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Wallonie

LE FONDS EUROPÉEN DE DÉVELOPPEMENT RÉGIONAL
ET LA WALLONIE INVESTISSENT DANS VOTRE AVENIR

LIÈGE université
Center for Interdisciplinary Research on Medicines
ViBra-Santé Hub

IDENTIFICATION OF FALSIFIED MEDICINES BY HANDHELD RAMAN SPECTROSCOPY AND CLASS MODELING

Conférence CHIMIOMÉTRIE 2019

30 janvier – 1er février

Montpellier SupAgro

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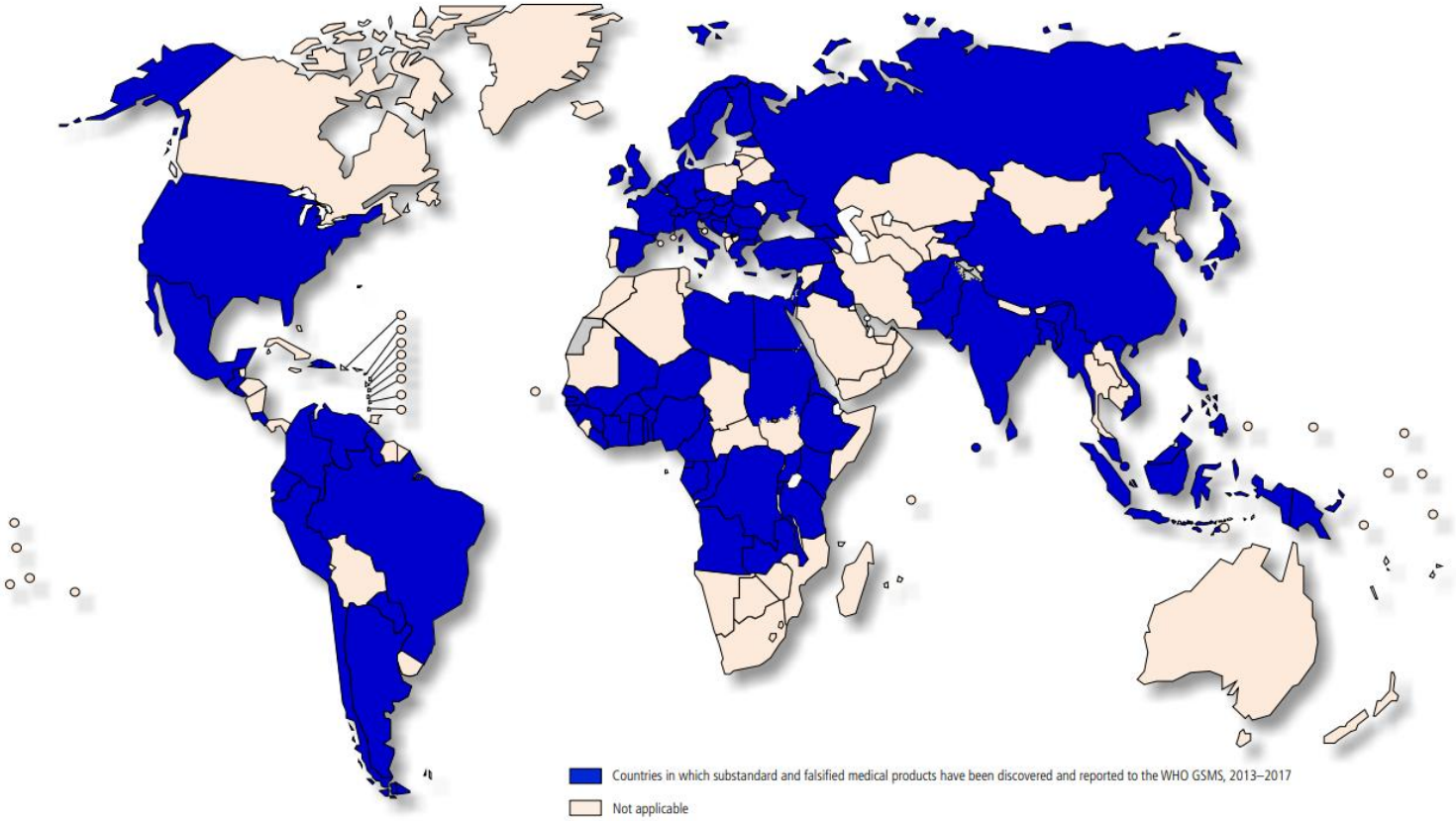
The falsification burden



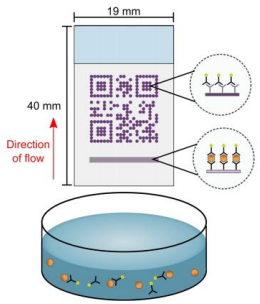
Countries in which substandard and falsified medical products have been discovered and reported to the WHO GSMS, 2013-2017

Not applicable

Source: WHO, 2017. Visualisable in : https://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/

Any solutions ?

- Tools developed last decades
  - Minilab by Global Pharma Health Fund (GPHF)[1]
  - Barcode embedded Rapid Diagnostic Tests[2]
  - Code on medicines boxes to send by SMS (SMS For Life project)[3]



- Is vibrational spectroscopy the solution ?
- Easy to use, green, non destructive, …
- Development of handheld spectrometers

Source : [1] : https://www.gphf.org/en/
[2] : DOI 10.1039_C6LC01580H
[3] : www.who.int/medicines/technical_briefing/tbs/SMSforlifeVanErps.ppt

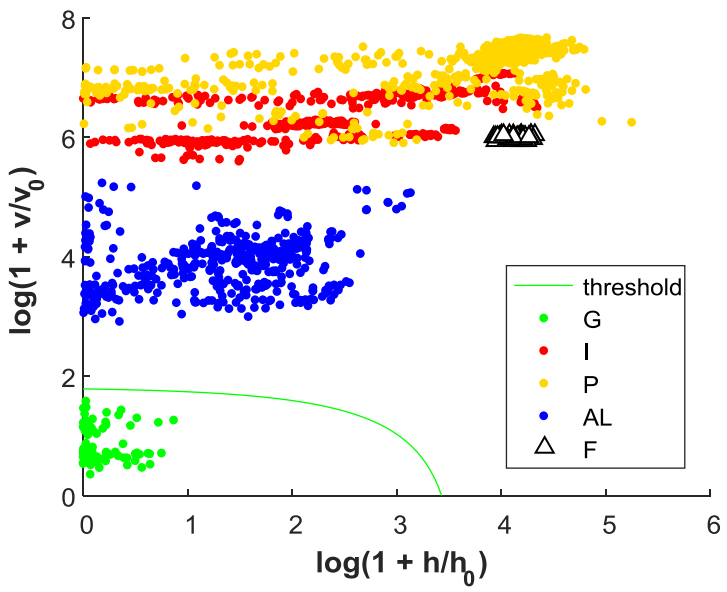
Preliminary analysis

- NIR-S-G1: from Inno-Spectra
  - Reflection mode
  - Wavelength range :900-1700 nm
  - Based on Texas Instrument DLP® technology
  - « Low cost » (~1000€)

    … Do not mean « low quality » !

