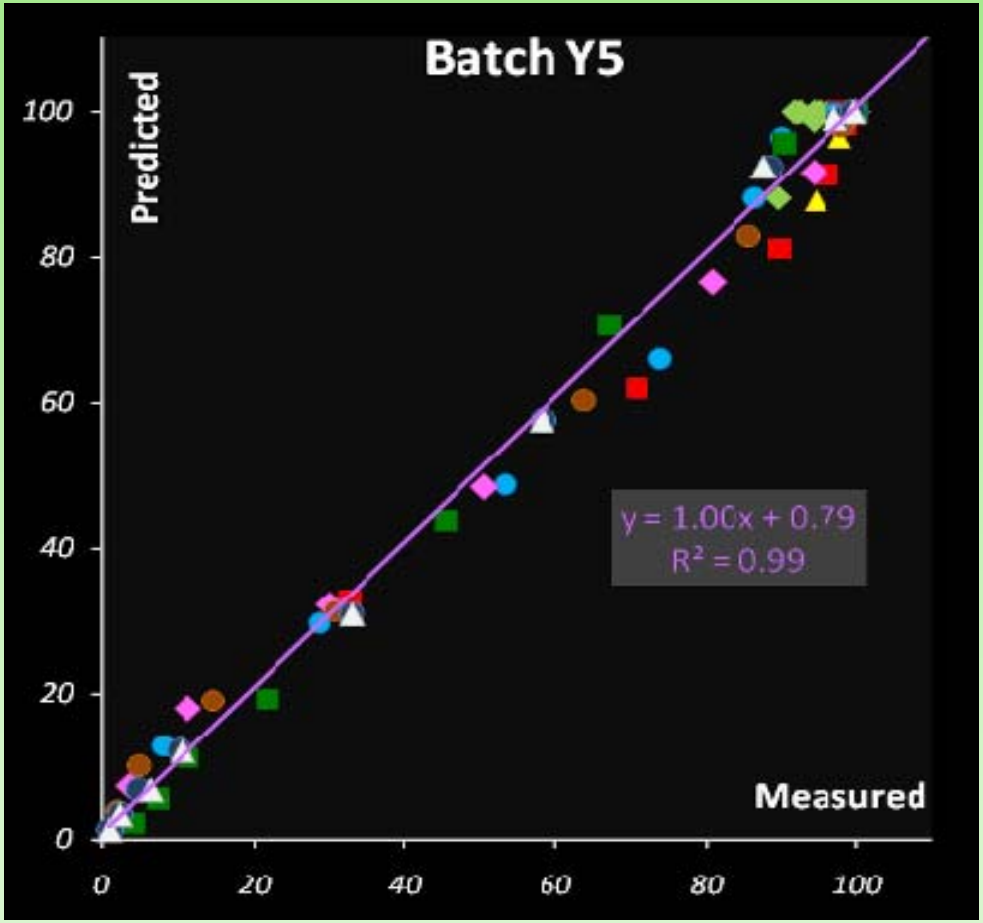
k_{41} , ... , k_{49} : for batch 4

PLS



Test set validation: W2 and Y5 prediction

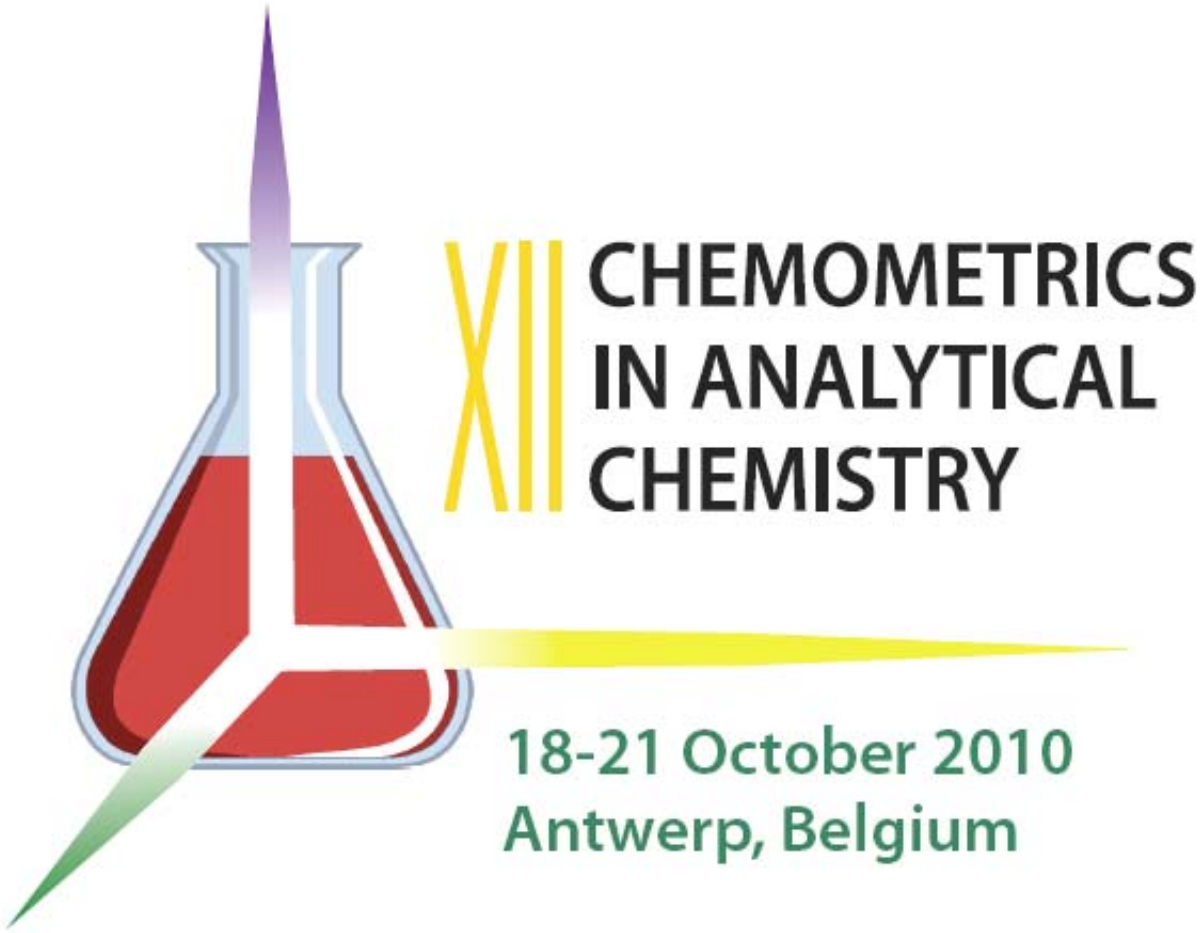




Conclusions

- PAT solution for the in-line release profile prediction
- novel “curve to curve” calibration approach via NLR
- autocatalytic model for the drug release

Details



IN-LINE PREDICTION OF DRUG RELEASE PROFILE FOR pH-SENSITIVE COATED PELLETS

Alexey L. Pomerantsev[1,2], Oxana Ye. Rodionova[1], Michael Melichar[3], Anthony J. Wigmore[3] and Andrey Bogomolov[4]

Case study 3: Outcoming Inspection

To design a quick and simple routine procedure for the in-line inspection of the finished pharmaceutical products