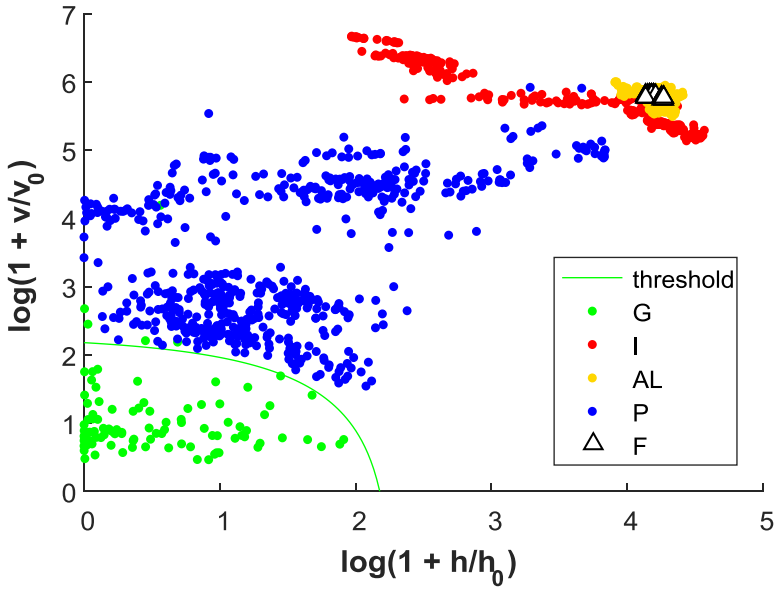
- Comparison between DD-SIMCA and the Hit Quality Index (HQI) for several pharmaceutical formulations

Results for DD-SIMCA for NIR-S-G1



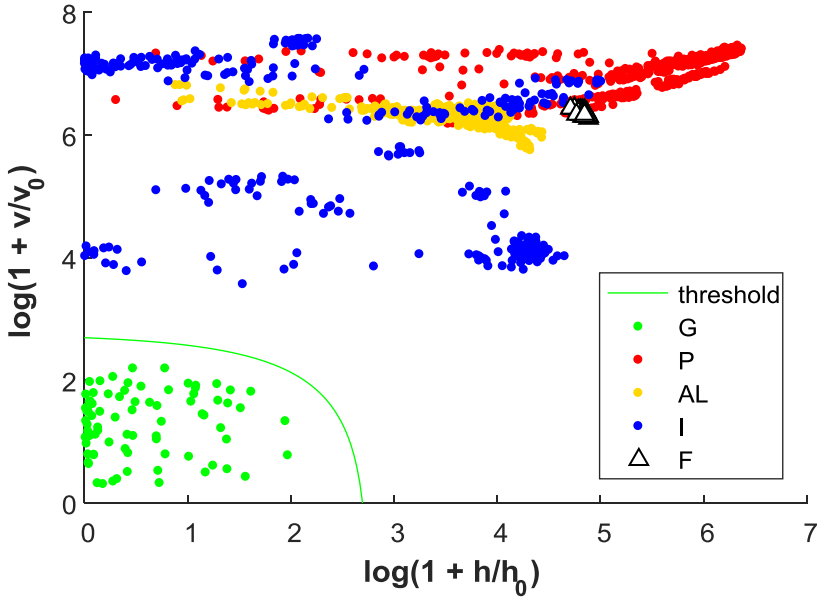
Artemether/Lumefantrine

MCC = 1
HQI = 0.879



Paracetamol

MCC = 0.971
HQI = 0.512



Ibuprofen

MCC = 1
HQI = 0.485

- Why not test it with a Raman handheld spectrometer ?

The choice of medicines

- Ibuprofen
  - Several galenic form available
  - Balanced signal between API/Excipient
- Paracetamol
  - Intense Raman scatterer
  - Several co-formulations available
- Artemether/lumefantrine
  - Intense Raman scatterer (lumefantrine)
  - Co-formulation with a weak Raman scatterer compound
  - Highly falsified medicines

API	Brand	Dosage	Batch	Galenic form	Spectra
Ibuprofen	15	4	48	3	480
Paracetamol	24	11	63	4	690
Artemether/lumefantrine	26	4	60	2	540

Data Driven-Soft Independent Modeling Class Analogy (DD-SIMCA)

- Based on Principal Component Analysis (PCA)
- A modified version of the original SIMCA one-class classifier
  - Allows to calculate the error of misclassification theoretically
- Optimisation of the parameters
  - The acceptance area : type I error α
  - Number of principal component

$c \leq c_{crit}$

$$c_{crit} = \chi^{-2}(1 - \alpha, N_h + N_v)$$

- Results
  - Orthogonal distance (OD)
  - Score distance (SD)
  - Extrem objects

One Class-Partial-Least Square (OC-PLS)

- Model built as a special PLS :
  - b_{PLS} : regression of 1 on K primary latent variables (LVs)
  - Computation of T^2 and T^2_{UCL} (upper confidence limit (UCL))
  - Computation of the centered model residual (ACR) with

$$1 = Xb_{PLS} + e$$

$$|e_{centered}|_{UCL} = Z_{\alpha/2} . \sigma_e$$

$$T^2 = \sum_{i=1}^{K} \frac{(t_{i,j} - t)_i^2}{s^2_{t,i}}$$

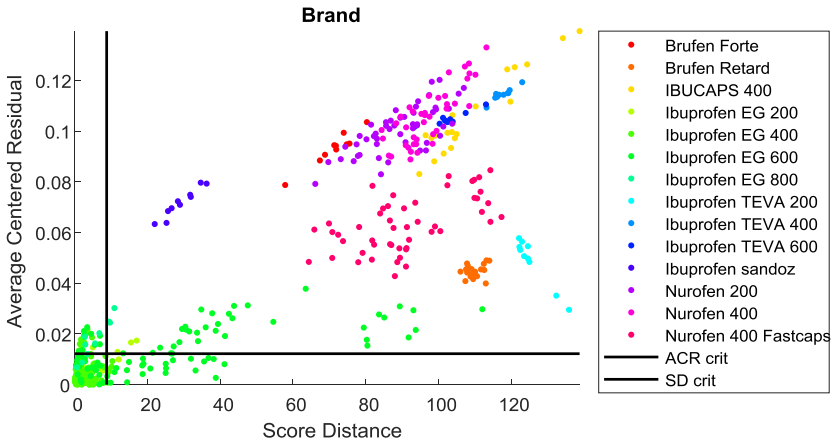
- Results :
  - Score distance (SD)
  - Absolute centered residual (ACR)
  - Extrem objects

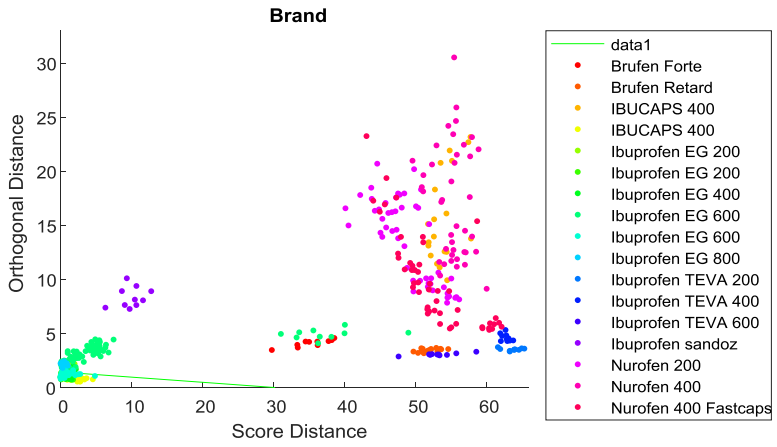
Matthews correlation coefficient (MCC)

- Independent from the size of the different class
- More confidence test to evalute the quality of the classification

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(FP + FN)(TN + FP)(TN + FN)}}$$

	Positive condition	Negative condition
Predicted positive condition	True positive (TP) Power	False positive (FP) Type I error
Predicted negative condition	False negative (FN) Type II error	True negative (TN)