Two years ago: April 2009

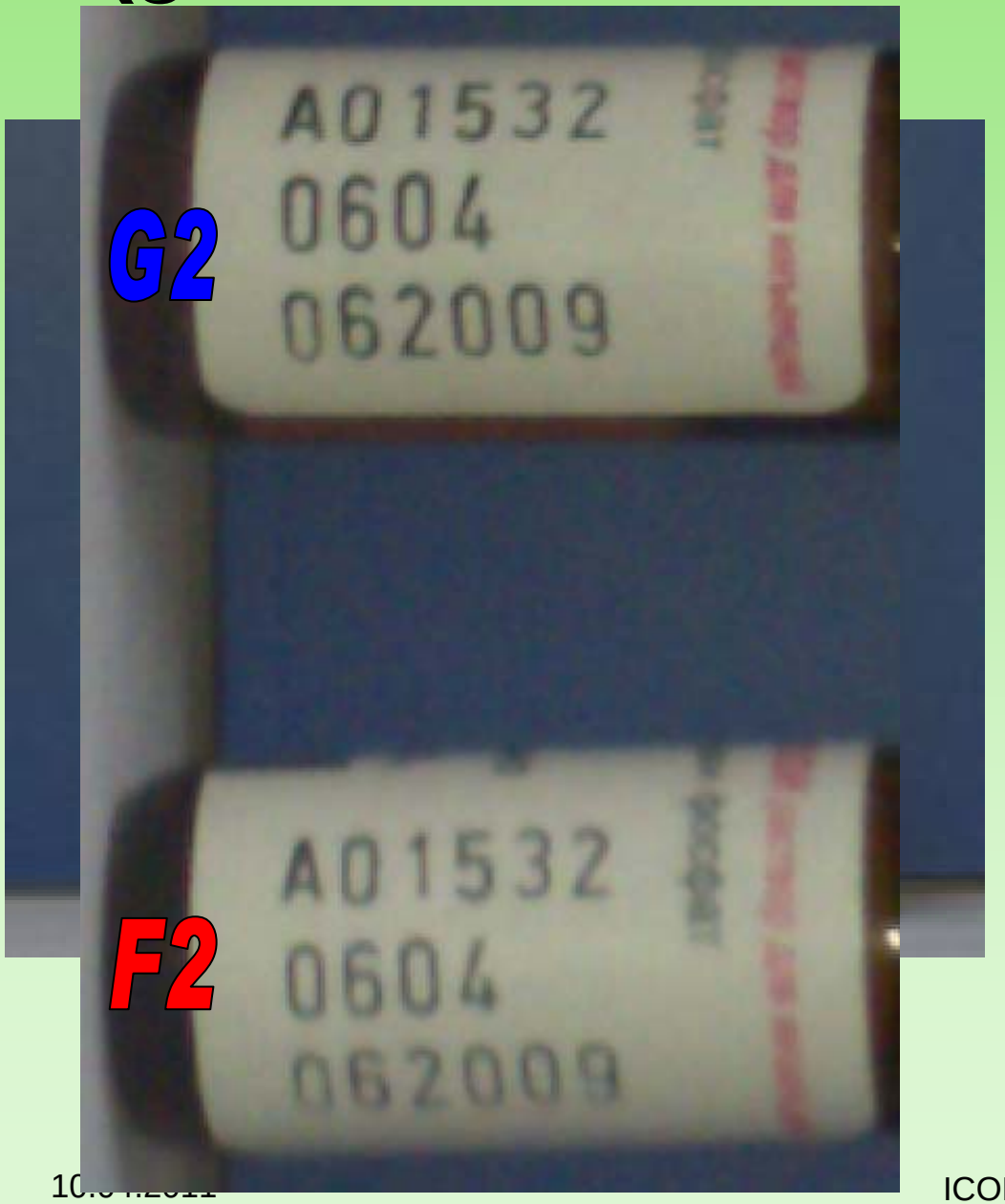
Mildronate

Soft remedy for treatment of the heart and blood vessel diseases

Listenon

Strong drug applied for the muscle relaxation in anesthesia and for intensive care

4% aqueous solution of dexamethasone (glucocorticosteroid remedy)