COMPARISON BETWEEN THE TWO CLASS-MODELING TECHNIQUES

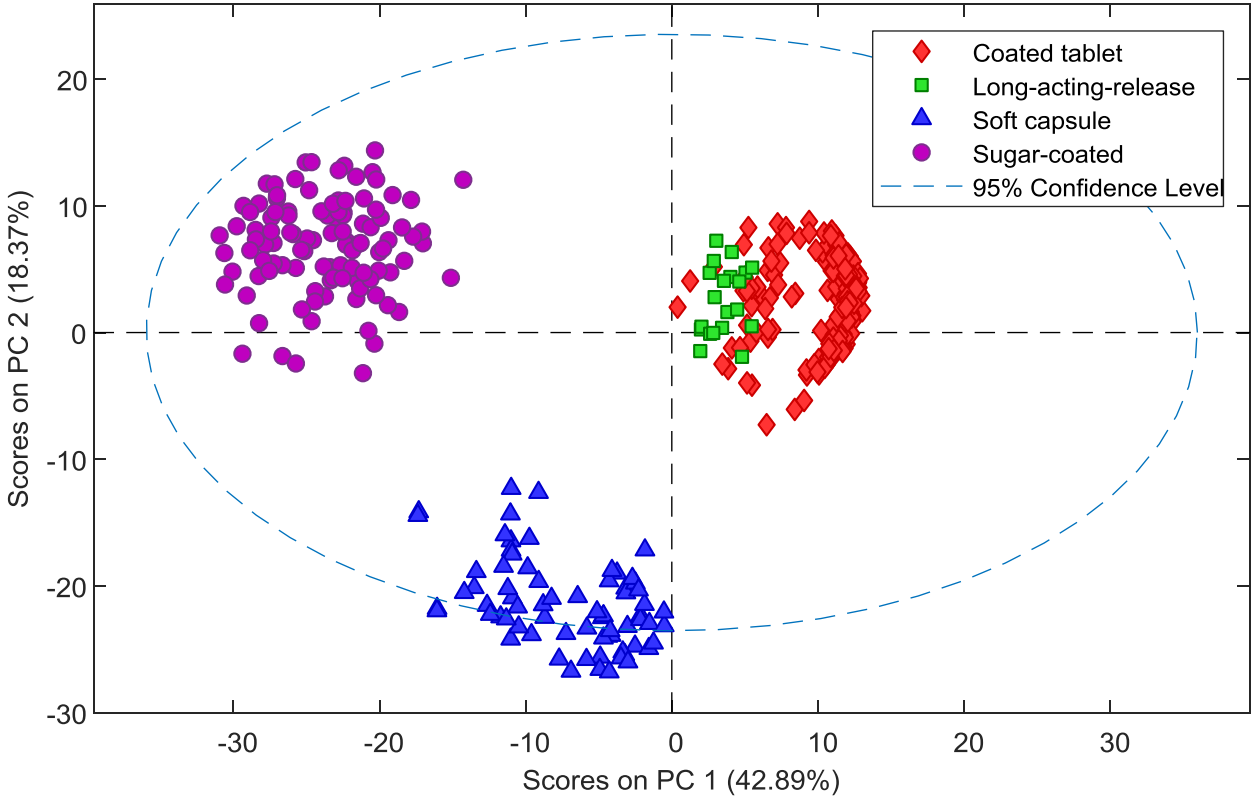
Ibuprofen

Paracetamol

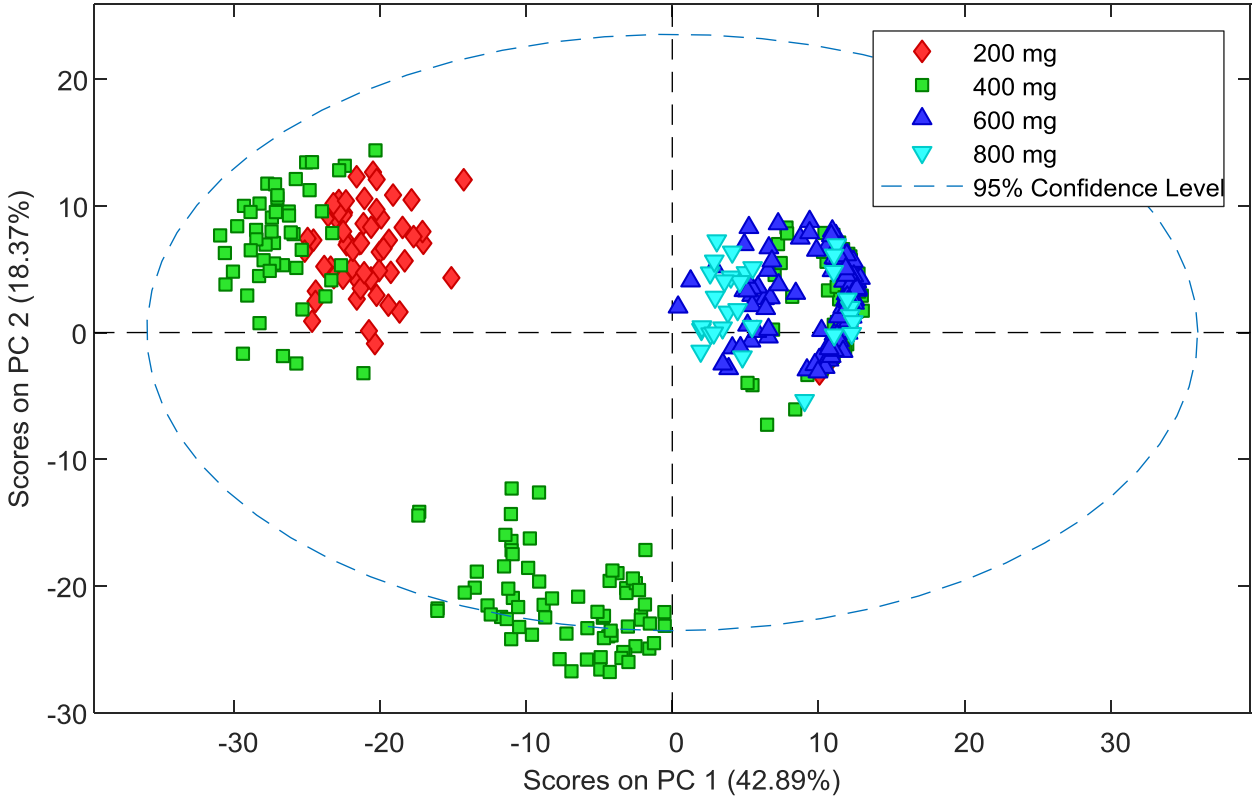
Artemether/Lumefantrine

Preliminary analysis : PCA on ibuprofen

Galenic form

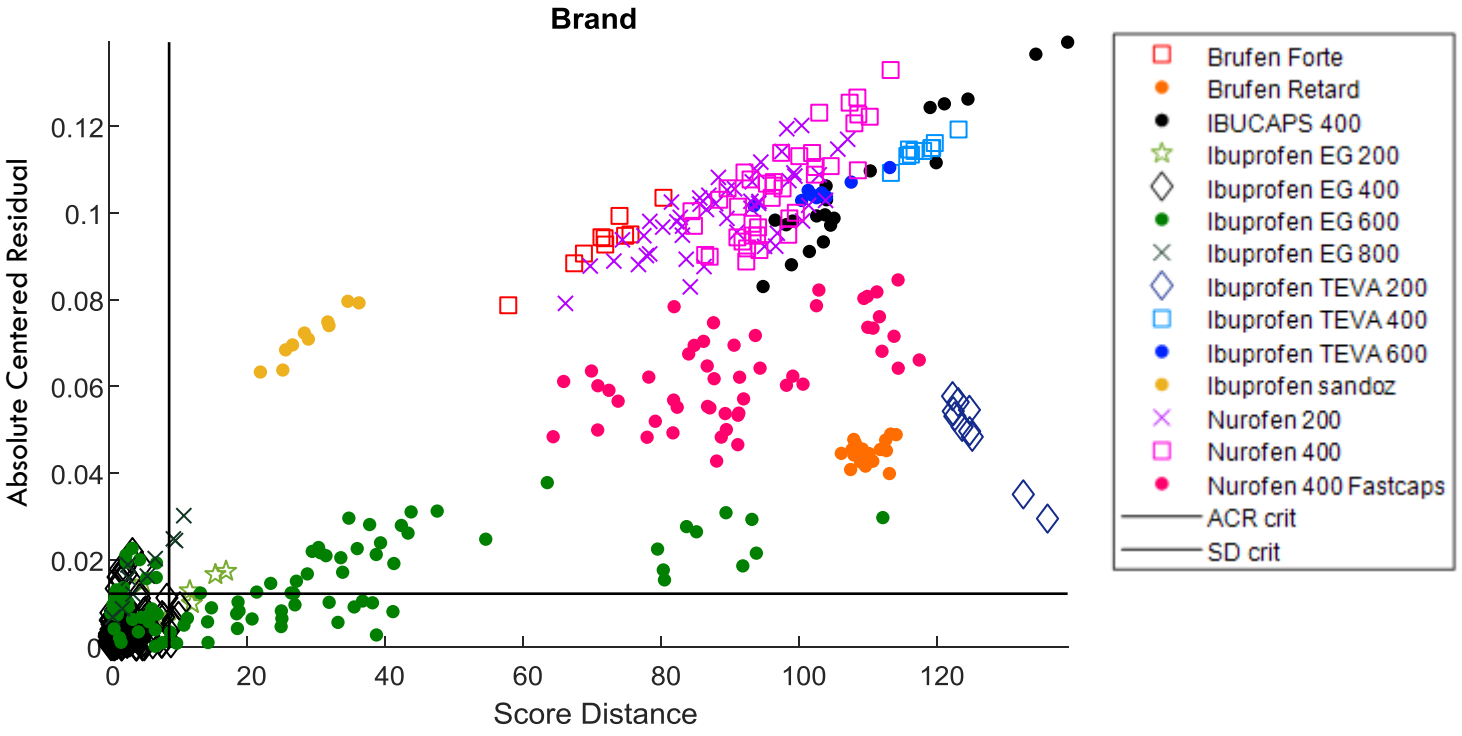


Dosage

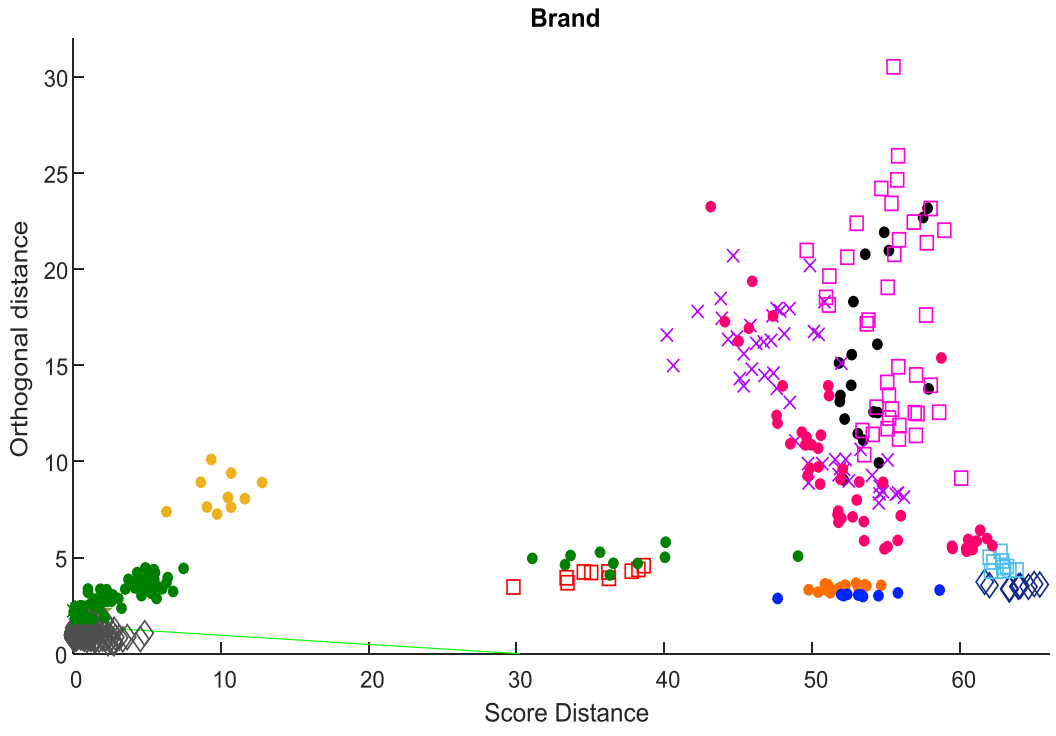


Projection of the ibuprofen medicines

OC-PLS



DD-SIMCA



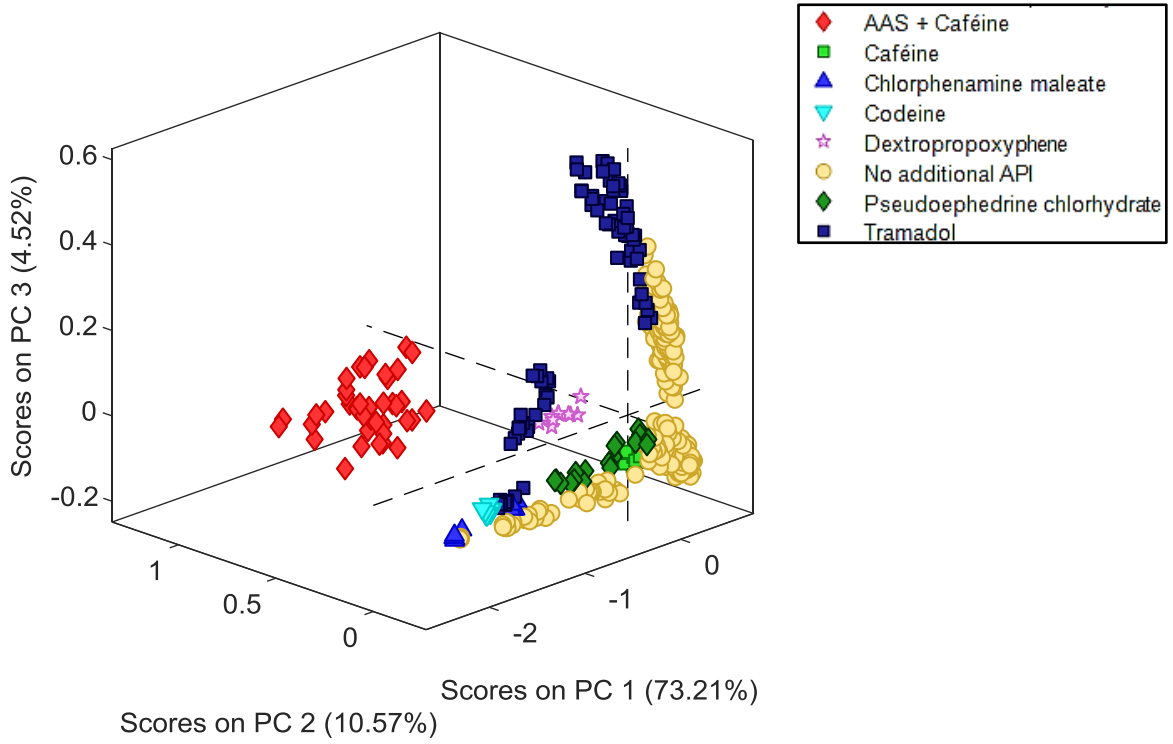
Evaluation of the quality of classification

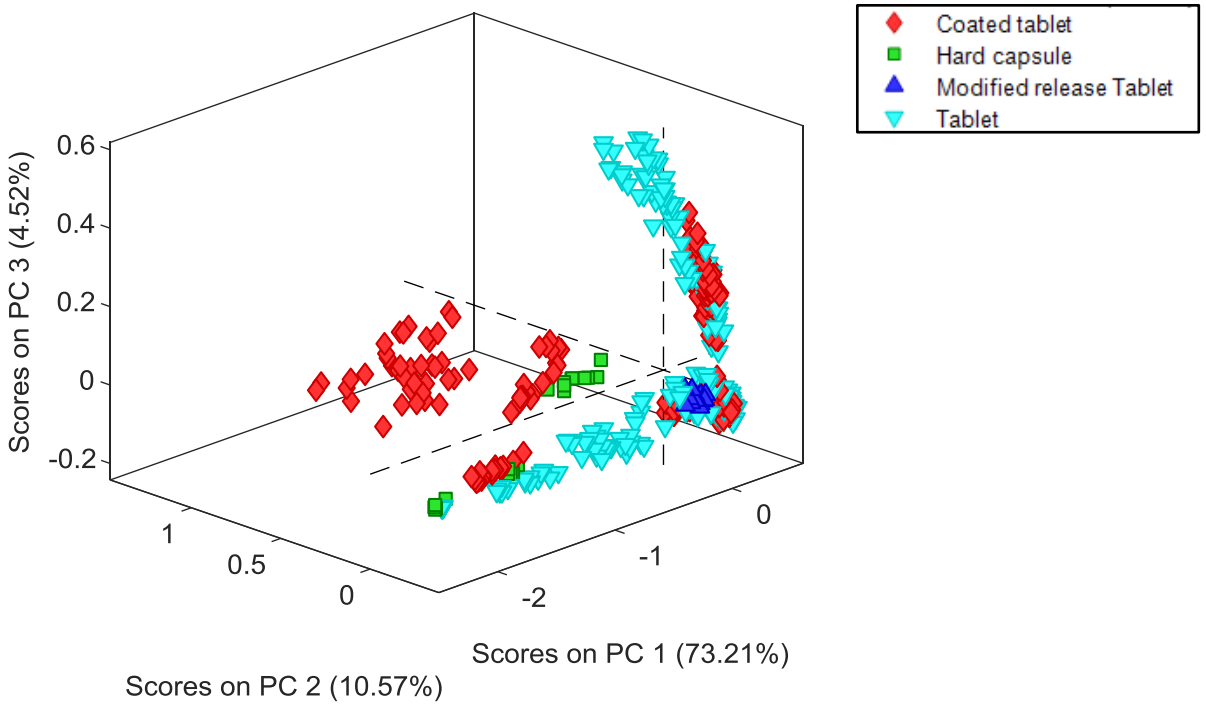
- Results of the MCC :

		OC-PLS	DD-SIMCA
Number of samples		420	
Number of « Ibuprofen EG 400 mg »		80	
True positive (TP)		68	77
False negative (FN)		12	3
False positive (FP)	9% !	31	0
True negative (TN)		309	340
MCC		0.701	0.977