Genuine objects

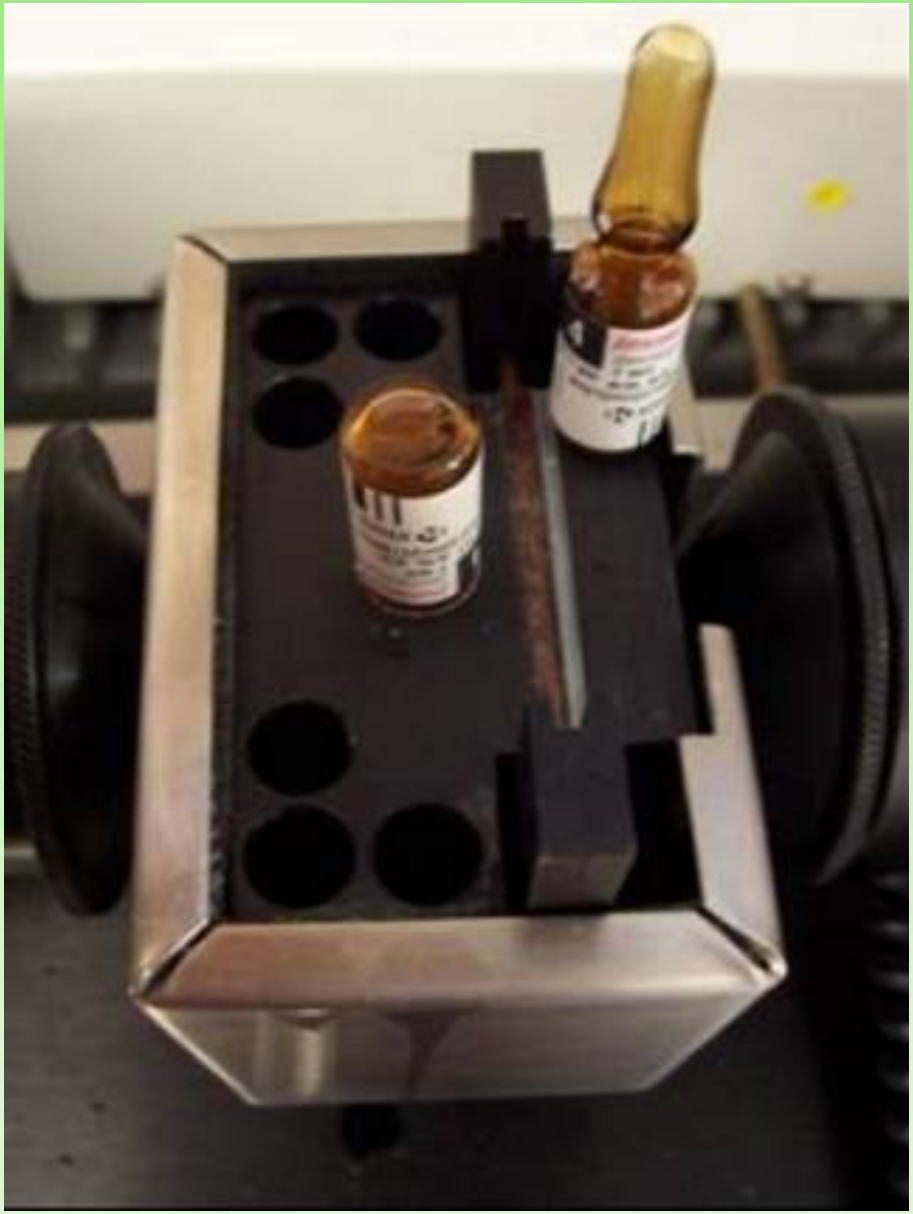
batch **G1**: 15 ampoules

batch **G2** : 15 ampoules

Counterfeit objects