Preliminary analysis : PCA on paracetamol medicines

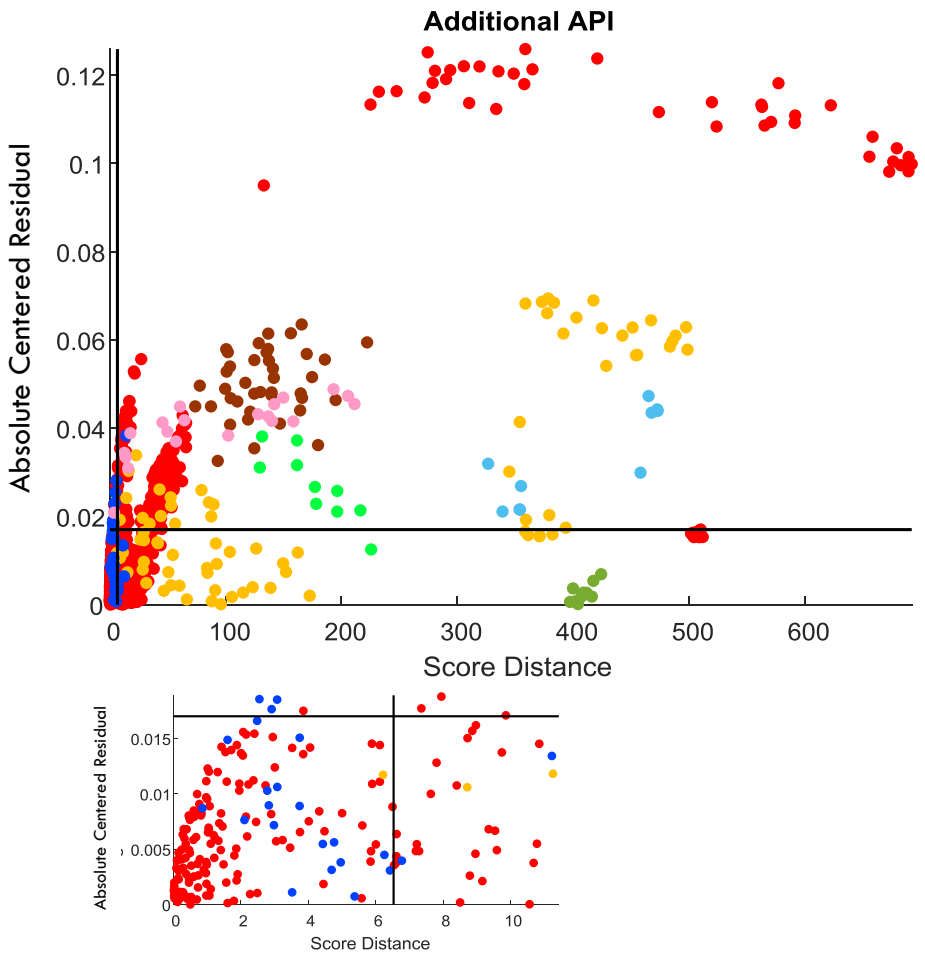
- Several dosage and co-formulation

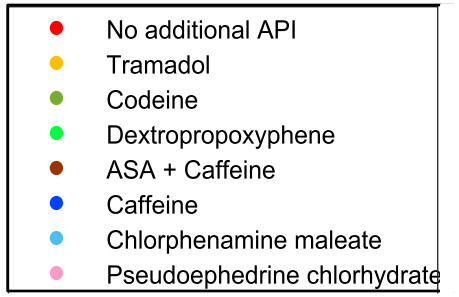




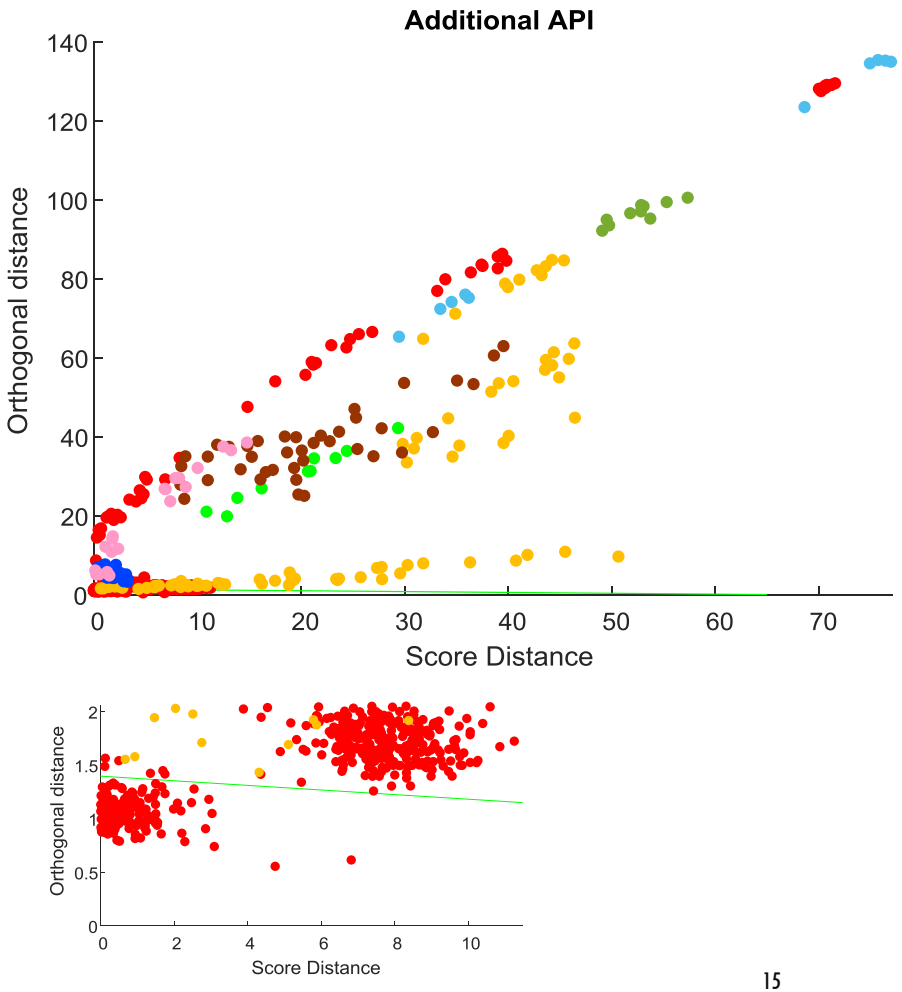
Projection of the paracetamol medicines

OC-PLS





DD-SIMCA

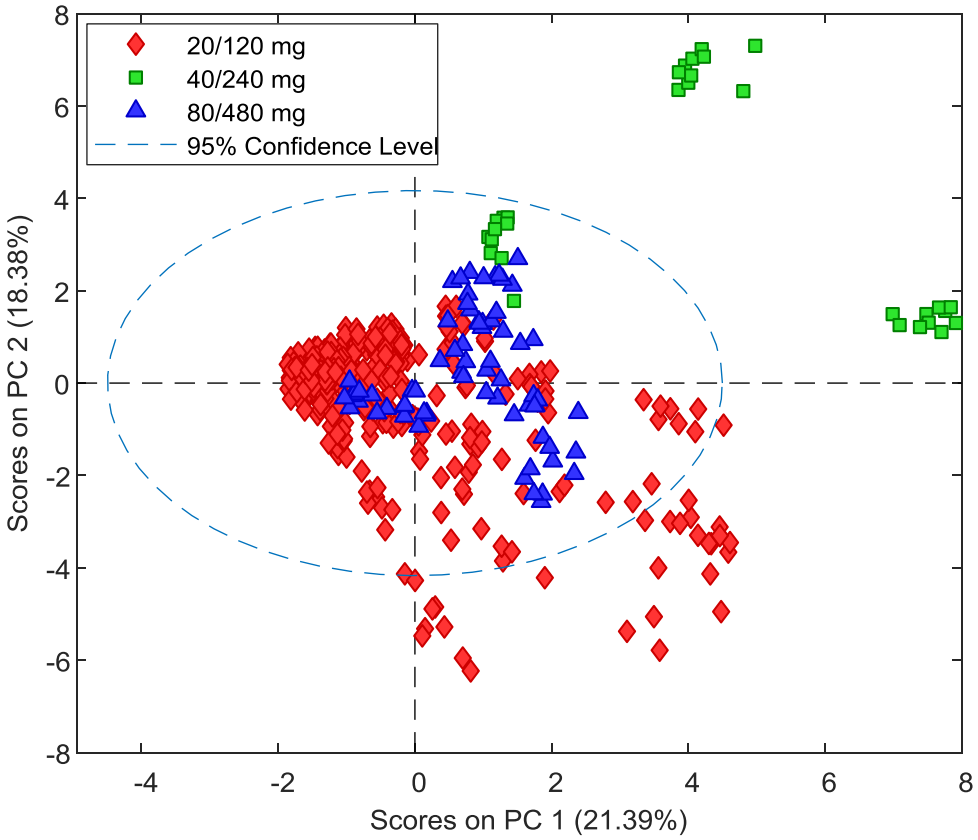


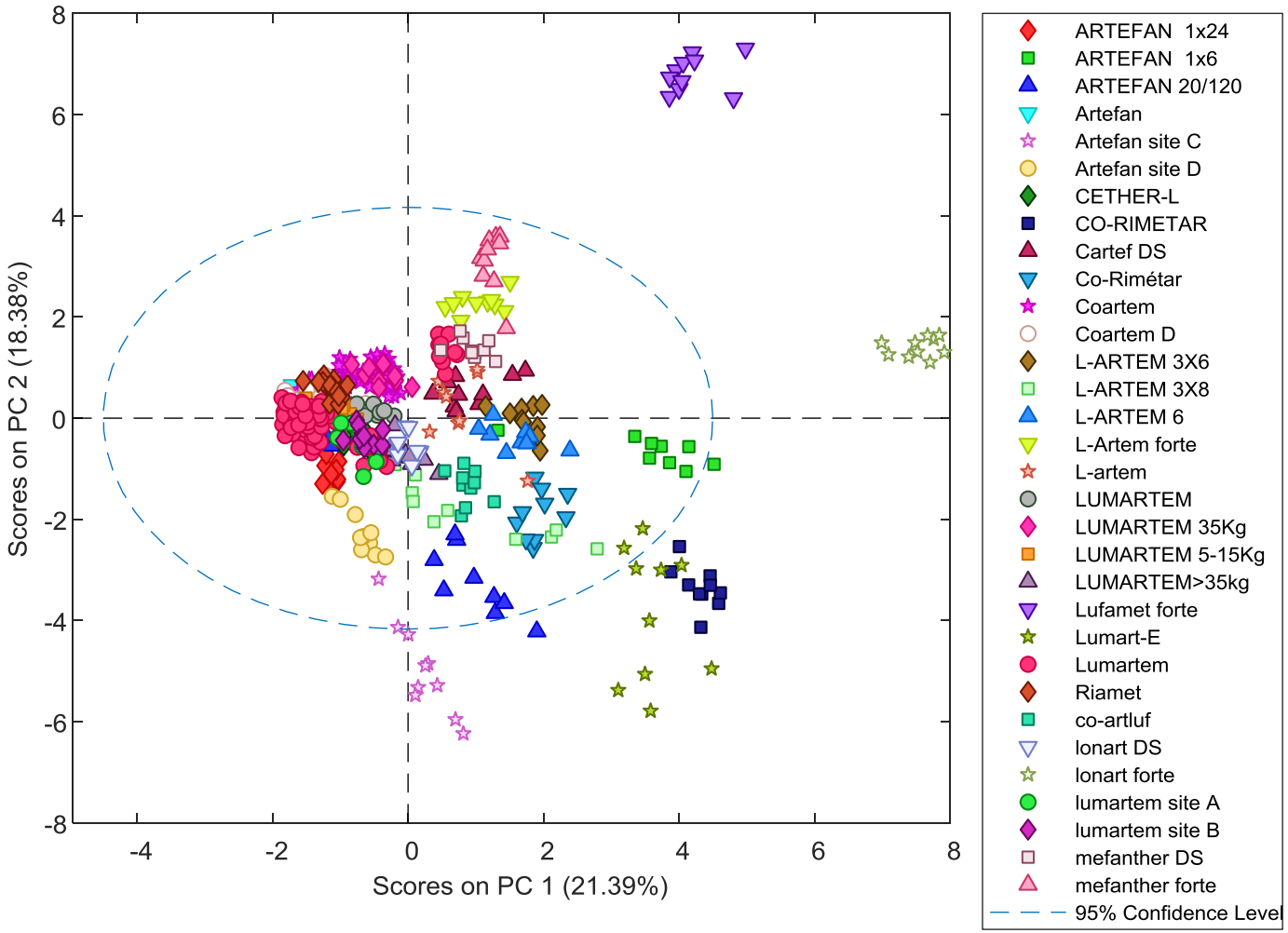
Evaluation of the quality of classification

- Results of the MCC :

		OC-PLS	DD-SIMCA
Number of samples		690	
Number of « Dafalgan 1g »		100	
True positive (TP)		95	93
False negative (FN)		5	7
False positive (FP)	10% !	61	0
True negative (TN)		529	590
MCC		0.712	0.960 ✓