batch **F2**: 15 ampoules

NIR layout



Bomem 160 FT NIR

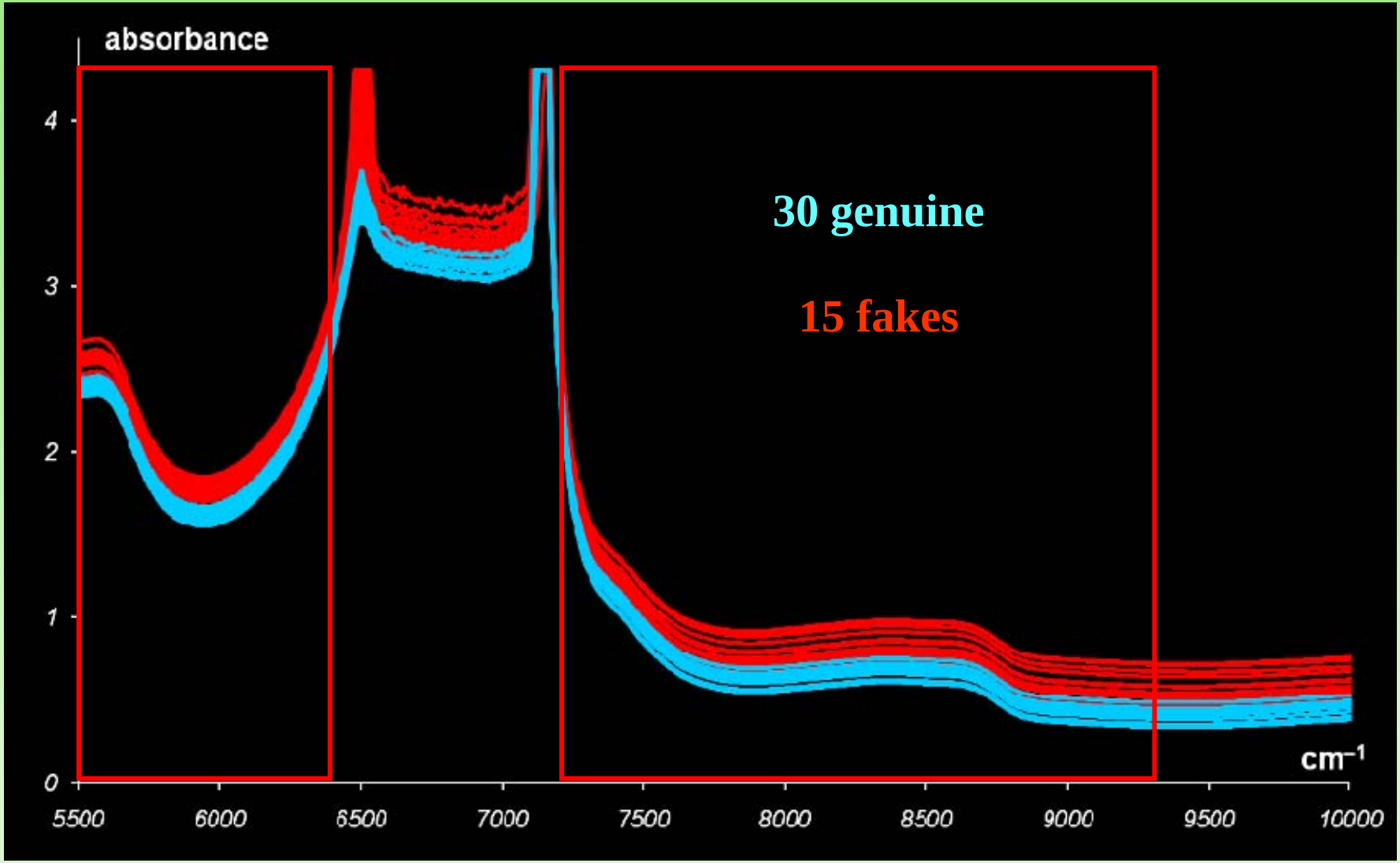
spectral range 5500 - 10000 cm^{-1}

resolution 8 cm^{-1}

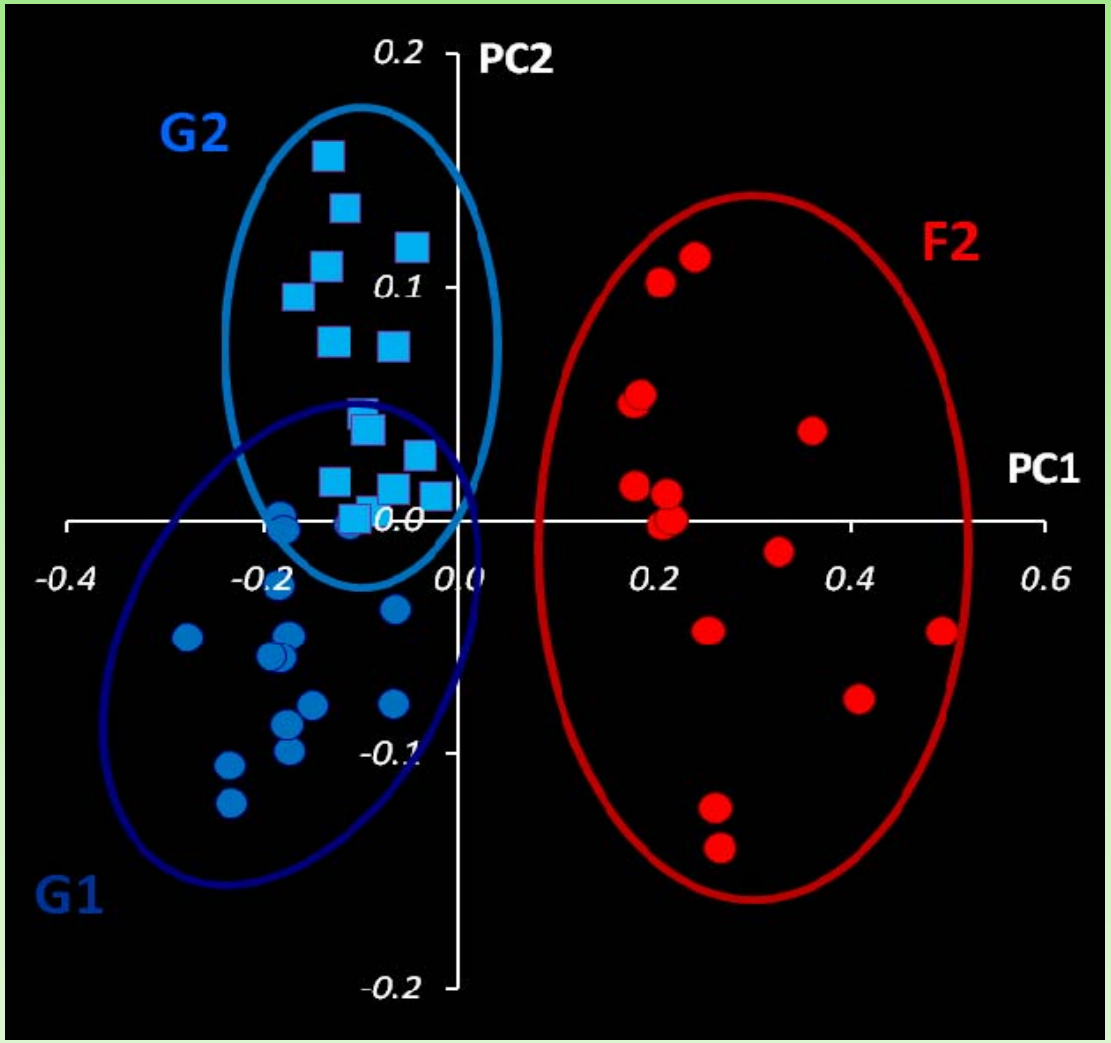
8 mm vial holder

T= 30°C

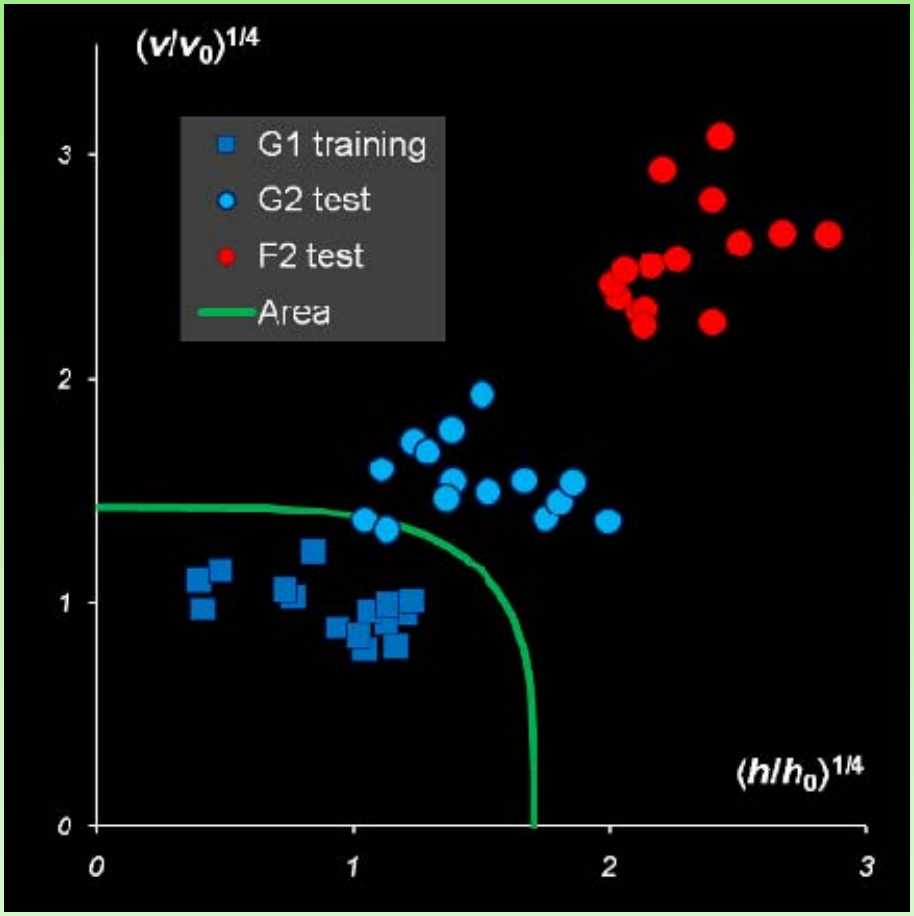
NIR spectra