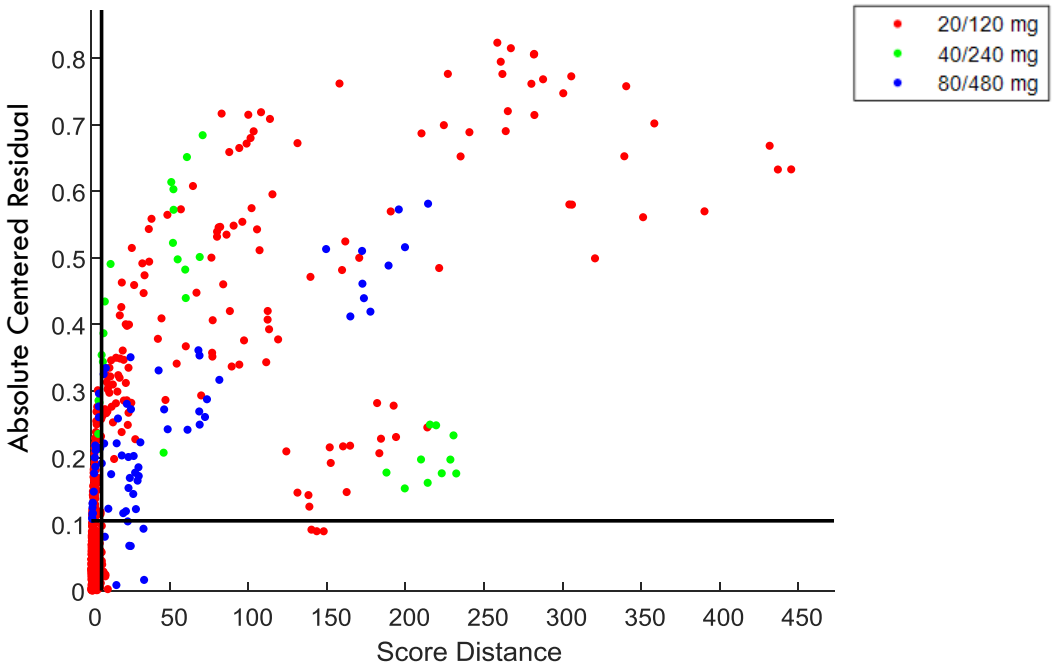
Preliminary analysis : PCA on A/L

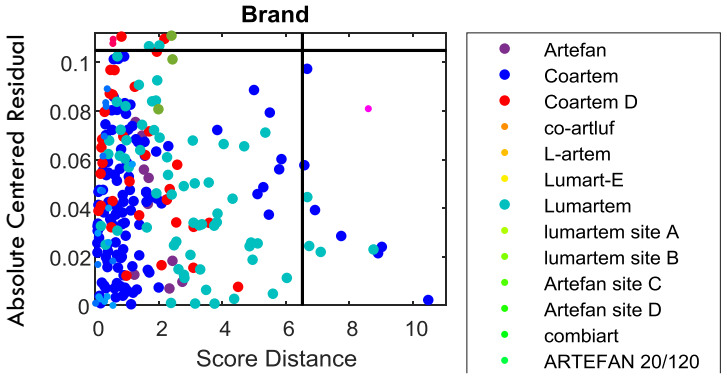




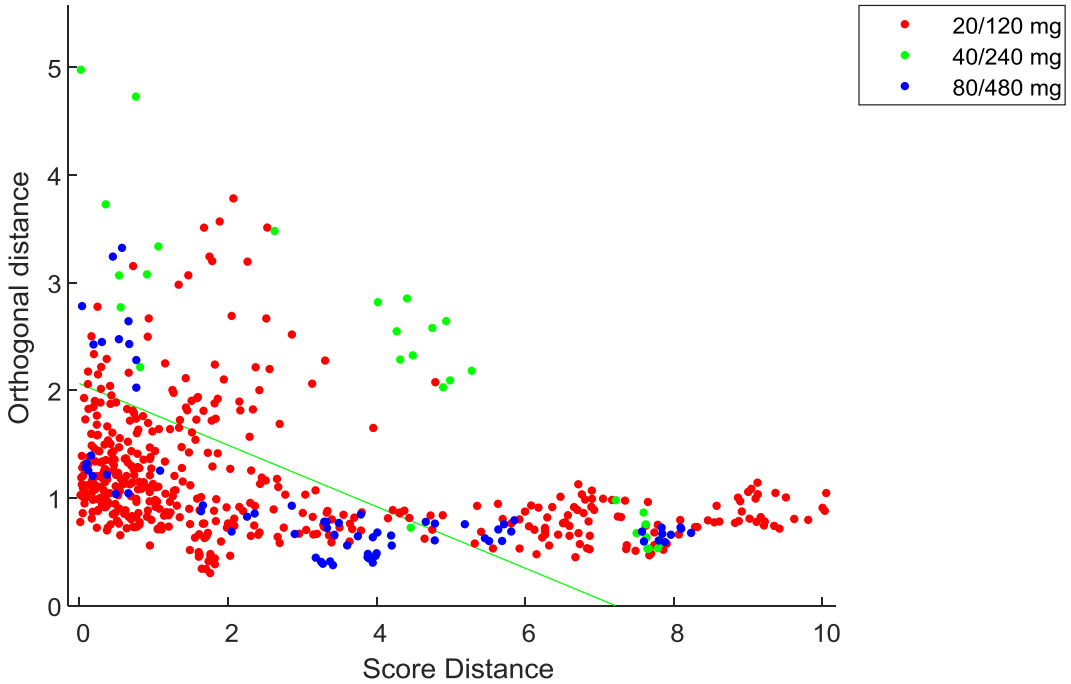
Projection of the A/L medicines

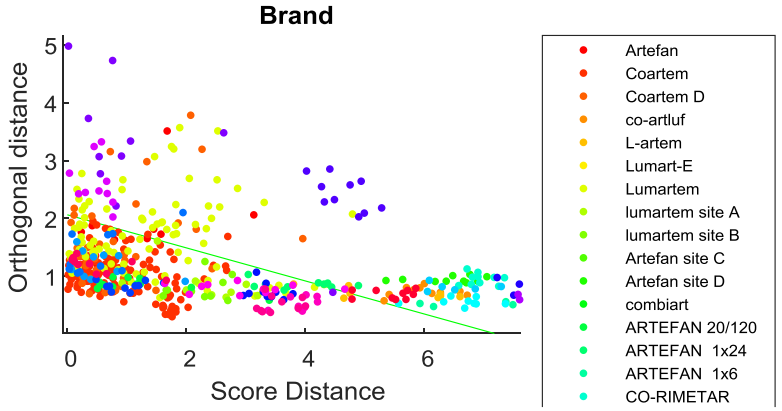
OC-PLS





DD-SIMCA

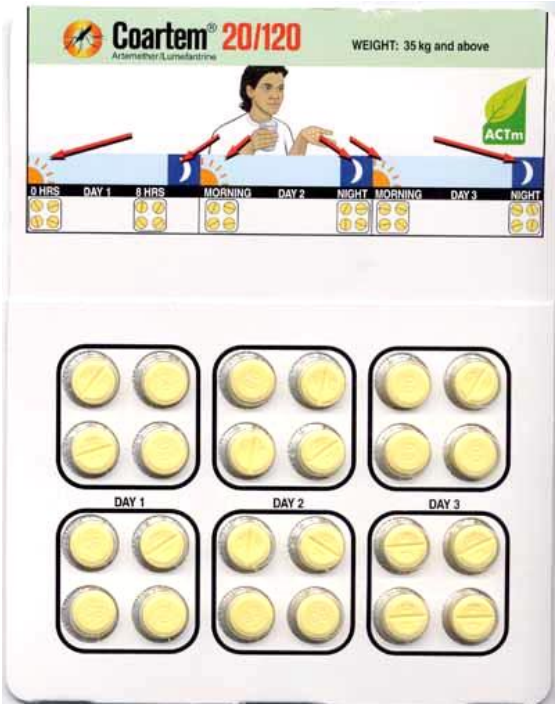




Evaluation of the quality of classification

- Results of the MCC :

	OC-PLS	DD-SIMCA
Number of samples	540	
Number of « Coartem 20/120 mg »	70	
True positive (TP)	56	69
False negative (FN)	14	1
False positive (FP)	89	162
True negative (TN)	381	258
MCC	0.463	0.421



Conclusion

- Raman handheld spectrometer has shown very interesting results comparing to the NIR S-G-1:

- Ibuprofen : $MCC_{truscan}$ =0.920 vs MCC_{NIR}=1.00
- Paracetamol : $MCC_{truscan}$=0.977 vs MCC_{NIR}=0.971
- Artemether/Lumefantrine : $MCC_{truscan}$ =0.45 vs MCC_{NIR}=1

- Thanks to class modeling, substandard or high-quality falsified medicines could be identified

Perspectives

- Develop PLS-Density Modeling (PLS-DM)
- Develop class modeling on several NIR and Raman handheld spectrophotometers data with other medicines
- Interesting to improve chemometrics in embedded system

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SUPPLEMENTARY DATA