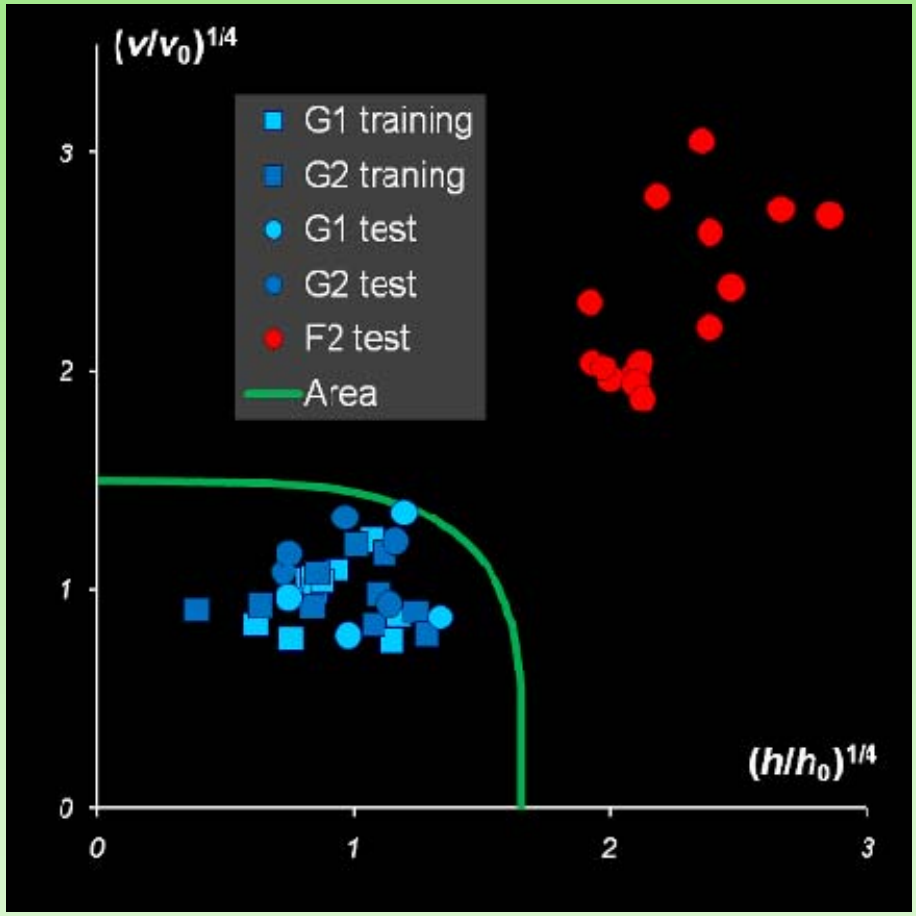

absorbance
4
3
2
1
0
30 genuine
15 fakes
cm⁻¹
5500
6000
6500
7000
7500
8000
8500
9000
9500
10000

PCA analysis



SIMCA classification

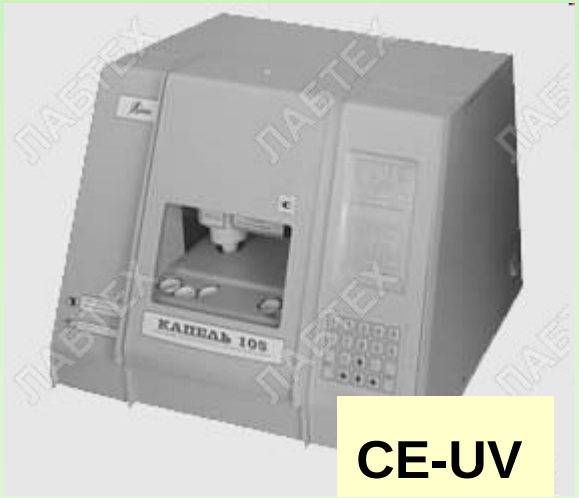


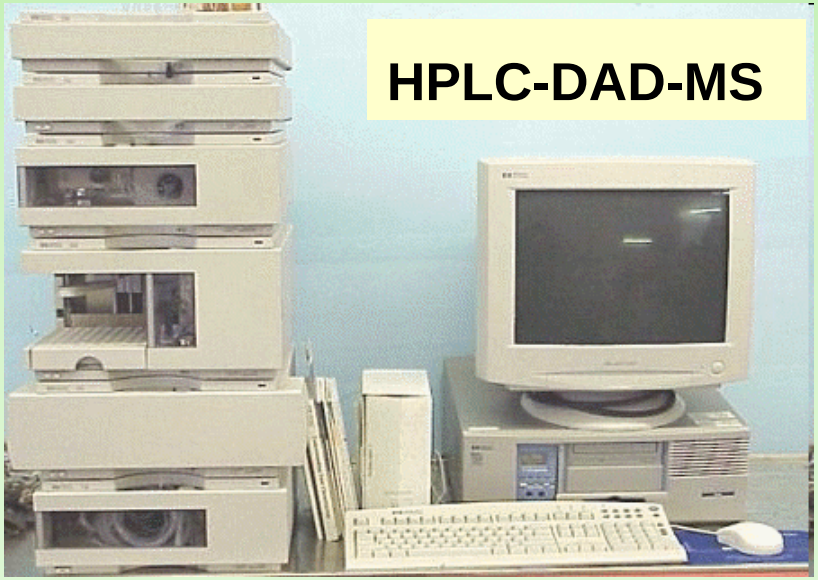


Training set is G1

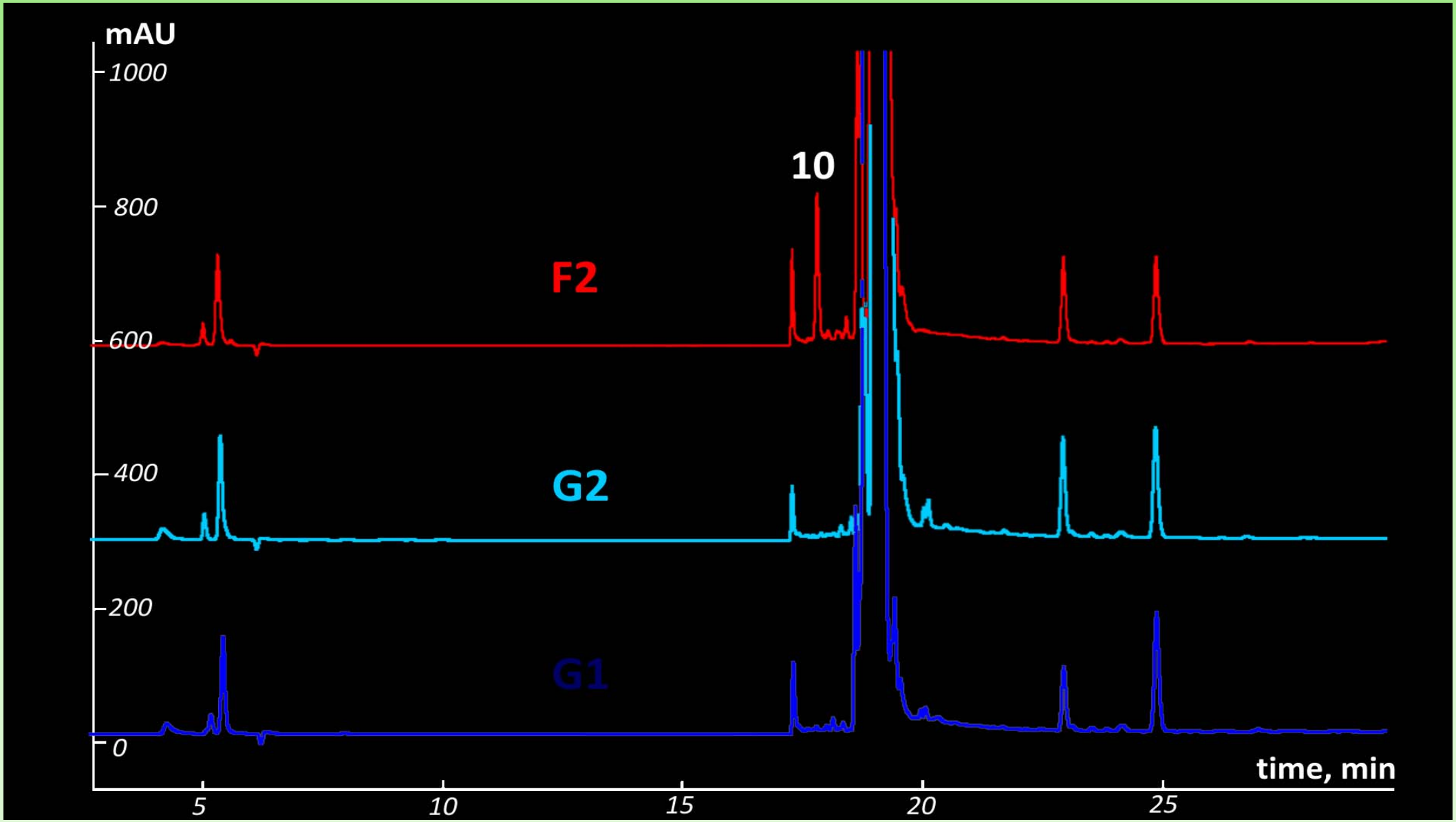
Training set is G1+G2

Wet chemistry analysis



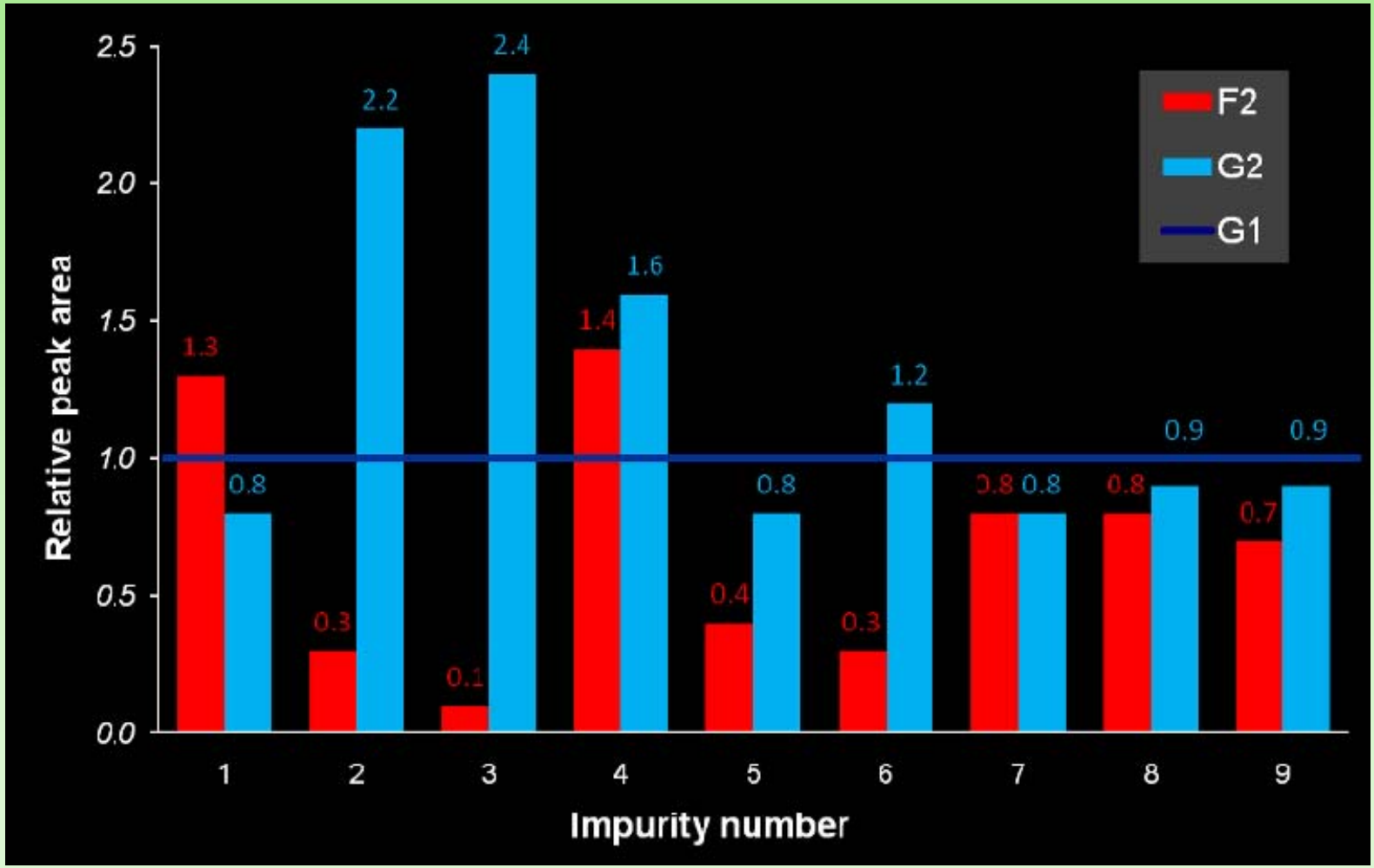


HPLC- DAD Chromatograms λ=254 nm



Peak areas of the common impurities

genuine sample G1 is used as the reference
(HPLC-DAD-UV at λ=254 nm)



Case study conclusions

- We do not check composition, e.g. the API concentration
- Qualitative analysis: yes / no
- 100 % inspection

Details

Anal Bioanal Chem (2010) 397:1927–1935
DOI 10.1007/s00216-010-3711-y

ORIGINAL PAPER

Noninvasive detection of counterfeited ampoules of dexamethasone using NIR with confirmation by HPLC-DAD-MS and CE-UV methods

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Thanks!